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Technology Report

Bio-digital convergence standardization opportunities

Executive summary

The term bio-digital convergence denotes the convergence of engineering, nanotechnology, biotechnology, information technology and cognitive science. While the concept is at least 20 years old, bio-digital convergence has been turbocharged by the fast-paced changes and evolution of information and digital technologies.

Innovations driven by bio-digital convergences range from a significant contribution to the advancement of scientific knowledge in the life-sciences to major developments in bioengineering, to the point that the body of knowledge and the range of applications of the latter discipline is very different than it was in the 1990s.

In a world challenged by climate change and the need to ensure that a growing population is not only well fed but enjoys a fulfilling life, the present and potential future impact of these innovations is major. For instance, bio-digital-driven innovations can and indeed are contributing to realization of the following nine UN sustainability goals: Zero Hunger (SDG 2), Good Health and Well-Being (SDG 3), Clean Water and Sanitation (SDG 6), Industry, Innovation, and Infrastructure (SDG 9), Sustainable Cities and Communities (SDG 11), Responsible Consumption and Production (SDG 12), Climate Action (SDG 13), Life Below Water (SDG 14) and Life on Land (SDG 15).

To address the complex topics described above, the technology report is structured as follows:

Out of the seven working groups of SEG 12, six have explored bio-digital convergence and its current standardization landscape and have identified pertinent standardization opportunities. This overall scope is introduced in Section 1.

Areas that have been explored include the reverse engineering of living systems, life systems and bioengineering, human augmentation technologies, agricultural bioengineering, environmental bioengineering and bio-digital social, risk and ethical aspects.

Understanding the machinery of life as well as structuring and codifying this acquired knowledge is a prerequisite for being able to engineer processes, devices and applications that are biological in nature or have a biological component.

Section 2: Reverse engineering of living systems – The initial mandate of Working Group (WG) 2 was thus to explore bio-digital standardization opportunities for supporting the reverse-engineering of living systems and systems of systems. This includes genomics, transcriptomics, proteomics, metabolomics, informatics, microbiomes, neurosciences and synthetics.

Section 3: Life systems and bioengineering – For WG 3, the task was to explore bio-digital standardization opportunities in life systems and bioengineering. This includes biosensors, biometrics, bio-foundries, bioprocessing, biofuels, drug discovery and engineering, synthetic biological circuit, metabolic engineering, genetic engineering, artificial life, organ-on-a-chip (OoC), and artificial organs and human digital twins.

Section 4: Human augmentation technologies – WG 4's mandate was to assess bio-digital standardization opportunities in the area of human augmentation, an emerging and thriving field which is focused on replicating, recovering, supplementing, amplifying, or enhancing human abilities for both healthy users and people with disabilities. This has included brain-machine interfaces, digital hardware enhancement,

ubiquitous and continual monitoring, enhanced strength, enhanced sensing, embodied computing, ambient intelligence, and biohacking.

Section 5: Agricultural bioengineering – The domain of agricultural bioengineering was assigned to WG 5. The initial mandate was to assess bio-digital standardization opportunities in the bioengineering of agricultural systems and systems of systems, including forestry, aquaculture, livestock farming, cellular agriculture, and molecular pharming. This includes internet of things applications (such as precision agriculture), embodied computing for animals, genetic engineering of food as well as UN Sustainable Development Goal 2: Zero hunger.

Section 6: Environmental bioengineering – WG 6 was given the mandate to explore bio-digital standardization opportunities in the area of environmental systems of systems. This has included geoengineering, sustainability, and the following UN sustainable development goals: SDG 13: Climate action, SDG 14: Life below water, and SDG 15: Life on land. WG 6 had few participating members, thus limiting the depth of its assessment. Nevertheless, it was able to come up with some key findings.

With all new technologies come opportunities, challenges and, in some cases, risks. This is the case with technologies arising from bio-digital convergence. Ethical questions raised by many of these technologies are not only associated with their use, but also, given the current challenges of our global society, their non-use.

Section 7: Bio-digital social risks and ethical aspects – SEG 12 mandated its WG 7 to explore a number of issues related to social risks, ethical aspects, resilience, and safety management, including data governance and related issues

Section 8 lists the recommendations of the working groups to the SMB as well as the results of the Board's decisions concerning their adoption.

Acknowledgments

This technology report was developed by the IEC Standardization Evaluation Group 12: Bio-digital convergence, as a deliverable to address the complex topic of bio-digital convergence, which denotes the convergence of engineering, nanotechnology, biotechnology, information technology and cognitive science.

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List of abbreviations

Technical and scientific terms

3D	three-dimensional
ADHD	attention deficit hyperactivity disorder
AI	artificial intelligence
ALS	amyotrophic lateral sclerosis
BCI	brain-computer interface
BTE	behind the ear (hearing aid)
CAGR	compound annual growth rate
CAR-T cell	chimeric antigen receptor T-cell
Cas	CRISPR-associated
CDS	clinical decision support
CDSS	clinical decision support system
CI	cochlear implant
CNN	convolutional neuro network
CoU	context of use
CRISPR	clustered regularly interspaced short palindromic repeats
CSD	cortical spreading depression
DBS	deep brain stimulation
DBTL	design, build, test, learning
DL	deep learning
EAS	electric acoustic stimulation
ECG	electrocardiographic / electrocardiogram
EEG	electroencephalographic /electroencephalography
EHR	electronic health record
EM	electron microscopy
EMG	electromyography
FAIR	findable, accessible, interoperable and reusable
FES	functional electric stimulation
FET	field-effect transistor

fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
GCP	good clinical practice
GLP	good laboratory practice
GMO	genetically modified organism
GMP	good manufacturing practice
GPT	generative pre-trained transformer
hDAA	harmonized data access agreement
HI	human intelligence
HMD	head-mounted device
ICT	information and communications technology
IoT	Internet of Things
IMU	inertial measurement unit
IT	information technology
LiOH	lithium hydroxide
LM	light microscopy
ML	machine learning
MPK	microprocessor-controlled prosthetic knee
MR	magnetic resonance
NK	natural killer
Neuro EP	neurointerventional electrophysiology
NMES	neural muscular electrical stimulation
OEM	original equipment manufacturer
OoC	organ-on-a-chip
OR	olfactory receptor
PB	petabyte
PBPK	physiologically based pharmacokinetic
PBS	phosphate-buffered saline
PFA	paraformaldehyde
PPRL	privacy-preserving record linkage
QCM	quartz-crystal microbalance

QoI	question of interest
SBGN	Systems Biology Graphical Notation
SCP	slow cortical potential
SDG	United Nations Sustainable Development Goal
SDO	standards developing organization
SOP	standard operating procedures
SPR	surface plasmon resonance
tACS	transcranial alternating current stimulation
TB	terabyte
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation
tES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
tVNS	transcutaneous vagal nerve stimulation
VHT	virtual human twin
VR	virtual reality
VVUQ	verification, validation and uncertainty quantification
XR	extended reality

Organizations, institutions and organizational structures, platforms, networks, ontologies, knowledgebases

ACM	Association for Computing Machinery
ANSI	American National Standards Institute
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials
BioRoboost	European Commission-funded initiative to enhance biosafety and risk assessment in synthetic biology standards
BRAIN	Brain Research through Advancing Innovative Neurotechnology (US initiative)
BRIDG	Biomedical Research Integrated Domain Group
CBER	Center for Biologics Evaluation and Research (of the FDA)

CDER	Center for Drug Evaluation and Research (of the FDA)
CEN/CENELEC	European Committee for Standardization/European Electrotechnical Committee for Standardization
CIE	Chinese Institute of Electronics
COMBINE	Computational Modeling in Biology initiative
COSMOS	(EU) Coordination of Standards in MetabOlomicS
CPM	Common Provenance Model
DUO	Data Use Ontology
EBMT	European Society for Blood and Marrow Transplantation
EDITH	European Virtual Human Twin Infrastructure
EHDS	European Health Data Space
EMA	European Medicines Agency
EU-GDPR	EU General Data Protection Regulation
EU-STANDS4PM	EU standards for in silico models for personalized medicine
FACT	Foundation for Accreditation of Cellular Therapy
FACT	Food and Agriculture Cyberinformatics and Tools (US Department of Agriculture)
FDA	US Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
FMA	Foundational Model of Anatomy
GA4GH	Global Alliance for Genomics Health
HUPO	Human Proteome Organization
ICD	(WHO) International Classification of Diseases
IEEE	Institute of Electrical and Electronics Engineers (IEEE)
Instand-NGS4P	EU-funded project for integrated and standardized next generation sequencing workflows for personalised therapy
ISCT	International Society for Cell & Gene Therapy
ISPE	International Society for Pharmaceutical Engineering
ISSCR	International Society for Stem Cell Research
ISO	International Organization for Standardization

ITU-T	International Telecommunication Union – Telecommunication Standardization Sector
JSFLG	Joint Smart Farming Landscape Group
LOINC	Logical Observation Identifiers Names and Codes
MIASE	Minimum Information About a Simulation Experiment
MINIMAR	Minimum Information for Medical AI Reporting
MIRIAM	Minimum information requested in the annotation of biochemical models
MML	Multiscale Modelling Language
MMSF	Multiscale Modelling and Simulation Framework
ORCHID	Organ-on-Chip in Development consortium
POSIX	Portable Operating System Interface
PRO	Protein Ontology
PSI	Proteomics Standards Initiative (of HUPO)
SAG	Standards Advisory Group (ISO)
SC	subcommittee
SEG	systems evaluation group
SNOMED CT	Systematized Nomenclature of Medicine, Clinical Terms
SyC	systems committee
TC	technical committee
TCNL	Tactile Communication and Neurorehabilitation Laboratory (University of Wisconsin-Madison)
UniProt	Universal Protein Resource
WG	working group

Section 1

Introduction: Bio-digital convergence

As illustrated in Figure 1, the term bio-digital convergence denotes the convergence of engineering, nanotechnology, biotechnology, information technology and cognitive science. By convergence, we mean the creative union of sciences, technologies, engineering and peoples, focused on mutual benefit. This is a process requiring ever increasing integration across traditionally separate disciplines and areas of relevance, and across multiple levels of abstraction and organization.

While the concept is at least 20 years old, the actual practice of bio-digital convergence has been turbocharged by the fast-paced changes and evolution of information and digital technologies.

Since the early 1970s, the number of transistors on commercially available integrated circuits has roughly doubled every two years, a process encapsulated in the data framework known as Moore's law (see Figure 2). This evolution was accompanied not only by an exponential increase in available computing power, but also by an equivalent decrease in unit cost. It also constituted a driver for the evolution of computing science and its associated engineering disciplines, hence the rapid development in the last 20 years of, for instance, the Internet of Things (IoT), big data analytics and artificial intelligence (AI).

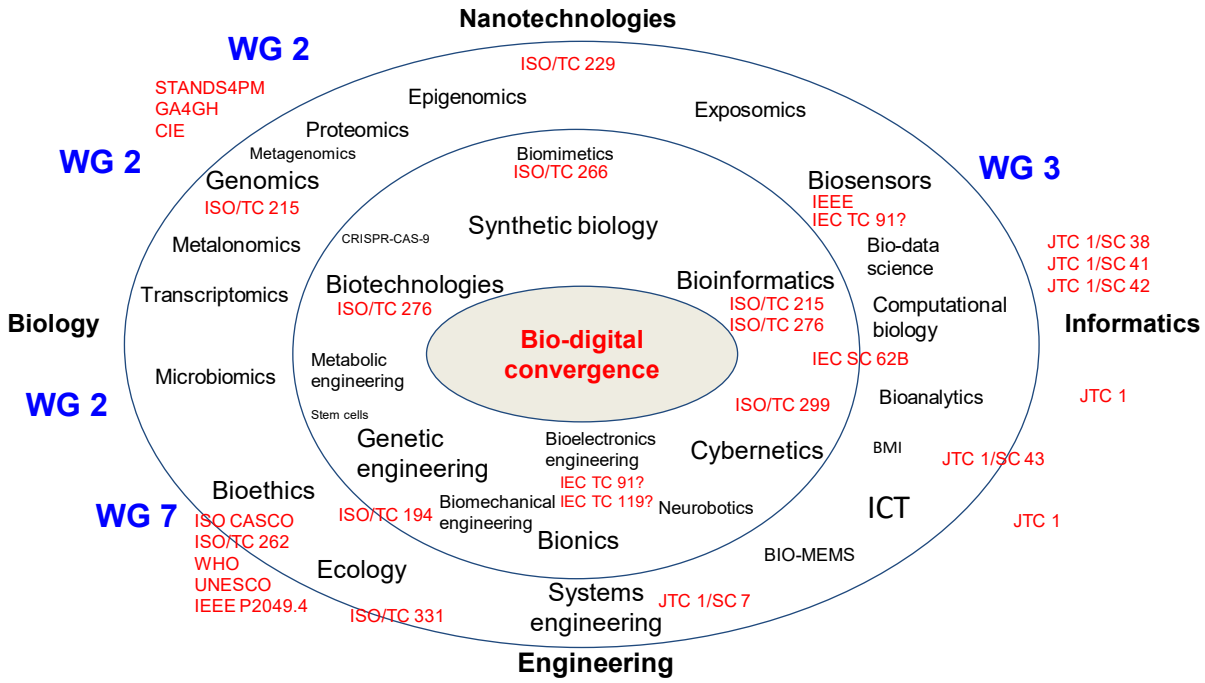


Figure 1 | Bio-digital convergence components

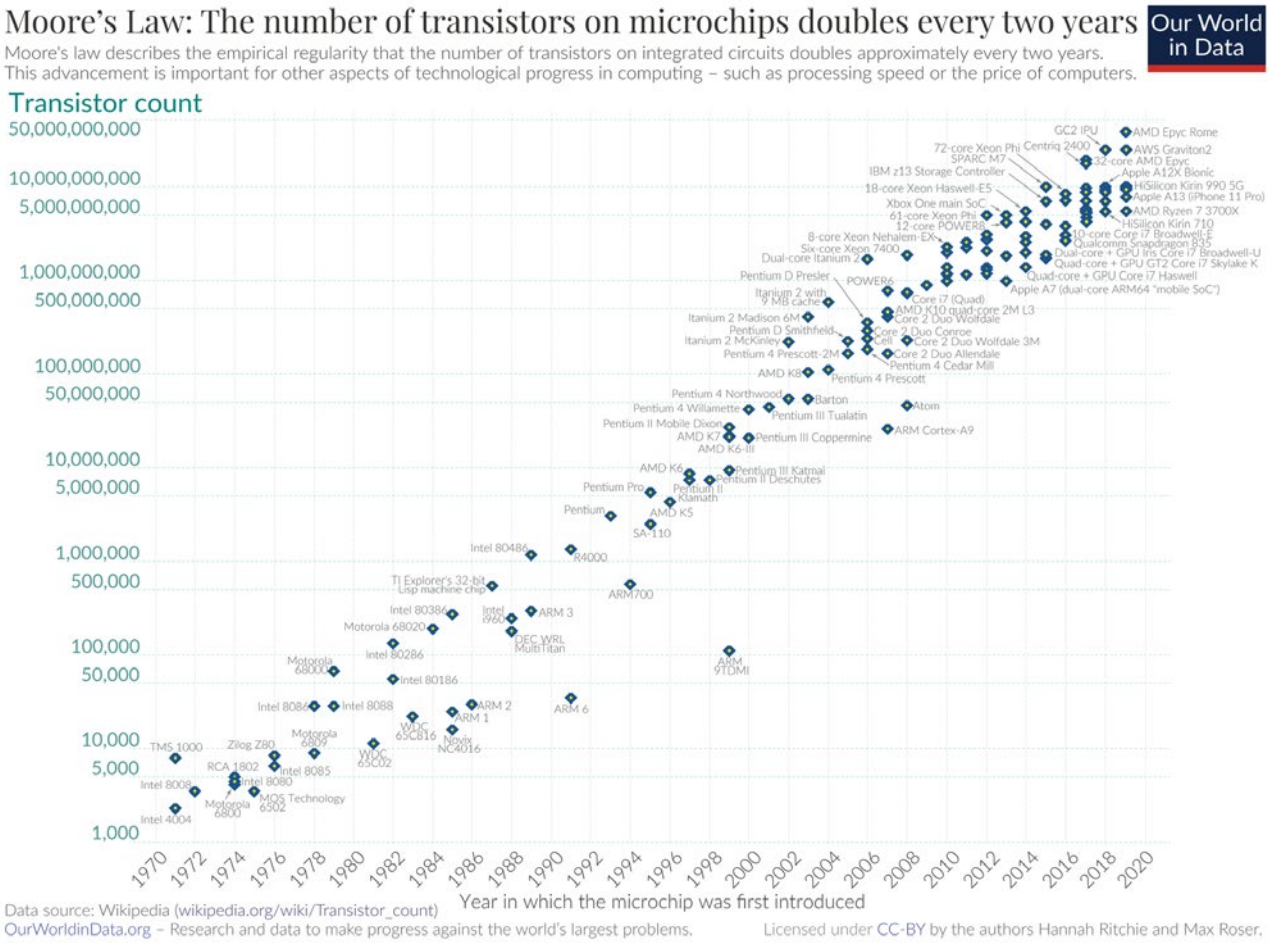


Figure 2 | Moore's Law (https://en.wikipedia.org/wiki/Moore%27s_law)

Life on our planet is the result of approximately 3,5 billion years of evolution, an evolution shaped not only by the laws of nature but also by our planet's cosmic environment and a series of random extinction events, some of them extensive enough to wipe out more than 70% of species existing at the time.

Understanding, and thus performing a reverse-engineering of life on our planet is very complex, with a scope encompassing not only the molecular machinery of living systems, but also their interactions in larger ecosystems up to the level of the entire biosphere (see Figure 3).

It is currently estimated that there exist around 8,7 million species of plants and animals (eukaryotes) on earth. The genome of one of these species, that of human beings (Homo sapiens), has about three billion DNA base pairs encoding approximately 22 000 genes. This corresponds to about 700 MB of complex "programming" requiring a cellular factory to be decoded. Approximately 20 000 proteins (composing the human proteome) and 110 000 molecules are processed in a human body. These numbers constitute only the tip of the iceberg when we start looking at structure, relationships, processes, etc.

Understanding life thus implies acquiring, processing and then comprehending a large amount of information. This acquired knowledge in turn has to be leveraged and complemented to be able to "engineer" useful solutions.

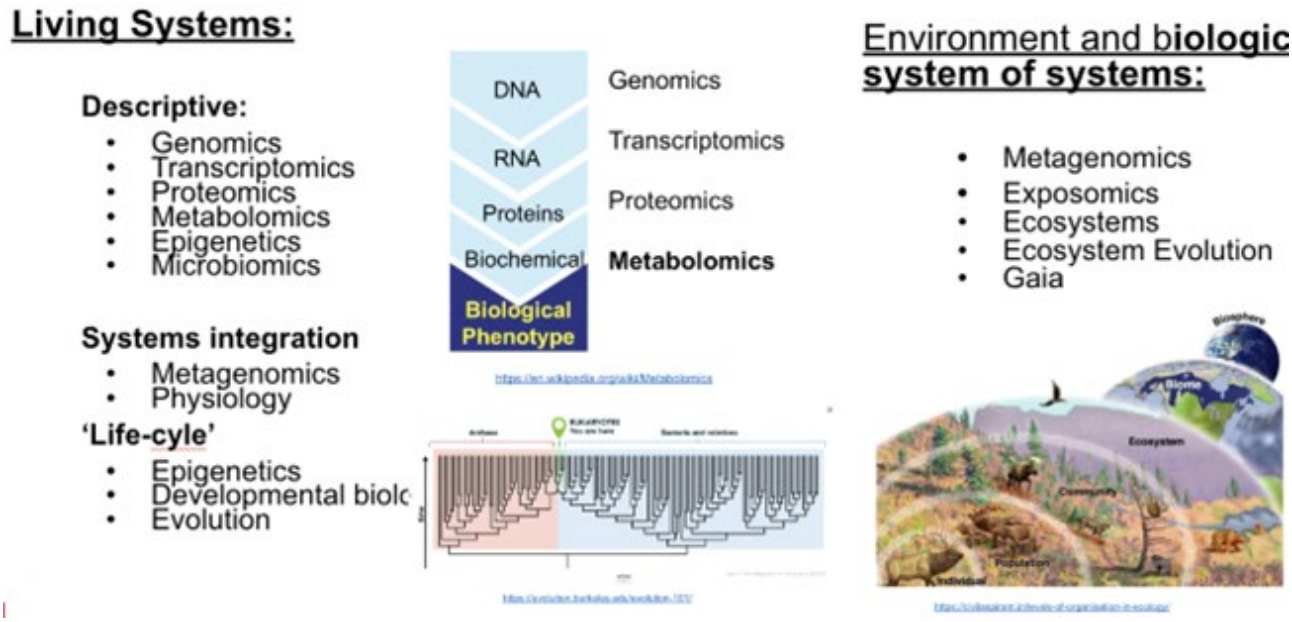


Figure 3 | Reverse engineering of life

Bio-digital convergence thus signifies more than a simple combination of various disciples. Rather it designates the creation of new areas of knowledge, technologies and engineering specialties through synergy.

Innovations driven by bio-digital convergences range from a significant contribution to the advancement of scientific knowledge in the life sciences to major developments in bioengineering, to the point that the body of knowledge and the range of applications of the latter discipline (See Figure 4) are very different than what they were in the 1990s.

In a world that is challenged by climate change and the need to ensure that a growing population is not only well fed but enjoys a fulfilling life, the present and potential future impacts of these innovations are of major consequence. For instance, bio-digital-driven innovations are contributing and can further contribute to the following nine UN Sustainable Development Goals (SDG): Zero hunger (SDG 2), Good health and well-being (SDG 3), Clean water and sanitation (SDG 6), Industry, innovation and infrastructure (SDG 9), Sustainable cities and communities (SDG 11), Responsible consumption and production (SDG 12), Climate action (SDG 13), Life below water (SDG 14) and Life on land (SDG 15)).

In the following sections, this technology report will elaborate on the scope of each of the 6 working groups (out of 12) of SEG 12 charged with exploring bio-digital convergence and its current standardization landscape and spell out some of their key findings.

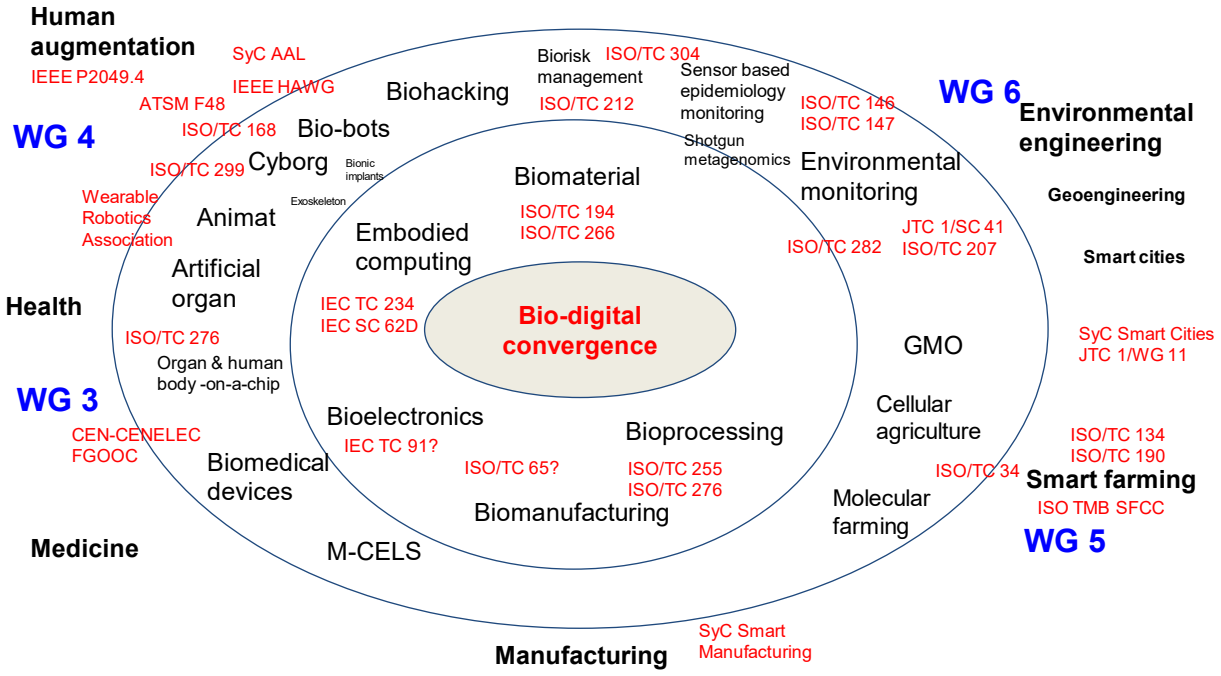


Figure 4 | Bio-digital convergence applications

Section 2

Reverse engineering of living systems

2.1 Overview

Reverse engineering of living systems (and systems of systems) is an advanced scientific approach that involves breaking down complex biological structures into simpler parts to understand how they function, such as biological organisms, cells or tissues, etc. It is a process of discovering how a biological system works by examining its components in detail and reassembling them to understand the whole system. Reverse engineering has a wide range of applications in areas such as medicine, biotechnology, and agriculture, and it has helped scientists gain a deeper understanding of how living systems operate. This approach involves the integration of interdisciplinary fields, such as biology, chemistry, physics, computer science, robotics, and materials science, among others.

Omics, a new term referring to various fields of biological research that aim to comprehensively characterize and quantify large numbers of biological molecules in complex samples[1][1][2], involves a cutting-edge biotechnology that can analyze molecular-level systems in detail. The technologies used in omics, such as massive parallel sequencing technologies, have decoded biological and living systems into a digital world, generating an enormous amount of data and enabling the digitalization of living systems.

Synthetic biology is another important field, in which researchers aspire to create artificial living systems by mimicking the natural principles of biological organisms. This approach is also relevant in the field of tissue engineering, where researchers aim to recreate functional tissues or organs for therapeutic applications.

Neuroscience is a new area that is advancing towards both new research breakthroughs and new clinical applications. However, it also generates a massive amount of data, such as imaging, scanning and interaction data. Researchers now have the opportunity to build a digital system for neuroscience, and people are starting to consider the building of a human-machine interface. This could be considered as one of positive applications in the reverse engineering of living systems.

The future development of such reverse engineering involves several challenges, including the need for advanced analytical techniques, computational models and simulation tools, as well as identification of effective biomaterials and genetic engineering methods.

One ambitious area of research in reverse engineering of living systems is the creation of artificial cells or synthetic organisms having the properties of living cells and the capacity to perform specific functions, such as sensing environmental changes, synthesizing new compounds, or producing energy.

Another area of research is the reconstruction of functional tissues or organs, by combining biomaterials with cells and growth factors, in order

1 The branches of science known informally as omics are various disciplines in biology whose names end in the suffix -omics, such as genomics, proteomics, metabolomics, metagenomics, phenomics and transcriptomics.

2 Numbers in square brackets refer to the Bibliography.

to create complex 3D structures and networks, which can mimic the natural tissues.

Machine learning and artificial intelligence also constitute promising approaches for reverse engineering of living systems, as they can analyze large data sets, identify patterns and correlations, and optimize the design of biological systems.

Overall, the development of reverse engineering of living systems has the potential to revolutionize many fields, from medicine and agriculture to energy and environmental sciences.

Many challenges and opportunities exist in the field of reverse-engineering of living systems and systems of systems. A revolution in concepts is currently taking place, moving from biology and biotechnology towards bio-digital convergence. Currently, a lack of standards exists relating to fundamental mechanisms, theory, instruments, data, and tools in these fields. We are using engineering perspectives and thinking to address this lack and to develop the standards necessary in these fields. We need to develop standards for frameworks, instruments, pipelines, procedures, reverse-engineering techniques, data relevance, and systems relevance.

There has been explosive growth in the use of these technologies in a wide range of industries, academics, and engineering fields. Many major breakthroughs have been achieved using these technologies. Additionally, more and more experts and standards developing organizations (SDO) are becoming involved in the development of standards relevant to these fields. The extensive activities taking place in this area of research are indicative of the significant opportunities for advancements in our understanding of living systems and systems of systems.

It is clear that standardization is beneficial to various groups, including industrial partners such as large and small companies that undertake billion-dollar projects and future applications. Another group that benefits from standardization are academic researchers who carry out fundamental research for theory, design, tools, and new living systems. Governments and regulatory authorities also require standardization to provide better and efficient support for industrial directions, while minimizing potential risks to humankind and the environment. Business development entities can participate in the revolution and accelerate their own business or activities through standardization, while users/individuals can better understand the technologies and gain power and knowledge for self-protection.

There currently exist a large number of SDO entities active in this field, such as ISO/TC 276 Biotechnology, ISO/TC 215 Health informatics, ISO/TC 215/SC 1 Genomics Informatics, ISO/TC 34/SC 9 Food Products/ Microbiology, ISO/TC 34/SC 16 Food Products/ Horizontal methods for molecular biomarker analysis, ISO/TC 212 Clinical laboratory testing and in vitro diagnostic test systems, ISO/IEC JTC 1/ SC 42 Artificial Intelligence, ISO/IEC JTC 1/SC 29/ WG 8 MPEG Genomic coding (standards for genome compression and storage), CEN/TC 140/ WG 3 – Quality management in the medical laboratory, the Human Proteome Organization (HUPO)'s Proteomics Standards Initiative (PSI), the Metabolomics Society, EU Coordination of Standards in MetabOlomicS (COSMOS), Fairsharing.org, the Global Alliance for Genomics Health (GA4GH), EU-STANDS4PM (EU standards for in silico models for personalised medicine), Instand-NGS4P (EU-funded project for integrated and standardized next generation sequencing workflows for personalised therapy), BioRoboost (European Commission-funded initiative to enhance biosafety and risk assessment in synthetic biology standards), etc.

Relevant standards published (examples):

- ISO 5058-1:2021, *Biotechnology – Genome editing – Part 1: Vocabulary*
- ISO 20397-1:2022, *Biotechnology – Massively parallel sequencing – Part 1: Nucleic acid and library preparation*

- ISO 20397-2:2021, *Biotechnology – Massively parallel sequencing – Part 2: Quality evaluation of sequencing data*
- ISO 20688-1:2020, *Biotechnology – Nucleic acid synthesis – Part 1: Requirements for the production and quality control of synthesized oligonucleotides*
- ISO 21710:2020, *Biotechnology – Specification on data management and publication in microbial resource centers*
- ISO 20691:2022, *Biotechnology – Requirements for data formatting and description in the life sciences*
- ISO/TS 24420:2023, *Biotechnology – Massively parallel DNA sequencing – General requirements for data processing of shotgun metagenomic sequences*

Standards under development (examples):

- ISO/AWI TS 9491-1: *Biotechnology –Predictive computational models in personalized medicine research – Part 1: Constructing, verifying and validating models*
- ISO/CD 20397-3: *Biotechnology – Massively parallel sequencing – Part 3: General requirements and guidance for metagenomics*
- ISO/FDIS 20688-2: *Biotechnology – Nucleic acid synthesis – Part 2: Requirements for the production and quality control of synthesized gene fragments, genes, and genomes*

Based on the scope of SEG 12 WG 2 Reverse Engineering of Living Systems, several significant and intriguing topics have been identified that require attention in this area. However, the WG is limited by its resources and must prioritize accordingly. Thus, following a thorough discussion with the leaders and experts in the WG, the focus has been narrowed to three of these topics: omics, synthetic biology, and neuroscience. The working group has therefore initiated research and analysis in these areas.

2.2 Omics

In recent years, the rapid progress of omics technology has revolutionized biological research by providing unprecedented insights into the functional landscapes of biological systems. Omics, which comprises a range of modern molecular biology and analytical techniques, enables the evaluation and characterization of biological molecules such as DNA, RNA, proteins, and metabolites at the cellular, sub-cellular, and organismal levels. This technology has emerged as a cornerstone in modern biology and medicine by providing high-throughput and comprehensive approaches to analyzing biological systems, such as 2nd generation sequencing, 3rd generation sequencing, microchip, mass spectrum proteomics, etc. Omics technology has enabled the identification of novel disease biomarkers, drug targets, and therapeutic strategies (see Figure 5).

Additionally, it has significantly enhanced our understanding of complex biological processes, such as diseases, host-pathogen interactions, and environmental responses. The progress in omics technology has drastically increased the pace of scientific discovery and is expected to transform personalized medicine and improve human health in the future.

Regarding standardization, efforts are ongoing to develop common data formats, vocabularies, and protocols across different omics applications. However, many challenges remain to be overcome, such as the heterogeneity and complexity of the data generated by omics technologies, as well as the lack of consensus among different stakeholders regarding which standards should be adopted (Figure 6). A first series of omics standards has already been published, such as ISO 20397-1:2022 *Biotechnology – Massively parallel sequencing – Part 1: Nucleic acid and library preparation* and ISO 20397-2:2021 *Biotechnology – Massively parallel sequencing – Part 2: Quality evaluation of sequencing data*. SDOs are beginning to quote these standards for further standards development.

OMICS (Genomics, Transcriptomics, Proteomics, Metabolomics, etc.)

Definition

Omics refers to a field of study in biology ending in -omics, such as genomics, transcriptomics, proteomics, metabolomics or epi-genomics, etc.
One of key characteristics is Big Data.

Omics layers and connections from genotype to phenotype. | **Instruments for OMICS** | **Applications (PM, agri, drug, etc) of OMICS**

By Dr. Yong ZHANG

Figure 5 | Omics, from systems to applications

Standardization for OMICS

	Key subjects	Key factors	Standardization potentials
Instruments	Mechanism, hardware, software, advantages/disadvantages	Quality, parameters, data, key algorithms	Mature ISO/TC 276, ISO/TC 215
Methods	Sample preparation, sample quality, protocols, bioinformatics, analysis, etc	Quality of sample, quality of data, requirements, etc.	Mature (ISO/TC 276, TC 212, TC 215, ISO/TC 34/SC 9/WG 25, CEN/TC 140/WG 3, etc.)
Applications	*Precision medicine, drug development, agriculture, etc.*	Pipeline structures, requirements, analysis process, database, etc.	Mature (ISO/TC 276, TC 212, TC 215, ISO/TC 34/SC 9/WG 25, CEN/TC 140/WG 3, etc.)

By Dr. Yong ZHANG

Figure 6 | Standardization for omics

Future standardization development efforts in omics could possibly include:

- Promoting collaboration and coordination among various stakeholders, including researchers, funders, journals, and standardization bodies, to develop and implement common standards that can facilitate data sharing and integration.
- Exploring new technologies and methods, such as artificial intelligence and machine learning, to automate data harmonization and normalization tasks, reducing the burden on human data curators and enabling the adoption of standards at scale.
- Encouraging the adoption of open-access policies, data sharing, and reproducibility in OMICS research as a means to promote transparency and accountability, which can ultimately facilitate the adoption of standards.
- Fostering the development of interdisciplinary collaborations and training programs in OMICS data analysis and standardization, promoting the integration of different perspectives, expertise, and tools across different domains.

A number of challenges still remain, such as:

- Data management: the increasing amount of data being generated in omics research has brought forward the challenge of managing, storing, and analyzing the data.
- Interpretation of big data: as the volume of data keeps increasing and as the vast number of interactions between molecules and cells creates a complex web of relationships, analysis and interpretation of big data are becoming extremely complicated.
- Ethical issues: the use of personal genome data poses ethical concerns about privacy, consent, and discrimination.
  - In conclusion, while standardization in omics is still an ongoing process, efforts to develop common data formats and protocols have made significant progress in recent years. We hope that the adoption of these standards can facilitate data integration, sharing, and reproducibility, ultimately leading to new insights and discoveries in the field of omics.

2.3 Synthetic biology

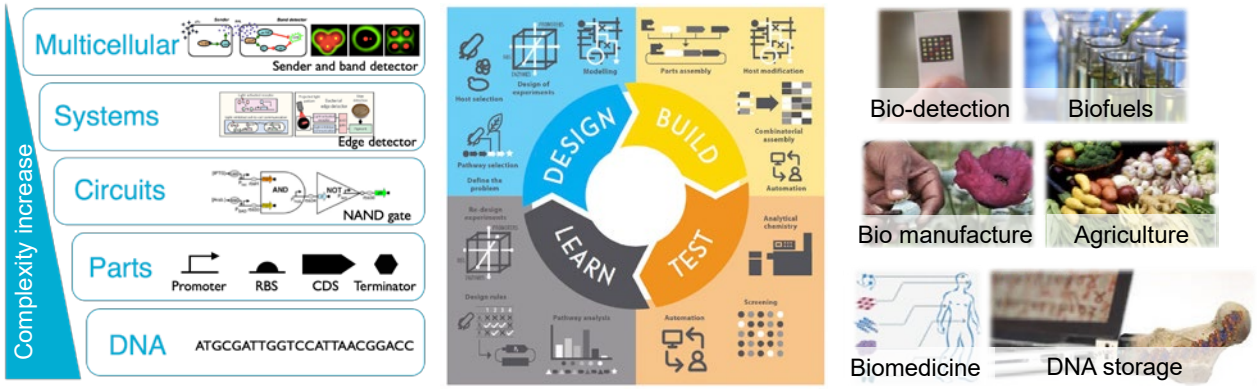
Synthetic biology technology involves the creation of artificial biological systems or the modification of existing biological systems for practical purposes. This interdisciplinary field combines principles from molecular biology, biochemistry, genetic engineering, and computer science to design and construct new biological systems, such as synthetic organisms, genetic circuits, and biomolecules with desired functions (see Figure 7). Synthetic biology has the potential to revolutionize various industries, including medicine, energy, agriculture, and environmental science. While it offers tremendous opportunities, it also raises complex ethical, legal, and safety issues, requiring careful consideration and regulation.

A number of challenges still remain (see Figure 8), such as:

- Safety and ethical concerns: With the advancement of synthetic biology, there is a growing concern about the safety and security of these engineered organisms. Proper regulations and safety measures need to be implemented to ensure that these organisms do not pose a threat to public health or the environment.
- Standardization: Synthetic biology needs better standardization for designing, building, and testing biological systems. Currently, no standardized language or protocols exist in synthetic biology.
- Complexity: Synthetic biology involves complex biological systems that are not fully understood. The need exists for better algorithms and computational tools to predict the behaviour of these systems.

Synthetic biology

Definition A new emerging multidisciplinary field that seeks to create new biological parts, devices, and systems, or to redesign existing systems for useful purposes and applications.



Abstraction of synthetic biology in different scales | **Classical iterative "DBTL" cycles of synthetic biology** | **Emerging applications of synthetic biology**

Figure 7 | Synthetic biology, from basic elements to applications

Synthetic biology

	Key factors	Methodologies/sources	Standardization potentials
DESIGN	Part repository	Computer aided tools	At early stage
	In silico design tools	Databases	Mature
	Data mining		
BUILD	Nucleic acids (DNA/RNA)	Nucleic acids/genome synthesis	Mature (ISO/TC276)
	Peptides	Peptide synthesis	
	Amino acids	Protein engineering/design	
	Proteins		
TEST & APPLY	*In vitro* (cloning, assembly)	PCR/ligation	
	In vivo (prokaryotes, eukaryotes)	Homologous recombination	
	Measurements (Omics, functions)	Sequencing, LC/MS, FCM	Mature
	Screenings & Automations	Colony picking, liquid handling	

Figure 8 | Standardization for synthetic biology

Based on the future applications involved in synthetic biology, standardization development should also be considered to map certain fields, such as:

- Medical applications: Synthetic biology offers opportunities for developing novel therapies and vaccines. These include the production of synthetic antibodies, cell therapies, and gene therapies.
- Sustainable agriculture: Synthetic biology can be used to develop sustainable agricultural practices, for example, engineering crops for higher yields, and resistance to diseases and adverse environments.
- Energy production: Synthetic biology offers opportunities for developing biofuels and renewable energy sources. These include the production of biofuels from biomass and algae.
- Environmental remediation: Synthetic biology can be used for environmental cleanup, such as the engineering of bacteria to break down pollutants.
- Industrial applications: Synthetic biology can be used to produce enzymes, chemicals, and other industrial products more efficiently and sustainably.

In conclusion, standardization is a critical component of the future of synthetic biology. With the rapid growth and innovation occurring in the field, it is essential to establish a common language and framework to ensure the safety, reproducibility, and reliability of synthetic biological entities. Standardization not only helps researchers standardize their practices but also enables better communication and collaboration among scientists and industries working in the field.

Moreover, it paves the way for future technological advancements and applications of synthetic biology in various domains, including medicine, energy, and agriculture. By developing and implementing standardized techniques, protocols, and tools, the synthetic biology community can accelerate the development of new and innovative synthetic biology solutions to address some of the most pressing global challenges faced today.

NOTE: This topic is also covered in SEG 12/WG 3: Life systems and bioengineering. More contents can be found in SEG 12 WG 3 parts.

2.4 Neurosciences

Description

Already at the end of the 19th century, Camillo Golgi and Santiago Ramón y Cajal observed detailed structures of neuronal morphology and neural circuits using optical microscopy and the Golgi staining method, which became the beginning of modern neuroscience. In recent decades, great progress has occurred in understanding the structural basis of brain organization and function, and actually, more than 100 years after the initial feats of Golgi and Ramón y Cajal, understanding the organization and function of the nervous system and its dysfunctions in brain diseases remains a primary priority.

The human brain is arguably the most complex entity in the known universe. Each individual neuron has fine structures in the form of dendritic and axonal morphology in brain-wide neural circuits with the result that the individual neuron extends axonal projections to multiple brain regions with distinct location in three dimensions. Billions of neurons are connected to each other through synapses, forming complex neural networks. In the course of the past decade, large-scale brain projects have been launched in major economies, with the aim of understanding how the brains works through its molecules, multiple cell types, brain-wide circuits and systems (see Figure 9).

The anatomical architecture is the material basis of brain functions. To understand the operating mechanism of a complex function such

Neuroscience

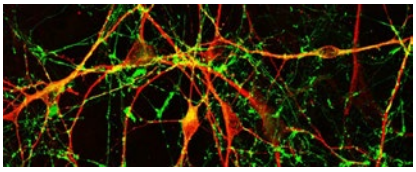
SEG 12

Exploring the Field

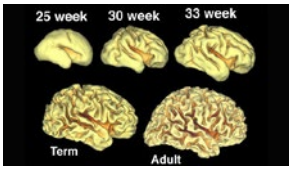
Neuroscience is the study of the nervous system, including the brain, spinal cord, and nerves

- Understand the brain and how it functions
- Understand neurological & psychiatric disorders, discover methods to prevent or cure them
- Simulate and even create a brain or brain-like machines/algorithms – AI / Brain organoids

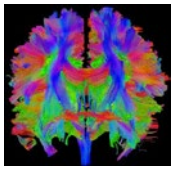
Molecular & cellular Neuroscience



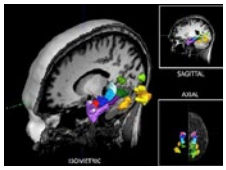
Development Neuroscience



Computational Neuroscience



Cognitive Neuroscience



IEC

By Dr. Jiangbo PU

Figure 9 | Neuroscience encompasses various studies in basic science, industry, and applications as an interdisciplinary field

Neuroscience

SEG 12

Subjects & fields

Fundamental research
- Cellular neuroscience
- Molecular neuroscience
- …

Neural engineering
- Neural imaging
- Neural informatics
- …

Behavioral & clinical
- Cognitive neuroscience
- Affective neuroscience
- …

Microscopic **Bottom-up** → **Bridging & tools** ← Macroscopic/system **Top-down**

Standardization Opportunities

- **Data:** ISO 20691:2022 Biotechnology – Requirements for data formatting and description in the life sciences
- **Devices:** IEC 63077:2019 Good refurbishment practices for medical imaging equipment

IEC

By Dr. Jiangbo PU

Figure 10 | Standardization opportunities for neuroscience

as cognition, we need first to investigate the organizational pattern of the neural circuit, i.e. how neural circuits are assembled from specific neuron types in different regions and how specific neural circuits perform signal processing during behaviours. These require profiling neural circuits at cell and sub-cell resolution in large volume, even throughout the whole brain.

Thanks to the rapid progress achieved in these technologies, including whole brain imaging, transgenic manipulation, optogenetics, tissue clearing, and brain-artificial intelligence technologies, researchers are more confident in analyzing brain structure and functions at macroscopic and mesoscopic levels. As a result, with the explosion of neuroscience-related technologies, the need has arisen for a series of technical standards in neuroscience (see Figure 10).

2.4.1 How the convergence of bio and digital technologies is affecting this domain

Today's development and convergence of biology, brain imaging and digital technologies is greatly advancing neuroscience. Scientists have developed a range of technologies for deconstructing the anatomical and functional organization of the brain.

Firstly, scientists are using neural tracing methods to label the specific neural circuits. The development of labelling technology, such as transgenic tools, animal models, viral tracers and optogenetic tools, are rendering investigation of the nervous system more specific.

Secondly, brain imaging technologies are contributing to mapping specific neural circuits including neuronal morphology, as well as local and long-range connections. The continuous development of holistic sample processing methods such as tissue clearing has promoted the fineness and completeness of neural anatomical analysis. Light microscopy provides the possibility to image intact brains at sub-cellular resolution.

Thirdly, in the domain of neurobiology, the data is truly big. A single neuroimaging data set can measure in the terabytes or even petabytes. Through the application of image recognition, big data and artificial intelligence, the characteristics of the nervous system are decoded and digitally presented, which enables digital rendering of a complete nervous system. Hence, the deep intersection and fusion of different technologies can promote the development of neuroscience.

2.4.2 Technology and market trends for neuroscience

2.4.2.1 Next 5 to 10 years

Major economies have invested heavily in neuroscience research. For instance, the US BRAIN (Brain Research through Advancing Innovative Neurotechnology) Initiative is spending USD 5 billion to develop tools for brain cell census and for recording or modulating brain circuit activity linked to behaviour, and Europe's Human Brain Project is costing USD 1,1 billion to understand the human brain by simulating its functions through the use of supercomputers.

Over the next decade, major economies and private foundations will spend more than USD 10 billion on neuroscience, which will greatly boost the development of the neuroscience industry to a scale of USD 100 billion. Among products developed, tools for dissection of specific neural circuits and brain imaging devices will have broad market prospects, and artificial intelligence research driven by neuroanatomical big data will also explode. In addition, the diagnosis and therapy of major brain diseases will be driven and expand significantly.

2.4.2.2 Outlooks

A brain-computer interface (BCI) serves as a bidirectional communication system between human brains and external devices. With great application potential in brain function enhancement, human-computer interaction

and nerve rehabilitation, BCI applications have become one of the most active research regions in neuroscience.

On the one hand, BCI research needs to be based on the brain's anatomical structure. The connectivity relationship between different brain regions and different neuron types will provide a "navigation map" for brain function decoding of brain-computer interfaces.

On the other hand, BCI development needs to be integrated with more cutting-edge technologies. For example, optogenetic brain-computer interfaces have been widely used in animal learning and memory recording, and new organic materials are contributing to the biocompatibility, safety and miniaturization of interfaces.

Brain-computer interfaces are expected to advance basic neuroscience research and treatment of neurological diseases. In the future, the rapid development of artificial intelligence will continuously improve the degree of brain-computer integration, promoting the transformation from brain-computer interaction to brain-intelligence. Moreover intelligent brain-computer interfaces will help human intelligence (HI) and artificial intelligence (AI) cooperate in adaptive learning and improving the human's information processing and decision-making ability.

From the earliest perceptions to convolutional neural networks (CNN) and more recently the generative pre-trained transformer (GPT), neuroscience and AI have always been side by side and complement each other.

In the field of neuroscience, artificial intelligence can help the researcher handle complicated data, such as the segmentation of biological images, the identification of neuronal signals, and the maintenance of homeostasis in the brain-computer interface system. In turn, for artificial intelligence, the natural neural network is a teacher to learn from.

As the visual circuit guiding users in the field of computer vision, the architecture of neural circuits responsible for higher mental functions may help in human-computer interaction as well. Moreover, the small size and low energy consumption of the natural neural network are also worth learning.

2.4.3 Standardization needs

Major international advocacy and brain projects are underway to characterize the neural circuit of the mammalian brain. To date, it is challenging to profile the nervous system with different neuron types in their 3D shape.

Electron microscopy (EM) and light microscopy (LM) are the imaging methods most commonly used for dissection of the circuit structure. EM offers nanometre resolution and is often constrained to relatively small brain regions. When whole-brain scale is the focus and complete neuron morphology is desired, LM is a more suitable imaging modality in which data is typically acquired at sub-micrometre resolution.

Recent extension of microscopy can help visualize neurons using LM approaches. Specific staining and high-resolution optical imaging help visualize the neuronal connection with long-range projection and local input circuits. However, data from multiple laboratories utilizing different units of measurements and different normal reference ranges present challenges when pooling the data to obtain population summary statistics (see Figure 11).

The global demand for 3D optical imaging is projected to increase. The growing prevalence of neurological disorders and emerging product trends are two of the factors driving market growth. The rising prevalence of neurological disorders, combined with an ageing population that is more prone to developing neurodegenerative diseases such as Parkinson's, Alzheimer's, dementia, epilepsy, and others, is expected to drive growth in the 3D optical imaging market.

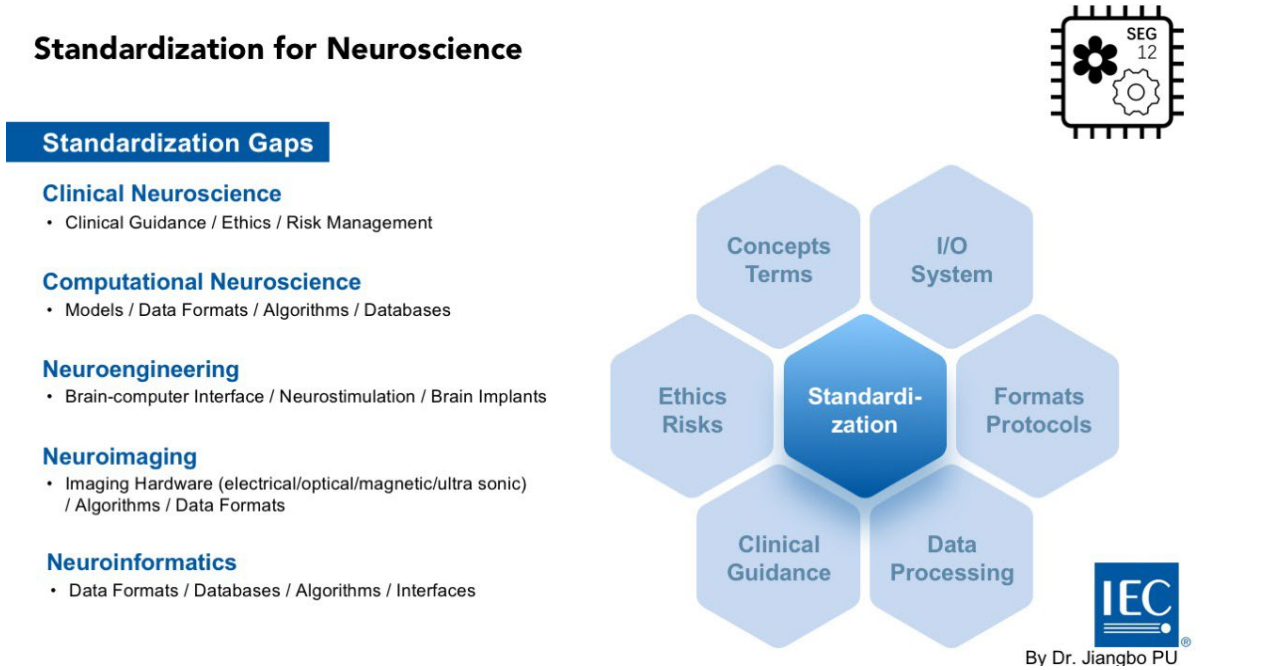


Figure 11 | Standardization gaps in neuroscience

In the field of biology and medicine, more and more research is focusing on the three-dimensional organization of biological structures and the pathological processes. The growing global geriatric population is expected to play a significant role in the growth of the studied market, because persons in this category are more vulnerable to various neurological disorders and injuries as they age, and when this is combined with new technological advancements, the studied market is forecasted to grow during the projected period.

3D light microscopy has been extensively developed, but no consensus exists on sample preparation for volumetric imaging. The relevant standard applies to the preparation of non-fluorescent/fluorescent thick samples, including staining, sample fixation and resin embedding steps, as well as whole-brain optical imaging, etc.

2.4.3.1 Now

The animal models

Neuron types are the basis for further study of the molecular mechanisms of brain function, but we still need reliable animal models to complete these studies. Mice are excellent model organisms for studying the cellular and molecular mechanisms of brain function, because they are easy to feed and handle, and their life cycle is generally 2~3 years. For example, transgenic technology was used to construct Cre tool mice initiated by specific markers.

These mice were then used with viruses/mice with fluorescent tags (enhanced green fluorescent protein (eGFP), tdTomato, etc.) or the target genes. This allows for in-depth studies of the function of specific neuron types at both the cellular and molecular levels. In addition, non-human primates, represented by macaques, are the best animal models to simulate the normal functioning of the human brain and the course of disease, because

their gene sequences and physiological structures are more similar to those of human beings, the study of which has also developed rapidly in recent years.

- **Sample staining and labelling**

Golgi staining

The Golgi method, a well-known method used for staining whole dendrites and axonal trees of neurons, has been used widely for studying dendritic morphology. In this standard, we address whether the modified Golgi-Cox staining method is suitable for whole tissue preparation with micron-sectioning. Briefly, the animals were deeply anesthetized and their entire brains was dissected. The brains were then immersed in fresh Golgi-Cox solution for fixation and staining. The Cox solution was replaced the next day, and then on a monthly basis to complete impregnation. After staining, the brain was immersed in lithium hydroxide (LiOH) and then rinsed with double distilled water. These stained brains were prepared for following Spurr resin embedding.

Nissl staining

The Nissl staining is a classic nucleic acid staining method traditionally used on nervous tissue sections for studying cytoarchitecture or lesions. In this standard, we propose that a modified Nissl staining method is suitable for whole brain preparation for brain-wide cytoarchitectonic and vascular atlas research. The animals were deeply anesthetized and then perfused intracardially with paraformaldehyde (PFA). After fixation, the brains were washed in PBS and stained with a thionine solution following the rinse. These stained brains were then prepared for following Spurr resin embedding.

Viral tracers labelling

Existing neurotropic virus tools can be used in multiple animal models for neural circuits labelling and investigating, including rats, mice, fruit flies, zebrafish, tree shrews, and non-human primates. However, some limitations still exist, such as the infection bias of different model animals, inability to resolve long-term functional circuits and low efficiency of virus expression. In the future, the existing virus tools can be improved by integrating various molecular probes, functional proteins, and gene manipulations into viral systems to meet the diverse needs of current neuroscience research.

- **Whole organ embedding**

Spurr resin embedding

The Spurr resin embedding procedure in this standard will certify the parameter in different steps: the nerve tissues (brain, spinal cord or other tissue) were dehydrated in a graded series of ethanol and acetone solutions. The tissues were then infiltrated in a graded series of Spurr resin solutions and placed in a rectangular plastic mold filled with fresh resin solution. The orientation was adjusted during the polymerization process to optimize the sectioning angle, which was followed by polymerization.

Fluorescent sample resin embedding

In general, the whole organ plastic embedding method for centimetre-sized samples mainly includes four key steps: fixation, rinsing, dehydration and resin embedding. In this standard we will certify the parameter in different steps (adjusted according to the sample size).

To achieve full tissue fixation, a combination of perfusion and immersion fixation is generally adopted, while the internal and outer surfaces of tissues are fully fixed to maintain the morphology, structure and immune activity of the cells and tissues. In order to maintain the fluorescent probe signal, PFA is usually used as the fixation solution. Ethanol or acetone is generally used as the dehydrating agent. Gradient dehydration is applicated to displace the water in the tissue and create conditions for resin immersion. Depending on the different resins involved, the degrees of dehydration of the samples are different.

For hydrophobic as well as hydrophilic resins, the tissue should be fully dehydrated with ethanol. The gradient concentration of the resin was used first for sample penetration, with the pure resin being used subsequently for penetration. After the embedding agent has completely immersed into the tissue, the embedding agent and samples are placed in the mold and heated in the oven to produce polymerization, forming the embedding tissue block with sufficient hardness and toughness. Hydrophilic resins, such as GMA, LR White, Technovit, etc., or hydrophobic resins, such as Lowicryl, etc., can be selected according to the experimental requirements.

The high activity initiator was selected to reduce the temperature of thermal polymerization to achieve full polymerization of the resin at the corresponding degree, while maintaining the fine structure and fluorescence signal of the samples.

- **Whole-brain imaging**

MR imaging reconstructs the morphologies of brains and their internal brain regions and nuclear masses in three-dimensional space. At the same time, virtual slices of the atlas can be made from any angle, so that users can accurately register the images to the correct anatomical position. However, the resolution of magnetic resonance imaging (MRI) is only at the macroscopic level, which is incapable of distinguishing single cells. Therefore, it is difficult for the brain map constructed on the basis of MRI data to accurately and finely divide brain regions or nuclear clusters.

The mapping of whole-brain mesoscopic neural connections in model animals such as mice requires technical tools that can achieve large-scale acquisition of high-resolution three-dimensional data in the centimetre scale. 3D optical imaging methods combined with whole-tissue preparation techniques can achieve sub-micron resolution in lateral directions and can realize “optical sectioning” by various means, which presents the natural advantage of observing neural circuits at the mesoscopic level. This is an ideal scheme for realizing the analysis of fine neural circuits in the whole brain.

Electron microscopy offers nanometre resolution and is often constrained to relatively small brain regions. This limits use of the technique to the analysis of brain structure in small model animals and requires a considerable amount of efforts to reconstruct huge amounts of individual cells.

- **Big data processing**

With the whole brain structural and functional profile, a digitized brain makes it more convenient to access these findings, in turn generating massive amounts of data. As a result, the storing, reading and processing of such data has become a challenge. More efficient compression algorithms are worth developing. High-performance computing clusters and cloud computing are also needed. In addition, the integration and information mining of multi-modality and multi-dimensional data also deserve attention.

2.4.3.2 Next 5 years

Through synaptic connections, long-range circuits transmit information among neurons and connect different brain regions to form specific neural circuits. In the future, dissection of the neuronal synaptome will further promote the understanding of neural circuits. This will generate new requirements and standardization needs for synaptic labelling, sample preparation and whole-brain synaptic optical imaging. Furthermore, sample preparation is also helpful if applied to the invasion path of tumour cells on the whole-body scale in small animals and the directional tracking of targeted drugs.

The involvement of various experts in the histological staining technology and application industry is essential to achieve the standardization of sample preparation techniques, including tissue

fixation, staining, embedding and cutting, and the standardization of pathological diagnostic applications. In addition, 3D light microscopy combined with spatial transcriptome analysis also contributes to global profiling of cell types and spatial location, in turn generating the need for sample preparation standardization needs in the future.

Brain organoids hold tremendous potential for the study of human brain development and for the diagnosis of major brain diseases and related drug screening. In the future, we can use organoids to study the logics of brain organization, brain development and brain diseases, which will intersect well with optical imaging.

2.5 Future work and recommendations

2.5.1 Continuation of work

- Coordinate with other existing TCs in ISO, IEC and other SDOs, such as ISO/TC 276, ISO/TC 212, ISO/TC 215, ISO/TC 34/SC 9/WG 25, ISO/IEC/JTC 1/SC 29, ISO/TC 34/SC 16, ISO/TC 34/SC 9, CEN/TC 140, CEN/TC 140/WG 3, EU-STANDS4PM, GA4GH, CIE, BIoRoboost, PSI, Fairsharing.org, Instand-NGS4P, etc.
- Identify user cases and continue the gap analysis.
- Analyze standardization requirements and identify gaps.
- Analyze the current status and activities of standardization.
- Select new topics that are relevant (currently selected topics: 1) Omics, 2) Synthetic biology, 3) Neuroscience).
- Establish task groups to propose standardization roadmaps for the selected topics.

2.5.2 Recommendations for new cooperative work

- Enhance cooperation between ISO/TC 276, ISO/TC 212, ISO/TC 215, ISO/TC 34/SC 9/WG 25, ISO/IEC/JTC 1/SC 29, ISO/TC 34/SC 16, ISO/TC 34/SC 9, CEN/TC 140, CEN/TC 140/WG 3, EU-STANDS4PM, GA4GH, CIE, BIoRoboost, PSI, Fairsharing.org, Instand-NGS4P, etc.
- Participate in relevant existing new standards projects, and co-lead the projects if possible.
- Try to evaluate the new cooperative work from the SEG 12 perspective (bio-digital convergence) to contribute to the projects and enhance the influence of SEG 12.

2.5.3 Recommendations for new work

- New standards proposals/projects
  - Omics: data relevant standards, such as storage, transfer, format, structure, analysis pipeline, hardware or information technology (IT) infrastructure standards, algorithms, database, hardware, interfaces, etc.
  - Synthetic biology: computational models, pipelines, data relevant, IT systems, algorithms, database, hardware, interfaces, etc.
  - Neuroscience: data systems, imaging systems, model, algorithms, databases, hardware, interfaces, etc.
- New TC proposals
  - Propose new relevant TCs, such as TC for Omics, TC for synthetic biology, TC for neuroscience, etc.
- New topics
  - New relevant topics, such as organoids, digital cells, digital metabolic models, etc.

2.5.4 Possible topics/keywords for standardization

- Basic technologies:
  - Omics (such as massive parallel sequencing, mass spectrum proteomics, bioinformatics analysis, and relevant data pipelines)
  - Synthetic biology (including design, building, tests, synthesis, and evaluation)
  - Neurosciences (involving image analysis, hardware development, interface, and informatics)
- Reverse engineering:
  - Strategies for reverse engineering of living systems, including design frameworks and processes
- Data:
  - big data (at the petabyte (PB) and terabyte (TB) levels)
  - Data format, integration, processing, interoperability, ownership, security, blockchain, etc.
- Systems:
  - Defining, designing, and transforming systems to meet specific needs
- Living systems (and systems of systems):
  - Definitions, management strategies, and evaluation for living systems
- Interfaces between living systems and “life systems and bioengineering” (WG 3):
  - Creating interfaces between systems as bridges to connect and link different components

Section 3

Life systems and bioengineering

3.1 Scope and objectives

SEG 12 Working Group 3: Life systems and bioengineering, was commissioned to evaluate standardization opportunities in life systems and bioengineering. The scope was broadly defined, covering the field of biosensors, biometrics, bio-foundries, bioprocessing, biofuels, drug discovery and engineering, synthetic biological circuits, metabolic engineering, genetic engineering, artificial life, organ-on-a-chip, and artificial organs.

3.1.1 Working method

WG 3 held 17 online meetings.

At the first and second meetings, the working group resolved to focus initially on four topics: human digital twins, organ-on-a-chip, synthetic biology, and biosensors (see Table 1). A task group was formed for each topic, and presentations and discussions on these topics took place at subsequent meetings. In further course, the working group extended the list to CAR-T cells, CRISPR technology and data quality issues. Organoids and organ-on-a-chip as targets for standardization were subsumed into “artificial organs and organoids”.

Table 1 | Task groups of WG 3

Task Group	Topic	Lead/Contributor
Convenor	General overview CRISPR technology CAR-T cells Data quality	Joerg Geiger William Wasswa
Task Group 1	Biosensors – Bio-electronic nose	Tai Hyun Park
Task Group 2	Human digital twins	Martin Golebiewski Claudia Cotca Gerhard Mayer
Task Group 3	Synthetic biology	Yue Shen Ran Wang Yong Zhang
Task Group 4	Artificial organs and organoids	Jiangbo Pu Pengyu Huang Yong Zhang

3.1.2 How the convergence of bio and digital technologies is affecting this domain

The interfacing of life systems with digital systems or the complete integration of life systems and digital systems are of great interest due to their wide range of applications and, in particular, owing to their importance in the healthcare sector.

The fast-paced advancement of bio-digital convergence of life systems demands close monitoring of the development, efficient and fast responses to standardization needs of emergent trends, and adequate, future-proof standardization concepts. For this purpose, it is necessary to identify the commonalities of diverse technologies to allow the elaboration of generic standards as a framework for harmonization of development trajectories, but also highly specific standards, which however need to be embedded in a common framework, to ensure the interoperability of bio-digital systems with distinct functions and in different areas.

3.1.3 Overarching standardization needs

Standardization of bio-digital life systems is required at all levels of the systems: the biological entity, the interface between the biological entity and the digital system, and the digital system itself. Standardization of the biological entity includes the draft and design, the creation including the necessary processes and tools, and the production of the biological entity. The interface between biological entities and digital systems can be understood on the functional level, i.e. in what way the digital system and the biological object interact, or on the procedural level, i.e. the role computational methods play in operating the bio-digital system.

The interaction can be unidirectional from the biological object to the computer system, such as for monitoring the state or properties of the biological object, or from the computer system to the biological object, for designing, controlling or actuating the biological system. Through a bidirectional interface the biological object can be controlled dynamically based on its current properties, and the responses of the computer system are modulated by the changing state of the biological object, thus providing for instance input to machine learning processes or enabling adaptive responses of the biological object.

On the digital system side, it is necessary to consider the mathematical procedures used for the data analysis, the algorithms and their implementation, as well as the methods of the training process.

Bio-digital convergence builds commonly on computational methods, in particular statistical data analysis and machine learning. Since data quality and the comparability of the data are basic requirements for reliable and proper functioning, particular attention should be paid to the quality of the data used.

For the entire bio-digital system, procedures must be provided to control and monitor the system and to detect and correct errors. Proper risk assessment and corrective action planning are also required.

3.2 Biosensors – Bioelectronic nose

3.2.1 Description

The concept of a new olfactory sensing technology known as “bioelectronic nose” that went beyond the possibilities of the conventional electronic nose started shaping up during the late 1990s. Owing to the random and non-selective binding in the conventional electronic nose and the fact that humans have a variety of olfactory receptors (ORs), imitating human olfaction using the electronic nose has been challenging. This means that a new technology that employs human ORs as the sensing elements, called bioelectronic nose, is necessary to precisely mimic the human sense of smell. Realizing an array sensor with up

to approximately 400 different types of human ORs would make such sensing achievable. When odour molecules are introduced into the bioelectronic nose, they attach to some of the ORs with different affinities. If the binding signal of each OR is measured and visualized as an overall image, odour information may be acquired in the form of a combinatorial pattern. This pattern information would be an identity of the smell that people experience; therefore, it may be directly correlated with how people feel.

There are four major component technologies in the bioelectronic nose. These are the technologies for producing ORs, measuring the binding of ORs to the odorants, processing the measured signals, and analyzing the pattern information. Ultimately, it is important to develop a bioelectronic nose by integrating these four technologies so as to mimic the human sense of smell (see Figure 12).

3.2.2 Olfactory receptors as sensing elements (biotechnology)

The utilization of ORs as sensing elements is the most crucial step in the development of a bioelectronic nose. ORs can be produced in large quantities via genetic engineering, which introduces DNA containing the information for expressing ORs in cells. The cells used in this process include mammalian cells, insect cells, yeasts, Escherichia coli, and others. Each expression host has benefits and drawbacks for expressing the ORs, so it is important to choose an appropriate one for standardization of OR production by considering both the production efficiency of the expression system and OR characteristics. In particular, when insoluble membrane proteins such as the ORs are expressed in high amounts, these proteins are synthesized in an aggregated state and lack original structures.

Both the solubilization and structural reconstitution processes are necessary for the ORs to be altered to soluble and stable states. The choice of detergent is important for solubilization, and membrane mimetics including nanovesicles, micelles, and nanodiscs can be utilized for reconstitution. To standardize the bioelectronic nose, it is essential to choose a strategy that considers the productivity, production costs, functionality, and stability of the ORs.

3.2.3 Transducer for generating electrical signals (digital technology)

The produced ORs can be used to assess binding with odorant molecules as they are immobilized on the transducers by covalent or noncovalent bonds. The conformations of the ORs change

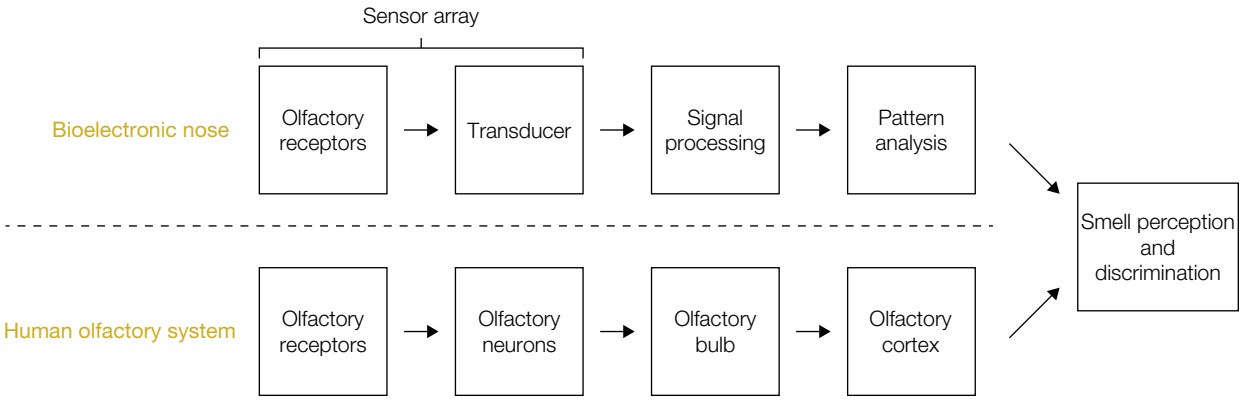


Figure 12 | Analogy between the bioelectronic nose and human olfactory system

when the odour molecules attach to them, and such conformational changes significantly alter the charge distribution or hydrophilicity of the receptors.

Therefore, it is necessary to utilize a transducer that can recognize these changes. Methods for directly measuring the binding between ORs and odorants are currently restricted, since the OR activities are mostly assessed at the cellular level. Quartz-crystal microbalance (QCM), surface plasmon resonance (SPR), and field-effect transistors (FETs) have been proposed as potential transducers for the bioelectronic nose. Considering the sensitivity, reproducibility, productivity, and production cost, it is important to choose the most suitable platform for standardizing the bioelectronic nose among these transducers.

3.2.4 Signal processing

One of the critical components for developing the bioelectronic nose is signal processing technology, which transforms electrical signals collected from standardized transducers with surface immobilized ORs into electrical signal (digital smell) patterns that can be used to analyze smells using a computer. The resultant signal pattern data, however, may be relatively restricted and provide distorted information without appropriate signal processing or protocols for standard operation, which can lead to issues with classifying or predicting the actual smell. As a result, it is essential to generate signal patterns using standard protocols and signal processing techniques. However, existing technologies for processing and normalizing sensor signal data employ digital filtering techniques that are not standardized in accordance with the properties of different types of sensors and measurement environments.

Furthermore, it is challenging to ensure reproducibility and continuity of the signal data pattern according to the smells detected by the sensor because there are no standard operating protocols. Therefore, it is necessary to establish a defined temporal data format based on the standard operating protocols for the bioelectronic nose through consensus to avoid issues while generating useful olfactory signal data patterns. It is also important to collect and analyze large amounts of smell data to obtain standard digital smell patterns.

3.2.5 Pattern analysis (analytics, computer science)

The majority of digital smell patterns obtained using the standard operating protocol of the bioelectronic nose can be described as matrices, where the horizontal axis represents OR sensitivity and vertical axis represents types of measured odours (or concentrations of the measured odours). It is possible to classify measured smells and build a prediction model by applying such digital smell pattern data as inputs and employing pattern recognition methods.

Generally, two types of pattern recognition techniques are employed in electronic nose applications, which are the exploratory and confirmatory techniques. While the exploratory technique is focused on unsupervised learning, the confirmatory technique aims to achieve supervised learning. For a long time, several learning algorithms have been used with the electronic nose to classify and predict smells. With the development of several software tools and ground-breaking advancements in AI technologies, it is now possible to quickly and precisely classify many detected smells. However, as the algorithm used for each industry (environment, medicine, factory automation, etc.) is unique, application-specific standards are required.

3.2.6 Technology and market trends

Next 5 and 10 years

Electronic nose technology has recently attracted much attention; this is because sensors that detect odorants have lately been reported to have greater sensitivity to a significant degree, and technologies that can evaluate and interpret digital and patterned data based on AI have emerged. The worldwide electronic nose market size was estimated to be USD 17,8 million in 2020 and is expected to increase annually to reach USD 34,78 million by 2026, according to a global market study for the electronic nose conducted in 2020. Ambient air quality monitoring and diagnostic medicine are two fields that have seen the most growth in this respect. The development of the conventional electronic nose technology has been underway for a long time, however, there are limitations to measuring complex odour compounds, because chemical materials, such as metal oxides or polymers, have been used as sensing elements.

On the other hand, different kinds of ORs that are more complex than chemical materials are used as sensing elements in the human nose. Therefore, ORs are preferable to chemical materials when mimicking the human nose. A bioelectronic nose is a device comprising OR, transducer, signal processing, and pattern analysis systems capable of recognizing odours. The bioelectronic nose is a new technology that is still under development and is not yet commercially available. However, recent publications have emphasized its potential, and in terms of the commercial growth potential, its application is virtually limitless.

The bioelectronic nose has the potential for use in a wide range of industries and applications, including quick and simple viral infection diagnosis, ambient air quality monitoring, measuring the freshness of foods, use in the perfume industry, for social safety, for olfactory display, smell standardization, and other uses, which cannot be implemented with the existing electronic nose. Given these directions, the market for the bioelectronic nose has enormous potential.

3.2.7 Current standardization situation

Commercialization and widespread use of the bioelectronic nose requires standardized technology, which can be achieved by developing a methodology that complies with stringent requirements for smell assessment. In essence, the most important consideration is the reproducibility of results, which requires precise smell sensing assessment criteria.

Since the early 2000s, there have been repeated attempts to standardize the conventional electronic nose, but standardization of the bioelectronic nose has not yet been accomplished:

- ISO and IEC

  The Second Network on Artificial Olfactory Sensing (NOSE II), CEN TC/264 WG41, NTA 9055:2012, VDI 3518-3:2018, UNI1605848, among others.

- Other SDOs

  IEEE 1451, IEEE 2700, IEEE P2520, among others.

3.2.8 Outlooks

Standardization needs

All elements that need to be measured have been attempted for standardization. There currently exist standards for measuring sight (colour), hearing (sound), and touch (pressure, temperature, etc.) in relation to the human senses. There are, however, no measurement techniques that can be used in place of the sensory capabilities of the human nose to detect smells.

The standardization of olfactory measurements is constrained by the inability of many electronic noses to mimic the human nose adequately. This barrier can be solved by development and

standardization of the bioelectronic nose based on human ORs. It is not practical to use previously established electronic nose technologies; hence, the bioelectronic nose technology has to be standardized instead. There are several factors that must be considered before using the bioelectronic nose as a standard technology.

To improve system reliability, stability, and performance, the standardization procedure is often carried out in accordance with the provided requirements. Therefore, necessary standards that can provide such assurance must be created.

Now

- Receptor: The process verification for OR manufacturing technology must be carried out effectively, and the technology must be reasonably priced, so as to be extensively employed in various areas. Thus, it is important to choose and standardize technologies that have good economic, repeatability, and stability characteristics. The introduction of a strategy for OR mass production is vital for economic reasons, and high reproducibility and stability requirements necessitate standardization of the manufacturing process and produced OR quality.
- Transducer: High sensitivity and selectivity technologies must be chosen and standardized as the best sensor platforms. Additionally, a standardized protocol is required to combine ORs with appropriate sensor platforms stably and effectively to measure signals from the ORs. The development of sensor systems with uniform quality will thus be a major factor in standardization. Similar to OR manufacturing, it is essential to choose and standardize technologies that are most advantageous in terms of productivity, cost, and practicality.
- Signal processing: It is vital to comprehend the viewpoint that data processing to generate signal patterns for the detected smells should be accomplished through standardization of reliable measurement protocols. Hence, it is necessary to establish systematic protocols for generating smell signal patterns using the bioelectronic nose with high signal-to-noise ratio, reproducibility, and selectivity.
- Pattern analysis: The primary goal of the bioelectronic nose is signal pattern analysis in accordance with the detected smell, which necessitates an algorithm standard for identifying and predicting smells. Since several algorithm models are needed depending on the intended application, adopting appropriate standard algorithm models based on the standard protocol in use as well as the type and amount of data are important.

Next 5 years

The types and number of receptors used in the bioelectronic nose, odour sample preparation and signal processing techniques, measurement environment, pattern recognition algorithm analysis methods, and other factors may all have significant impacts on the results of smell measurements.

The direction of standardization will thus be toward integration and optimization of these components. The bioelectronic nose will also be helpful if implemented on smartphones. The involvement of various experts at each manufacturing stage and application industry are critical for achieving standardization of various olfactory-related technologies, including standardization for various industrial applications and smell standardization.

3.3 Human digital twins/virtual human twins

3.3.1 Description

The human digital twin or virtual human twin (VHT) is an integrated multiscale, multi-time, and multi-discipline digital representation of quantitative human physiology and pathology that plays an important role for personalized medicine approaches. Its realization through

collaborative distributed knowledge and resource platforms is specifically designed to accelerate the development, integration, and adoption of patient-specific predictive computer models, which can be used as clinical decision support systems, for personal health forecasting or as methodologies for the development and de-risking of personalized medical products (see Figure 13).

The aim is to use such methods to simulate and predict physiological and disease-related pathological body functions and processes in the body of a single individual (e.g. patient) or cohorts of individuals (patients) that share certain commonalities. The clinical questions that are addressed by these approaches include the individual response to a certain therapy, individual risk prediction for common as well as rare diseases, the simulation of pharmacodynamics and pharmacokinetics of xenobiotics and drugs in the body, in silico clinical trials of new drugs, and many more.

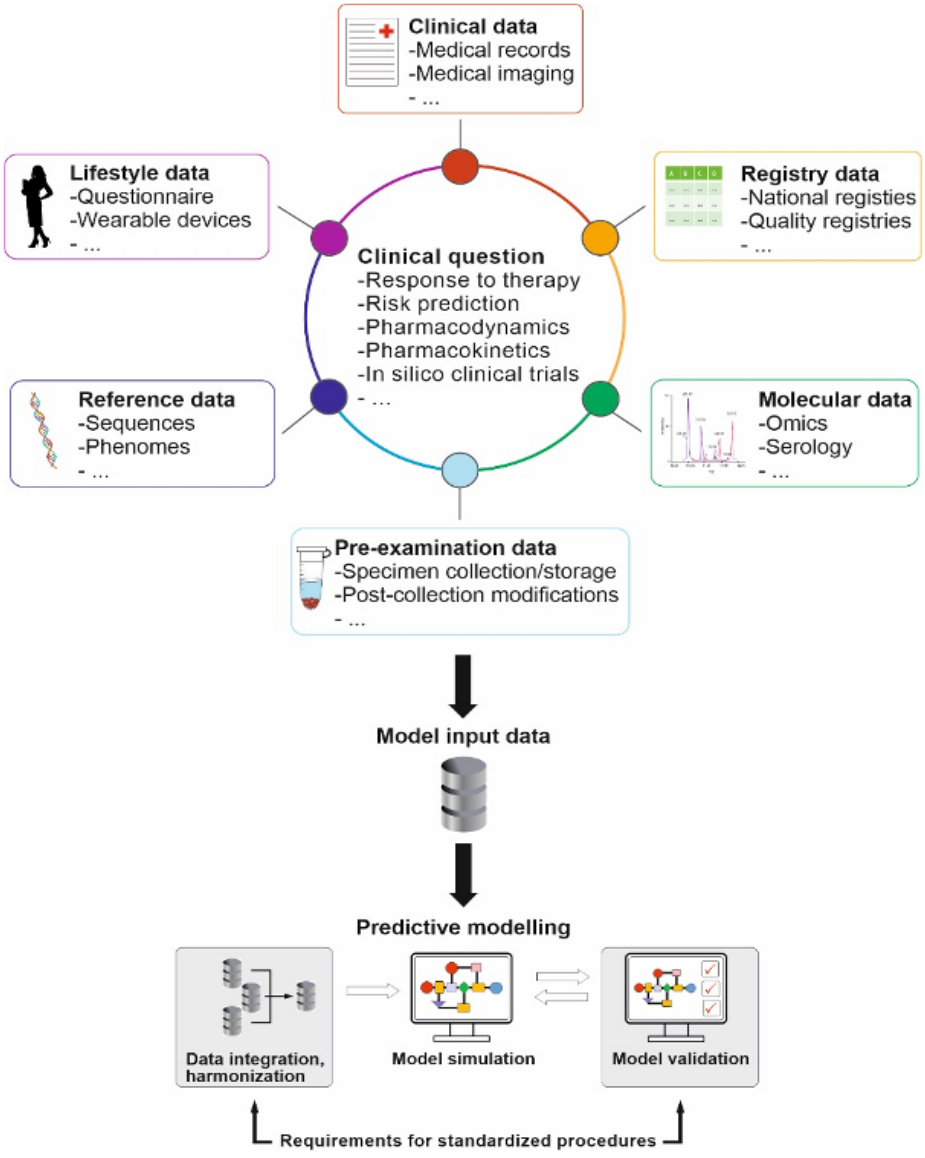


Figure 13 | Modelling workflow for personalized medicine

Federated and cloud-based computational infrastructures can be built to facilitate the realization of the opportunities presented by virtual human twins for the benefit of patients, healthcare providers, regulatory bodies and industry.

Such virtual human twin infrastructures heavily depend on standardized interfaces between their components and on interoperable data and metadata formats, metadata catalogues ("minimal metadata information models"), as well as harmonized semantic descriptions of the body parts, their comprised entities (tissues, cells, subcellular and molecular entities, etc.) and their functional and pathological features and interactions, described by commonly agreed terminologies and ontologies.

3.3.2 How the convergence of bio and digital technologies is affecting this domain

The field is highly dependent on bundling and integrating health data from single individuals, patient cohorts and other data Sources and making them digitally available for computational modelling and forecasting processes. Such health data includes data from various Sources and in different formats, ranging from clinical data (medical records and electronic health records, medical imaging and radiomics data, etc.), pre-examination data on specimen collection and storage, as well as on post-collection modifications and sample/data provenance, lifestyle data gathered from questionnaires, wearable devices and the like, to medical laboratory and molecular data (omics or serology data and similar), data from physiological measurements and examinations, up to medical registry data from (inter-)national or quality registries and similar Sources or reference data from online resources (databases for sequences, phenomes, etc.).

The capturing and collection of such manifold health data must be linked to consistent data structuring, formatting and semantic description to make this data "FAIR" (findable, accessible, interoperable and reusable). This includes the development and application of sophisticated methods of data access and data governance for this sensitive and person-related health data that often is under controlled access. Here legal and ethical limitations and frameworks play an important role and also have to be considered on the national and the international level.

Also, the validation and quality measurements of the outcomes and predictions of the digital modelling and forecasting, as well as of clinical decision support systems that build on them, need to be developed and harmonized across the different methods applied. More and more of these computational processes apply AI approaches, especially methods that apply machine learning and deep learning. In such AI-based approaches the quality and validation methods are especially important, as in those cases the modelling and forecasting is data-driven and often constitutes a "black-box". However, also in more knowledge-driven mechanistic approaches validation of the modelling and simulation outcomes is an important aspect.

3.3.3 Technology and market trends

Next 5 to 10 years

Currently, the infrastructure for virtual human twins is planned and prepared in many different countries and regions, e.g. by the emerging European Ecosystem Digital Twins in Health (EDITH) initiative [2]. Many industrial, as well as academic and public health institutions and regulators are involved in those efforts. Commercial companies currently invest largely in building up corresponding knowledge and capacities. These efforts are supported by the building of harmonized health data spaces that will facilitate access to health data, e.g. the European Health Data Space (EHDS) in Europe [3]. This is accompanied worldwide by national as well as international approaches to

digitizing health data, especially medical records in the form of electronic health records (EHRs).

Once the health data is fully digitalized, personalized medicine efforts based on multiscale and individualized computational modelling and simulation technologies can be efficiently implemented and exploited for medical diagnostics, therapy planning and outcome predictions, risk predictions, drug development and many more applications. This will have a huge impact on the entire medical field, including the biotechnology, diagnostics and pharma industries.

3.3.4 Outlooks

Data infrastructures for virtual human twin technologies are expected to be implemented within the next 10 years, including some proof-of-principle applications during the construction of regional international infrastructures such as the emerging European EDITH ecosystem for digital twins in healthcare. Once fully implemented such federated, cloud-based international human digital twin data infrastructures will revolutionize the way healthcare professionals will work with the support of individualized computer model predictions and clinical decision support systems. The pharmaceutical industries will largely profit from in silico trials that partially, if not fully, could replace animal testing and to some extent complement clinical trials in humans. Also the diagnostics market will profit from digitalization as already can be observed today, e.g. by live measurements of blood-glucose levels in diabetes patients.

3.3.5 Existing standardization and standardization needs

A white paper from the European project EU-STANDS4PM [4] outlines the standardization needs in the field of human digital twins/virtual human twins [5]. Clinical and health-related data is usually generated in different medical environments and by various Sources and systems. With the advent of health data created outside the health care setting, Sources and formats become even more diverse. Such heterogeneous data requires harmonized strategies for data integration utilizing broadly applicable standards that allow for a reproducible data exploitation to generate new knowledge for medical benefits.

For the development of validated predictive computational models in personalized medicine, two key factors of the model-building process, for which standardization is essential, are:

- Data integration – Harmonized strategies and methods for integration of data
- Model validation – Validation of models and simulations through the underlying clinical question

Standards on an international level for secure interoperable data integration and predictive computational models are essential to utilizing the wealth of information that big data in health contains – specifically and efficiently to push a pro-active personalized medicine forward.

Regarding big data in health, the specific challenges are to:

- Develop data-driven computational approaches that are tailored (personalized) to the individual or stratified patient groups addressing clinically relevant questions.
- Harness, utilize and understand (exploit) high volume, high diversity biological, clinical, environmental, and lifestyle information.
- Develop harmonized standardization guidelines for data integration strategies.
- Ensure that integration of personal and patient-derived data is performed lawfully, ethically and fairly, including in full respect of patients' rights.

To achieve these goals both the "technical" element of standardizing data input and modelling, and the legal and ethical framework supporting data integration and interoperability must be addressed.

Health data from different Sources and recorded at different times must be integrated in order to set up predictive computer models in personalized medicine.

Consistent documentation of data, models and simulation results based on standards ensure that the data and corresponding metadata (data describing the data and its context), as well as models, methods and visualizations are structured and described in a FAIR manner (Wilkinson et al. 2016 [6]). Hence, data and model standards support the reliable exchange of health-related data, making the data FAIR for their integration into computer models used in personalized medicine.

Such data and model standards, together with harmonized ways to describe their metadata, also ensure the interoperability of tools used for data integration and modelling, as well as the reproducibility of the simulation results of the models. In that sense, modelling standards are agreed ways of consistently structuring, describing and associating models and data, their respective parts, their graphical visualization, as well as information about applied methods and the outcome of model simulations. Such standards also assist in describing how constituent parts interact together, or are linked, and how they are embedded in their physiological context.

Major challenges in the field of personalized medicine are to harmonize the standardization efforts that refer to different data types, approaches and technologies, as well as to make the standards interoperable so that the data can be compared and integrated into models. Reproducible modelling in personalized medicine requires a basic understanding of the modelled system, as well as of its biological and physiological background. There exists a relevant checklist that provides guidelines on the minimum amount of metadata information required in order to understand a model: Minimum information requested in the annotation of biochemical models (MIRIAM) [7].

This information about data and models can be transferred by using metadata in the form of semantic annotations. These annotations can improve the shareability, and interoperability of the data or model (Neal et al. 2019) [8]. To render data and models FAIR, it is important that all their elements (entities) in their context are understood in exactly the same way, independently from the individual or tool that processes or analyzes them. For this purpose, it is necessary to consistently use the defined terminologies, such as controlled vocabularies and domain ontologies that can be defined and applied independently of the data/model format.

For many different data types used in personalized medicine, domain-specific annotation standards and terminologies are available. For example, the Universal Protein Resource (UniProt) [9] or the Protein Ontology (PRO) [10], can be used to uniquely identify proteins in a particular biological context which can then be linked to specific entities in the computational model or virtual human twin. Similarly, the Gene Ontology (GO) [11] could be used to identify specific genes or cellular components, whereas the Foundational Model of Anatomy (FMA) [12] can be used to localize an entity in the computational model to a specific spatial location or anatomical structure in the human body. If not found completely or partially unstructured, which is often the case for medical records, health-related data is most commonly structured and codified by specific formatting standards for medical data. These can be the interoperability standard HL7 Fast Healthcare Interoperability Resources (FHIR) [13], or the standard for electronic health records (openEHR) [14].

Semantic content is usually annotated with domain-specific clinical terminologies, e.g., International Classification of Diseases (ICD) [15] of the WHO, as well as the widely used international terminology “Systematized Nomenclature of Medicine, Clinical Terms” (SNOMED CT) [16] and

its national derivatives, or Logical Observation Identifiers Names and Codes (LOINC) [17]. Thus, the wheel does not have to be reinvented for the semantic data annotation of virtual human twins in personalized medicine, but existing annotation standards have to be consistently applied.

3.3.5.1 Standards for data formats, data integration and data input into models

Data integration

The ISO 20691:2022 standard "Requirements for data formatting and description in the life sciences" [18], developed by ISO/TC 276/WG 5 Data Processing and Integration, provides rules and requirements to render data in the life sciences (including construction and validation data for computational models and virtual human twins) FAIR [19]. The data used in models and simulations of human digital twins has to follow formatting rules and recommendations from ISO 20691 and the corresponding metadata must encompass the information described in the minimum information standards and follow the FAIR principles. For being FAIR, the data must have a unique ID, must be clickable, must have an assigned license and must be annotated by metadata describing for instance the disease, the tissue, the cell type and the used modelling parameters. Other requirements described in ISO 20691 are about the consistent formatting and documentation of data, models and metadata as well as the requirements concerning storing, sharing, accessing, interoperability and reuse of data, models and metadata in the life sciences.

ISO 20691 acts as a reference framework or hub standard for other life science data and integration standards. It describes the requirements and rules for applying standards for formatting, description and documentation of data types in the life sciences and contains a catalogue of criteria and requirements for interoperable life science data formats and semantic data description standards. Annex A of ISO 20691 contains a list of common recommended formats for life science data of different datatypes and Annex B of that standard contains a list of minimal reporting standards for data, models and metadata, as well as domain-specific terminologies and ontologies, including specific ones for the field of medicine, health and diseases (clause B.3.1). This set of metadata describes the context of the data and models of virtual human twins. The ISO 20691 FAIRSharing collection [20] contains a listing of all formatting and metadata standards from the annexes of ISO 20691 as a kind of an online "live annex", which should be used to represent life science data and to annotate it using ontology terms.

- **Harmonized access to data across resources**

Harmonized data access agreements (hDAAs), i.e. strategies to control the access to restricted (e.g. person-related) data by researchers are still lacking.

- **Standards for medical imaging**

BIDS: Brain Imaging Data Structure, a standard of the INCF [21] (International Neuroinformatics Coordinating Facility) for capturing data/metadata of MRI datasets. For different imaging techniques the following extensions [22] to BIDS are available:

  - ASL-BIDS: for arterial spin labelling
  - EEG-BIDS: for electroencephalographic data
  - iEEG-BIDS: for intracranial electro-encephalographic (EEG) data
  - MEG-BIDS:: for magnetoencephalographic data
  - Microscopy-BIDS for microscopy imaging data
  - PET-BIDS: for positron emission tomography
  - DICOM: A standard for medical imaging-based modelling; stores the data as 2D layers

  - NifTI-2: Neuroimaging Informatics Technology Initiative; 2nd Version of a special image format for neuroimaging, where the data is stored in a true 3D volume format
  - GifTI: Geometry (surface) file format
  - CifTI-2: Connectivity Informatics Technology Initiative (grayordinate surface +volume)

- **Standard formats for electro- and neurophysiology, biosignal and vital sign data**
  - ECG-XML: an XML-based format for electrocardiogram data
  - EDF/EDF+: European Data Format, a format for exchange and storage of multichannel biological and physical signals, e.g. polysomnography
  - GDF: General Data Format; for biomedical signals, e.g. EEG and electrocardiographic (ECG) data
  - FEF: File Extension Format; a general data format for vital signs and biosignals
  - HL7-aECG: HL7-annotated electro-cardiogram; an annotated XML-based format for electrocardiogram data
  - ISO/IEEE 11073: A standard for device interoperability of point-of-care medical device communication
  - MEF: Multiscale Electrophysiology Format for EEG data
  - MFER: Medical waveform Format Encoding Rules, a file format for encoding medical waveforms from ECG and EEG data
  - NIX: Neuroscience Information eXchange for neurophysiology data
  - NSDF: Neuroscience Simulation Data Format based on HDF5
  - NWB:N 2.0: Neurodata Without Borders: Neurophysiology for neurophysiology data
  - OpenEP: a cross-platform electroanatomic mapping data format
  - SCP-ECG: Standard Communications Protocol for ECG data
  - SignalML: a XML-based meta-format for biomedical time series data
  - SONATA: Scalable Open Network Architecture TemplAte; for large-scale modelling of neuronal brain network models and simulation output
  - VSIR: Vital Signs Information Representation
  - WFDB: WaveForm DataBase format of the PhysioNet (physio.net) repository;
  - a combination of MIT format and EDF/EDF+

- **Standardization of modelling**
  - Data preparation

The process and the different types of models are described in detail in ISO/DTS 9491-1, *Biotechnology – Recommendations and requirements for predictive computational models in personalized medicine research – Part 1: Guidelines for constructing, verifying and validating models* [23], which describes in detail the data preparation steps for integrating the data into the models.

  - Model types

Knowledge-driven top-down models based on prior knowledge and hypotheses concerning the causal relationships (mechanistic models); and data-driven bottom-up models e.g. artificial intelligence (AI), machine learning (ML) and deep learning (DL) models.

  - Standards for models

Models are often defined by community efforts such as the COMBINE consortium and are listed in detail in Annex A of ISO/TS 9491-1 “Biotechnology – Predictive computational models in personalized medicine research –

Part 1: Constructing, verifying and validating models", as well as in Annexes A and Annex B of ISO 20691 "Biotechnology – Requirements for data formatting and description in the life sciences", as well as in the corresponding ISO 20691 FAIRsharing collection. They are also registered in different registries, for instance the BioSimulators FAIRsharing collection, the Bio-simulation website and the Normsys registry.

- BioPAX: Biological Pathways eXchange for exchange and visualization of biological pathway data
- CellML: XML-based description and exchange format for cellular models
- FieldML: Human Physiome Field Markup Language, an XML-based format using mathematical field descriptions of cells, tissues and organs; can be used to represent finite element models
- MDL: Model Description Language for pharmacometric models
- MorpheusML: for agent-based multicellular models
- MultiCellDS: MultiCellular Data Standard for center-based models (CBMs)
- MultiCellML: Standard for agent-based multiscale and multicellular spatial models
- NeuroML v2: Neuroscience eXtensible Markup Language; an XML-based description and exchange format for models in neuroscience with its four parts Biophysics, ChannelML, MorphML, and NetworkML
- OpenBEL: Biological Expression Language, a triple-based (subject-predicate-object) modelling language for representing biological knowledge by causal, correlative and associative relationships
- PharmML: Pharmacometrics Markup Language, an exchange format for pharmacokinetic and pharmacodynamic models
- PK-Sim [24]: Standard model for whole-body physiologically-based pharmacokinetic modelling
- SBML :Systems Biology Markup Language, an XML-based description and exchange format for differential-equation models of biological processes.

  SBML Level 3 is a modular format with a core and packages for extending that core functionality

- Standards for model simulations and documentation of results
  - GSP: Good Simulation Practice, a quality standard for in silico simulations, which is currently under development by the Avicenna Alliance.
  - NuML: Numerical Markup Language, a XML-based format for exchanging numerical data
  - OMEX: Open modelling exchange supports the exchange of all the information necessary for a modelling and simulation experiment in biology. An OMEX file is a .zip container containing a manifest file, an optional metadata file and the data files.
  - SBRML: Systems Biology Results Markup Language for encoding results of SBML simulations

  - SED-ML: Simulation Experiment Description, a XML-based exchange format for encoding of simulation setups following the MIASE guidelines
- Standards for graphical model visualization
  - SBGN: Systems Biology Graphical Notation, a graphical notation for representing biological processes
  - KGML: KEGG (Kyoto Encyclopaedia of Genes and Genomes) Markup Language

- **Standards for metadata of data and models**
  - Metadata requirements

  Annotation with metadata is a prerequisite to make the data findable and accessible, i.e. to fulfill the FAIR principles. Metadata should consider the minimum information guidelines. A complete list of minimum information guidelines is given in Annex B.2 of the ISO 20691 standard. For systems biology models MIRIAM [25] (Minimum Information Requested in the Annotation of biochemical Models) and for simulations MIASE [26] (Minimum Information About a Simulation Experiment) shall be used. MINIMAR [27] (Minimum Information for Medical AI Reporting) is a proposed standard for reporting of healthcare prediction models based on artificial intelligence methods. For the exchange of metadata information, one or several of the following metadata formats should be used if feasible:
    - ISA-Tab: investigation-study-assay, a tab-separated format with data, model and standard operating procedures (SOP) stored under an ISA instance
    - ISA-JSON: investigation-study-assay in JSON format
    - FHIR: Fast Healthcare Interoperability Resources, a collection of semantically richly annotated healthcare data
  - Minimum reporting guidelines for clinical decision support systems
    - Part 2 of ISO 9491 describes CDSSs based on AI models. MINIMAR (describes the minimum set of required metadata. It also describes recommendations for clinical studies involving computational models for personalized medicine. Other minimum reporting guidelines for a CDSS, are defined by the EQUATOR [28]. (Enhancing the QUAlity and Transparency Of health Research) network or by the TRIPOD [29] (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) consortium.
    - Examples are CONSORT (Consolidated Standards of Reporting Trials) for reporting of randomized trials, SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), a standard for trial protocols, STARD (STAndards for the Reporting of Diagnostic accuracy studies), DECIDE (Developmental and Exploratory Clinical Investigations of Decision), CLAIM (Checklist for artificial intelligence in Medical Imaging), PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) and PROBAST (Prediction model Risk Of Bias Assessment Tool). There is a corresponding set of guidelines for models and trials, which are based on artificial intelligence (AI) techniques, e.g.

    - TRIPOD-AI: for diagnostic or prognostic prediction models based on AI
    - CONSORT-AI: for clinical trials evaluating interventions with an AI component
    - SPIRIT-AI: for clinical trial protocols with an AI component
    - STARD-AI: for reporting of diagnostic accuracy studies based on AI
    - DECIDE-AI: for CDSSs driven by AI
- Terminologies and ontologies for the description and annotation of data, models and their components
    - BCTEO: Bone/Cartilage Tissue Engineering Ontology
    - BRICKS: Describes recurring concept in SBGN models
    - CBO: The Cell Behaviour Ontology is designed to describe multi-cell computational models
    - CNO: Computational Neuroscience Ontology
    - CO: Cell Ontology
    - COMODI: An ontology to characterize differences in versions of computational biology models
    - DEB: Devices, Experimental Scaffolds, and Biomaterials Ontology
    - DO: Disease ontology
    - DUO: Data Use Ontology
    - FMA: Foundational Model of Anatomy for localizing anatomical structures at a specific spatial location
    - HUPSON: Human Physiology Simulation Ontology containing concepts for simulations, models and algorithms
    - KISAO: Kinetic Simulation Algorithm Ontology for describing simulation algorithms
    - MAMO: Mathematical Modelling Ontology
    - NPO: NanoParticle Ontology
    - OBCS: Ontology of Biological and Clinical Statistics
    - OGMS: Ontology for General Medical Science
    - OPD: Ontology of Physics for Biology containing physics concepts to describe the dynamics of biological systems
    - PK: ontology An ontology for pharmacokinetic models
    - PreMedOnto [30]: Precision Medicine Ontology
    - SBO: Systems Biology Ontology with terms useful for describing computational modelling
    - SBOL-VO: Synthetic Biology Open Language Visual Ontology
    - TEDDY:Terminology for the Description of Dynamics. An Ontology for the description of control elements and dynamics in systems biology and synthetic biology

Ontologies for Systems Biology/Systems Medicine/ Systems Pharmacology simulation shall be used for the semantic annotation of algorithms and the dynamic behaviour of models. Some ontologies are listed in Annex B.3 of ISO 20691. Others are linked by ontology web portals e.g. the Open Lookup Service (OLS), BioPortal, OboFoundry, or the semantic lookup platform.

Clinical languages, terminologies and code systems

Clinical terminologies and code systems are mainly used for semantic annotation of electronic Health Record (I) data and in FHIR resources. Clinical languages such as Arden syntax and CQL allow the representation of medical knowledge in clinical decision support systems (CDSSs) and can be used as a basis for explainability components.

- Arden syntax [31] a HL7 standard for the representation of medical knowledge, e.g. for use by CDSSs
- ATC [31] Anatomical Therapeutic Chemical code, a classification system for the active substances of biomedical drugs
- CQL [32]: Clinical Quality Language, a HL7 standard for the expression of clinical knowledge used for CDS and electronic Clinical Quality Measurement (eCQM); can also used for querying complementing FHIR search
- EMDN [33]: European Medical Device Nomenclature
- GMDN [34]: Global Medical Device Nomenclature
- ICD-10/11 [35]: International Classification of Diseases
- ICF [36]: International Classification of Functioning, Disability and Health
- ICHI [37]: International Classification of Health Interventions
- LOINC [17]: Logical Observation Identifiers Names and Codes for reporting laboratory test results
- MedDRA [38]: Medical Dictionary for Regulatory Activities
- NCIt [39]: the National Cancer Institute thesaurus
- ORDO [40]: Orphanet Rare Disease Ontology
- ORPHAcode [41]: Encoding of rare diseases and orphan drugs
- RxNorm [42]: Normalised Names for clinical drugs
- SNOMED-CT [16]: Systematized Nomenclature of Medicine – Clinical Terms
- TNM [43]: Tumor Node Metastasis, a classification system for malignant tumors
- UMDNS [45]: Universal Medical Device Nomenclature System of ECRI institute

Model quality and validation

One prerequisite for model quality is the quality of the used data. Whenever possible, before processing the data, the data shall be cleaned in order to detect and correct inaccurate data.

A general standard for model validation, independent of the model purpose, is currently still missing. On the other hand, for specific models with a well-defined purpose (e.g. in medical devices) ASME V&V 40 standard is available. Viceconti et al. [45] proposed to use an approach similar to the risk-based credibility assessment of ASME V&V 40 for the evaluation of new drugs.

ASME V&V 40 standard

ASME V&V 40 is a quality standard for medical devices. According to it, the model quality assessment starts with a clear definition of the scientific / medical question of interest (QoI) and the context of use (CoU). The COU is a complete description of the planning use and defines the role and scope of the model used to address the question of interest.

In the next step the model risk (with its two components, model influence and decision consequence) – the possibility that the results of the model simulation are wrong and lead to negative consequences for the patient – must be assessed. The applicability of a model is given by the evidence to support the use of the model in the defined CoU, taking into account the risk.

Then a risk-informed credibility assessment can be performed. That credibility assessment

encompasses model verification, validation and uncertainty quantification (VVUQ)

Model verification (mathematical evidence) means the confirmation that the mathematical elements of the model behave as intended, and consists of two parts: code verification and simulation verification.

Model validation (experimental evidence) is the comparison between the output of the calibrated model and the measured data, independent of the data set used for calibration, i.e. the question of whether the problem was solved correctly. One must distinguish between technical and clinical validation.

For uncertainty quantification (statistical evidence), uncertainties on all inputs are identified and quantified, and are propagated to the simulation results to quantitatively assess the effect on the simulation results (sensitivity coefficient method).

Verification, validation and uncertainty quantification (VVUQ) for medical devices are defined in the ASME V&V 40 [46] standard, which defines codes, standards & conformity assessment and is accredited also by the American National Standards Institute (ANSI).

The credibility is the trust in the predictive capability of the used computational model for the defined context of use. To assess the credibility of a model, the verification, validation and uncertainty quantification shall be evaluated and transformed into a credibility score.

According to ASME V&V 40 one has to assign credibility factors to each verification, validation and applicability activities. Based on that information the overall credibility can be assessed.

CBER (Center for Biologics Evaluation and Research) and CDER (Center for Drug Evaluation and Research) of the FDA (Food and Drug Administration) are exploring the use of the ASME V&V 40 standard for risk-informed credibility assessment in drug development [47], e.g. for the assessment of physiologically based pharmacokinetic (PBPK) models.

Validation recommendations from ISO/TS 9491-1

The ISO standard ISO/TS 9491-1 Biotechnology – Recommendations and requirements for predictive computational models in personalized medicine research – Part 1: Guidelines for constructing, verifying and validating models defines specific recommendations for model validation of the following approaches:

- Cellular systems biology models
- Risk prediction for common diseases
- Disease course and therapy response prediction
- Pharmacokinetic/-dynamic and in silico trial simulations
- Artificial intelligence

Data provenance

The ISO standards ISO/TS 23494-1 [48] and ISO/TS 23494-2 define a provenance information model for biological material and data, whereas ISO/TS 23494-1 defines the design concepts and general requirements, and ISO/TS 23494-2 defines the Common Provenance Model (CPM) in detail.

PROV-O [49] is a W3C standard for a general provenance ontology and used by the common provenance model.

The PROV-N [50] is a notation for writing instances of the PROV-DM [51] data model aimed at human consumption. PROV-DM and PROV-N are described in Annexes B and C of ISO/TS 23494-2.

The provenance information encompasses sample provenance (sample collection, sample processing, transportation, sample storage) as well as data provenance (data generation, data processing, data validation and data retrieval).

In general, each time the sample or data are somehow used or processed, the provenance information shall be updated, i.e. each step in handling the sample or data shall be documented in detail and annotated by a timestamp to finalize it. The SPREC-Code [52] (Standard PREanalytical

Code) shall be used to encode the preanalytical treatment of biological probes and is an important part of the sample provenance information.

Interoperability

There are two types of interoperability: technical interoperability, which includes technical interface specifications, e.g. Portable Operating System Interface (POSIX), and data interoperability, which is about the structure of the data and metadata and the semantics, which is important for data integration.

Such an interoperability can be reached by semantic annotation of the data with metadata and by using well-defined standard formats or data structures. Whenever possible these data structures should be described by schemas (e.g. XSD for XML, RDFS for RDF, JSON schema [53] for JSON, YAML schema for YAML [54] or for describing the hierarchy of HDF5 [55], Apache Avro or protobuf formats). Furthermore, the REST APIs should be OpenAPI [56] compliant.

Biomedical Research Integrated Domain Group (BRIDG)

BRIDG [57], [58] is a domain model specified in UML that can bridge standards and organizations as well as the gap between clinical research and healthcare. It is also the ISO 66767 [59] standard for biomedical and clinical research supporting semantic interoperability. Among the stakeholders are CDISC, NCI, FDA, HL7 and ISO and the BRIDG standard is jointly balloted by ISO, HL7 and CDISC. The BRIDG standard version 5.3.1 UML representation currently defines more than 300 classes in 9 subdomains (Adverse event, Biospecimen, Common, Experiment, Imaging, Molecular Biology, Protocol Representation, Statistical Analysis and StudyConduct). Subdomains for modelling and simulation are missing and still must be defined, to allow the use of BRIDG as technology for the VHT.

As a domain model, BRIDG can be implemented using varying technologies. One way to implement BRIDG is to map it to FHIR [60] (Fast Healthcare Interoperability Resources) resources, which make intensive use of semantic annotation.

Alternative interoperability models for solving interoperability problems with clinical or research study data and/or implementing BRIDG would be openEHR (open Electronic Health Records, ISO EN 13606), CDISC-OMOP (Observational Medical Outcome Partnership), VA-FHIM (Federated Health Information Model), HL7 V3 CDA [61] (Clinical Document Architecture, an information model for text-based documents) and DCM (Detailed Clinical Model, ISO 13972:2022 [62]).

FHIR (Fast Healthcare Interoperability Resources): ISO/AWI TR 24305

HL7 FHIR is a standard used for data exchange and/or storage of semantically annotated clinical or administrative health data and is useful for data integration and data interoperability.

The standard FHIR resources [60] – there are about 150 of them – have very generic definitions. The content of these FHIR resources can have multiple representations, e.g. as XML, JSON, UML or RDF turtle format.

In case no proper resource is available for the intended use, one can:

- define custom FHIR resources as a specialization of DomainResource. The drawback of custom resources is that they are less interoperable.
- use the Basic resource and add extensions to already existing resources.

By use of FHIR profiles and extensions one can “profile” the standard resources [63]. That means that the profiles are customized, i.e. either restricted or extended to fit one’s needs. Also, the information of base elements can be changed or elements can be sliced.

A FHIR profile [64] allows one to specify a set of constraints and/or extensions [65] in order to define more specific resources.

Integration of multiscale models

Multiscale models have model features at multiple scales of space and/or time. The Multiscale Modelling and Simulation Framework (MMSF) based on the Multiscale Modelling Language (MML), which describes the coupling of the sub-models, can be used for it.

Phenotypic data exchange

- Phenopackets [66] version 2 is a Global Alliance for Genomics and Health (GA4GH) and ISO 4454 [67] open standard for sharing disease and phenotype information of a patient/sample, especially in the context of diseases – especially rare diseases and cancer, but also for common diseases. A Phenopacket links detailed phenotypic descriptions with disease, patient, and genetic information, diagnosis and treatments. The phenotypic features are e.g. signs, symptoms, laboratory and imaging findings, behavioural manifestations or the results of physiological tests.
- The Human Phenotype Ontology [68] (HPO) and other disease ontologies like e.g. Mondo, OMIM (Online Mendelian Inheritance in Man), ORDO (Orphanet Rare Disease Ontology), NCIT (National Cancer Institute Thesaurus), ICD (International Classification of Diseases) etc. contain many terms describing phenotypic abnormalities. Mondo tries to harmonize the different disease definitions and is coordinated with HPO. The Phenopackets schema is specified as a protocol buffers (protobuf) schema [69].

Standardized bundling of data for individuals / patients

For healthcare applications the data integration has often to be done for the individual patients. Such data integration on the level of individuals means to integrate all data types from a patient into a collection of data that can be used to support model-building and to conduct simulation with that data collection for that patient. This allows one to build and simulate personalized medicine models.

Such an integration on the patient level requires that the data protection laws, especially the EU-GDPR (General Data Protection Regulation) are regarded. The patient has to give his informed consent or the national data protection laws must be followed. Without consent the data is not allowed to contain personally identifiable information.

If consent is given, the Data Use Ontology (DUO) contains standardized terms for documenting the consented data uses. In case no consent is given, one can at first bundle the data of that patient and then anonymize them. If that is not possible one shall use pseudonymised data and then bring the data of one patient together. For that, the pseudonymisation method must be the same for all data Sources.

A special problem is record linkage, where different data sets from a patient (who potentially was treated in more than one clinic) should be linked together across organizations or even countries. This is for example necessary to get large enough case numbers for the analysis of rare diseases with data-driven AI or ML methods. For that, one needs a method to link datasets of a patient from more than one organization without making reidentification of the patients possible.

The outcome of such Privacy Preserving Record Linkage (PPRL) [70] algorithms depends on the configuration of several algorithm parameters. Therefore, if two organizations want to filter datasets on the basis of Bloom filters, it is a must that they use the same set of parameters for the Bloom filter generation.

3.4 Synthetic biology

3.4.1 Description

Synthetic biology is a new emerging multidisciplinary field that seeks to create new biological parts, devices, and systems, or to redesign existing systems for useful purposes and

applications. Compared to conventional chemical synthesis, synthetic biology is miniature, reusable and safer, and its cellular intervention is targeted.

By testing large-scale combinations of different components, circuit modules, networks, and chassis, extensive experimental data is collected to serve as a basis for rational design and optimization of synthetic biological systems. The development of synthetic biology mainly involves four important technologies:

- Sequencing. With the development of high-performance sequencing techniques, an improved understanding of the original systems is gained, which contributes to the design and development of new innovative systems.
- Computer design and simulation modelling. With the understanding of the underlying systems, the composition and structure of the entire living systems can be achieved, allowing new systems to be assembled and models to be obtained through the analysis of computer simulation models.
- DNA/gene construction. This is the necessary step to developing new functional components/systems with functional parts/systems from scratch.
- Genetically engineered cells. Establishment and maintenance of cell lines with artificial genomes that exhibit new functions and properties.

Initially, synthetic biology was only able to design push-button gene switches with two or three genes or oscillators. Today, under the guidance of engineers and computer designers, synthetic biology can use efficient DNA synthesis and assembly technologies to design complex gene programs with more than a dozen genes that endow synthetic organisms with various new biological functions, such as microbial synthesis of plant drug components like artemisinin or paclitaxel, artificial T cells that could be used in tumor therapy, and intelligent control of biological fermentation.

The recent increase in the speed of development in synthetic biology is mainly due to the strategy of establishing so-called “biofoundries” that provide full integration of development cycles based on end-to-end process automation and data integration [71]. Forming the construction core of the engineering platform, biofoundries are organizing the development process according to the closed-loop strategy of design-build-test-learning (DBTL).

The development of biobricks represents a decisive advance, as it enables a standardized approach to the construction of synthetic genes. BioBricks can be thought of as defined building blocks that can be combined in different ways to build more extensive synthetic biological circuits that have new, unique functions. These biological circuits can then be inserted into living cells to construct new biological systems that perform specific functions. Typical elements of the BioBrick technology include coding sequences, binding sites or promoters.

3.4.2 How the convergence of bio and digital technologies is affecting this domain

This domain is a typical example for the convergence of biological and digital technologies. From the very beginning, synthetic biology has gradually moved towards “data-driven” mode instead of the traditional “experiment-driven” mode. During the design and creation phase of BioBricks various computational tools, in particular deep learning technologies, are used for optimization, which requires high quality data.

3.4.3 Technology and market trends

Next 5 to 10 years

At present, the synthetic biology industry is facing a historic development opportunity, and its products are widely used in medical and health care, the chemical industry, agriculture, food, consumer goods and many other fields. The global synthetic biology market in terms of revenue is poised

to reach USD 35,7 billion by 2027, growing at a CAGR of 25,6% from 2022 to 2027 [72]. As core technologies continue to change, the scale of the synthetic biology industry is expected to expand rapidly, the market is expected to witness a dollar opportunity of USD 150,4 Mn in the upcoming 10 years [73]. According to data released by McKinsey, the annual direct and indirect economic impact of synthetic biology on the fields of materials, chemistry and energy could amount to between USD 200 billion and USD 300 billion over the next 10 to 20 years.

The industrial application of synthetic biology begins with the generation of the genetically modified strain and culminates in its use in a biological production process. Depending on the starting point of company development, some platform-based companies are more focused on the design and generation of new strains, while others have particular strength in manufacturing products. Looking at the industry as a whole, the production of cell lines is the foundation and the subsequent production is the guarantor of a company's success.

3.4.4 Outlooks

With the increasingly serious global ecological and environmental problems that are arising, traditional synthesis technology based on chemical methods will face greater challenges, while biological synthesis has great potential and is expected to become an important development direction of synthesis technology in the future. Breakthroughs in various fields have provided more room for imagination and possibilities for the application of synthetic biology technologies. Transforming the structure of microbes, creating those that do not exist in nature is the key point now and combining them with man-made substances such as semiconductors to "precisely produce" what we need will be the essential topic from now on.

3.4.5 Existing standardization

ISO

Synthetic biology has been noticed by ISO and mentioned in the foresight trend report 2022. Two ISO technical committees are involved in synthetic biology standard development.

One is ISO/TC 276 "Biotechnology", which is focused more on fundamental aspects of synthetic biology, while ISO/TC 34/SC 16 "Horizontal methods for molecular biomarker analysis" is more concerned with practical applications of synthetic biology. Standards applicable to synthetic biology are:

- Published standards
  - ISO 5058-1:2021 Biotechnology-Genome editing-Part 1: Vocabulary
  - ISO 20688-1:2020 Biotechnology- Nucleic acid synthesis Part 1: Requirements for the production and quality control of synthesized oligonucleotides
  - ISO 16578:2022 Molecular biomarker analysis – Requirements for microarray detection of specific nucleic acid sequences
- Standards under development
  - ISO/FDIS 20688-2 Biotechnology – Nucleic acid synthesis – Part 2: Requirements for the production and quality control of synthesized gene fragments, genes, and genomes
- Alliance standards

  The American Society for Testing and Materials (ASTM) has published a standard on the terminology for industrial biotechnology and synthetic biology. In China, the Chinese Institute of Synthetic Biology initially focused on the application aspect of synthetic biology for DNA storage and has been developing a technical specification for the coding system in DNA-based information storage, see following:

  - ASTM E3072-22A – Standard Terminology for Industrial Biotechnology and Synthetic Biology
  - CIE Technical specification for the coding system in DNA-based information storage

- Non-SDO standards

The international scientific community has put significant efforts in development and dissemination of standards for data and models in synthetic biology [74], [75]. Here, the COMBINE (Computational Modelling in Biology) initiative takes a central role in coordinating the numerous activities. Generally accepted major standards are:

  - BioPAX (Biological Pathway Exchange)
  - SBGN (Systems Biology Graphical Notation)
  - SBML (Systems Biology Markup Language)
  - SED-ML (Simulation Experiment Description Markup Language)
  - CellML
  - SBOL (Synthetic Biology Open Language)
  - NeuroML

3.4.6 Standardization needs

The standards published or currently under development pertaining to synthetic biology mainly cover the area of DNA synthesis and only one or two refer to aspects of applications of synthetic biology.

From this it is obvious that standardization in synthetic biology is still in its infancy. Standardization needs (see Figure 14) can be summarized in three layers according to the technology route.

- **Now**
  - Fundamental
    - Terminology
    - General technical requirement

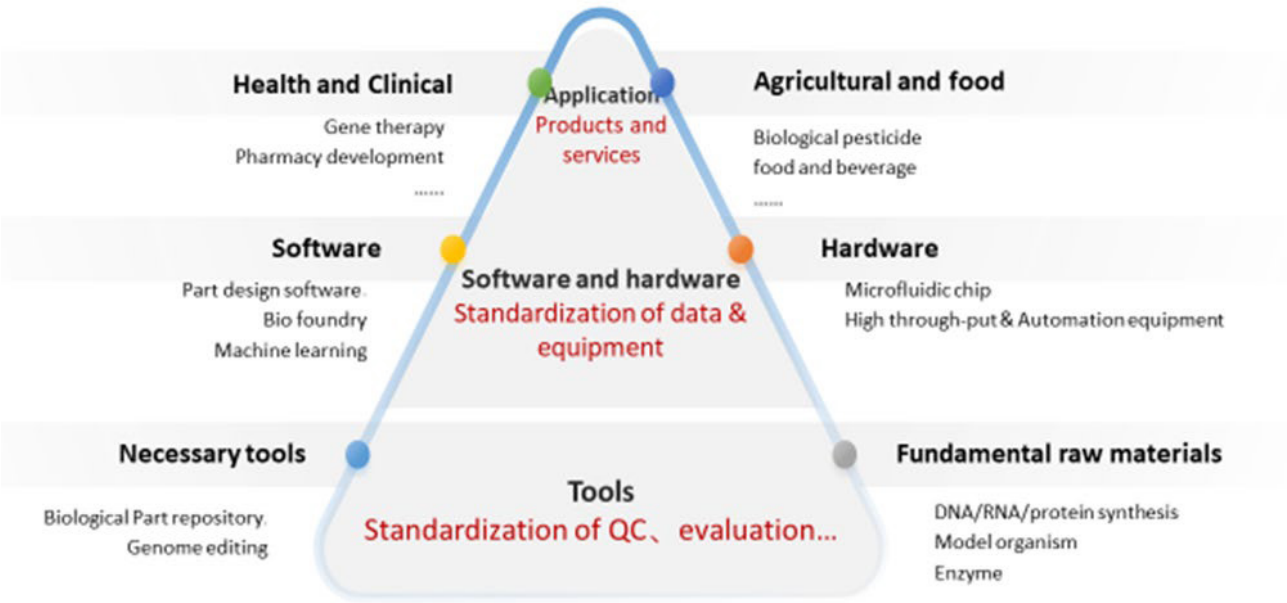


Figure 14 | The layers of standardization needs for components and applications of synthetic biology

  - Open issues:
    - Standardization of biological parts
    - Quality control and evaluation of fundamental raw materials
    - Design requirements for software
    - Data format and processing standardizations for interoperability.
- **Next 5 years**
  - Application standards
  - Healthcare and clinical service and productions
  - Agriculture
  - Others

3.5 Artificial organs and organoids

3.5.1 Description

Advances in our understanding of cell biology and material science have led to the establishment of complex organ products. Organoids are three-dimensional (3D) cell structures composed of a large number of organ-specific cells formed by differentiation of stem cells and forming the organoid by self-assembly. In fact, they are in vitro formed, miniaturized and simplified model systems of organs [76]. Organ-on-a-chip is a microscale system that mimics the environment of the human body, using microfluidics along with organoids to replicate physiological and functional conditions in the body.

Organoids and organs-on-a-chip have already been successfully applied in drug development. Model systems using organoids and organs-on-chip are of particular interest in modelling tissue development, pathogenesis and disease progression, and for personalized medicine, drug screening, cell therapy, and toxicology [77].

Despite considerable success in culturing physiologically relevant organoids, challenges remain to achieving real-life applications. The ultimate goal for organ-on-a-chip is to develop human tissue models for disease modelling and drug testing.

However, the human body consists of a complex interaction of different organs. Modelling this complexity requires the cultivation of different artificial tissues on a single chip, while allowing fluid exchange between the tissues. This fluid exchange poses a problem because different tissues require different growth media to develop and sustain to maturity.

With the rapid development of advanced material processing technologies, the production of bioartificial organs has also become increasingly attractive. Bioartificial organs involve the design, modification, growth, and maintenance of living tissues embedded in natural or synthetic scaffolds to perform complex biochemical functions, including adaptive control and replacement of normal living tissues. The concept builds on a number of techniques that can be used to create human organs based on bionic principles. Over the past decade, significant progress has been made in the development of various organ-manufacturing technologies.

3.5.2 How the convergence of bio and digital technologies is affecting this domain

One way digital technologies can be used in organoid-based drug screening is through high-throughput screening platforms. High-throughput screening uses robotic systems to rapidly test large numbers of drugs for their effects on organoids. This can be combined with automated microscopy, which uses high-resolution imaging of organoids to enable cell analysis, thereby generating large data sets. Machine learning algorithms can then be used to analyze these data sets and identify patterns and potential drug targets.

Another technique that uses digital technologies in organoid-based drug screening is microfluidics. Microfluidics involves the manipulation of fluids

at the microscale, which can be used to create miniaturized organoids and microenvironments that mimic the in vivo conditions of organs. This enables drug testing in physiologically relevant contexts and can lead to more meaningful results. Digital technologies are used to control and monitor the microfluidic devices, enabling precise and automated drug screening.

Digital technologies can also be used to model and simulate the behaviour of organoids and predict the effects of drugs. This involves the use of computational models that can simulate the behaviour of organoids and predict the response of organoids to different drugs. These models can be used to identify potential drug targets and optimize drug screening protocols.

3.5.3 Technology and market trends

Next 5 to 10 years

The market size of organoids and organ-on-a-chip technologies is expected to grow significantly in the next 5 to 10 years. These technologies have the potential to revolutionize drug development, disease modelling, and personalized medicine.

According to a report by Grand View Research, the global organoids market size was valued at USD 689,22 million in 2020 and is expected to grow at a compound annual growth rate (CAGR) of 18,9% from 2021 to 2028 [78]. Based on this projection, the market size of organoids is expected to reach USD 2,44 billion by 2028.

Similarly, the organ-on-a-chip market size is also expected to grow significantly in the next few years. According to a report by MarketsandMarkets, the global organ-on-a-chip market size was valued at USD 9,6 million in 2020 and is projected to reach USD 117,6 million by 2025 [79], at a CAGR of 65,4% during the forecast period.

Looking further ahead, the same report forecasts that the global organ-on-a-chip market size will reach USD 1,7 billion by 2030, at a CAGR of 63,3% from 2025 to 2030. The market size of organoids and organ-on-a-chip technologies is expected to experience significant growth in the coming years, driven by factors such as increasing investments in research and development, rising demand for personalized medicine, and advancements in tissue engineering and microfluidics.

3.5.4 Outlooks

Some possible developments in the long-term future of organoids and organ-on-a-chip products include:

- Integration of multiple organoids or organ-on-a-chip systems to create more complex and realistic models of human physiology and disease.
- Incorporation of advanced imaging and sensing technologies to monitor cellular and tissue behaviour in real-time and gain deeper insights into disease mechanisms.
- The development of personalized organoids, tailored to an individual's specific genetic makeup, to enable personalized drug testing and disease modelling.
- Expansion of organoid and organ-on-a-chip technology to include non-human models, enabling more comprehensive testing of drugs and therapies across a range of species.
- The development of fully implantable organoids or organ-on-a-chip devices that could replace damaged or diseased organs in the body.
- The use of organoids and organ-on-a-chip systems to develop new therapies and treatments, such as cell-based therapies, gene therapies, and drug delivery systems.
- The long-term future of organoids and organ-on-a-chip products is likely to be shaped by ongoing technological advancements, as well as by the growing demand for more effective and personalized approaches to healthcare.

3.5.5 Standardization needs

Organoids and organ-on-a-chip technologies are rapidly advancing fields with great potential for use in various applications such as drug discovery, toxicity testing, and personalized medicine. However, there is a need for standardization in these fields to ensure reproducibility, comparability, and reliability of results [80], [81]. Some of the standardization needs for organoids and organ-on-a-chip are:

- Definition of terms: There is a need to establish a common language and a set of standard terms to describe the different types of organoids and organ-on-a-chip models. This will help to avoid confusion and improve communication among researchers and stakeholders.
- Quality control and validation: Standard protocols for quality control and validation of organoids and organ-on-a-chip models need to be established to ensure that the models are reliable and reproducible. This includes assessing the viability, functionality, and consistency of the models.
- Characterization: There is a need to standardize the characterization of organoids and organ-on-a-chip models. This includes the use of standardized markers to identify the different cell types present in the models, as well as the use of standardized assays to measure their functional properties.
- Culture conditions: Standardization of culture conditions is essential to ensure the reproducibility and comparability of organoids and organ-on-a-chip models. This includes standardizing the media composition, growth factors, and other culture parameters.
- Data sharing: A standardized data sharing platform will allow researchers to share their data and protocols, which can help to improve the quality of research in the field.
- Regulatory considerations: Standardization of organoids and organ-on-a-chip models will also aid in regulatory considerations. Establishing standardized protocols and guidelines will help to ensure that the models meet regulatory requirements for use in drug discovery and toxicity testing.

3.5.5.1 Standards for organoids and organ-on-a-chip models

In this field, standardization is crucial for the advancement of the technologies required and the development of reliable and reproducible models for use in research and clinical applications [82]. SDOs and several national and international organizations have recognized the urgent need for standards in the field of organoids and organs-on-a-chip as well as the need to take appropriate action. The ORCHID (Organ-on-Chip in development) consortium funded by the European Union has analyzed the organ-on-chip ecosystem and identified the needs and challenges involved, which led to a workshop investigating the standardization needs in 2021 [83] and the European Committee for Standardization/European Electrotechnical Committee for Standardization (CEN/CENELEC) launching a focus group on organ-on-chip in 2022.

3.5.5.2 Now

Organoids and organ-on-a-chip technologies are rapidly advancing areas of research, and there is an ongoing effort to establish standardization in these fields.

For organoids, the International Society for Stem Cell Research (ISSCR) has published guidelines for the use and development of organoids in research. These guidelines provide recommendations for the generation, characterization, and use of organoids, as well as ethical considerations. Additionally, several working groups and consortia have been established to promote standardization in organoid research, including the Human Cell Atlas's Organoid and Organ-on-a-Chip Technology Working Group and the NIH Microphysiological Systems Program.

Similarly, for organ-on-a-chip technologies, there is an ongoing effort to establish standardization in terms of device design, cell culture protocols, and functional assays. The International Society for Pharmaceutical Engineering (ISPE) has developed a special interest group on organ-on-a-chip, which aims to create a roadmap for standardization and regulatory guidance. Additionally, the NIH Microphysiological Systems Program has established a tissue chip validation consortium together with ASTM in the Standards Advancement Program [84] to evaluate and standardize the use of organ-on-a-chip technologies for drug development.

While standardization efforts are still in progress, there is a growing recognition of the importance of establishing standards for the development and use of organoids and organ-on-a-chip technologies, which will help to ensure the reproducibility and reliability of these models for research and drug development.

3.5.5.3 Next 5 years

The standardization of organoids and organ-on-a-chip technologies is an important goal for the field of regenerative medicine, as it would allow for greater reproducibility and comparability of experimental results. In the next five years, it is likely that efforts to standardize these technologies will continue to gain momentum.

One approach to standardization is through the use of reference materials, which can be used to benchmark and compare different organoid and organ-on-a-chip models. The development of such reference materials will require collaboration across multiple disciplines, including cell biology, materials science, and engineering.

Another key area of focus will be the development of standardized protocols for the production and maintenance of organoids and organ-on-a-chip devices. This will require careful consideration of factors such as culture conditions, cell types, and biomaterials, as well as the development of quality control measures to ensure consistency between different labs and experiments.

In addition to standardizing the production and maintenance of organoids and organ-on-a-chip devices, efforts will also be needed to standardize the methods used to analyze and characterize these models. This will include the development of standardized assays for assessing their physiological and functional properties, as well as the development of standardized protocols for imaging and data analysis.

To conclude, the standardization of organoids and organ-on-a-chip technologies is likely to be an ongoing process over the next 5 years and beyond, as the field continues to mature and new challenges arise. However, by working together to establish common standards and best practices, researchers can help to ensure that these technologies realize their full potential for advancing our understanding of human biology and disease.

3.6 CAR-T cells

3.6.1 Description

Cell therapy by adoptive cell transfer via infusion of lymphocytes was developed in the 1980s and successfully used in the treatment of organ transplant rejection, leukemia, and skin tumors [85]. With the advent of gene transfer techniques in the 1990s, it was possible to target T cells using genetically engineered T cell receptors (chimeric antigen receptors (CAR)). These receptors confer high specificity to the immune effector cell and improve the T cells' ability to be used.

T cells with chimeric antigen receptors (CAR-T cells) are now approved and established for the treatment of leukemia (see Figure 15a). Many recent studies show the great potential of CAR-T cells as a highly innovative immunotherapeutic approach in cancer treatment.

The method is based on genetically engineered T cells that express receptors for specific antigens that recognize cancer cells. By combining the role of T cells in immunoreactivity and antigen receptor function, CAR-T cells are an effective means of fighting cancer cells.

The production of CAR-T cells is complex and requires a large number of steps. It begins with the isolation of T cells from the patient's blood by leukapheresis, followed by several washing steps to remove other blood cells, enrichment of the T cell fraction, and depletion of the fraction of natural killer (NK) cells. The T cells are usually activated with anti-CD3/CD28 antibody-coated beads. Gene transfer of the CAR can be done by viral transfer, usually with lentiviruses, or with plasmids. Finally, the cells are taken into culture and expanded in flasks, bags, or bioreactors before being transferred to the patient. After infusion, the CAR-T cells grow and multiply rapidly in the patient. A single CAR-T cell can kill many tumor cells, and CAR-T cells can promote immune surveillance to prevent tumor recurrence by releasing antigens and helping tumor-infiltrating lymphocytes fight tumors.

3.6.2 How the convergence of bio and digital technologies is affecting this domain

The isolation, gene transfer and expansion of the CAR-T cells remains the major challenge of CAR-T cell therapy.

3.6.3 Technology and market trends

Next 5 to 10 years

While the clinical use of CAR-T cells is currently mainly focused on cancer of the hematopoietic system (blood cells/bone marrow), in current clinical studies CAR-T cell therapy targeted at solid tumors is also investigated. But studies for the application of CAR-T cells are also under way [86] for non-malignant diseases (see Table 2) such as autoimmune diseases, retroviral infections or cardiovascular diseases (see Figure 15b). Further developments are aimed at performing gene transfer in vivo so that the time-consuming isolation and processing of T cells can be dispensed with.

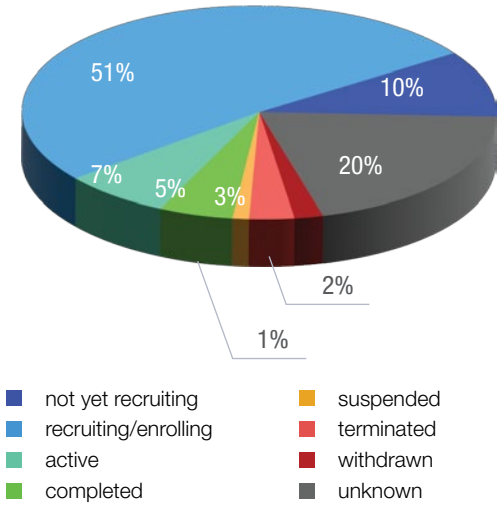


Figure 15a | Status of current CAR-T cell trials (Source: clinicaltrials.gov 2/2023)

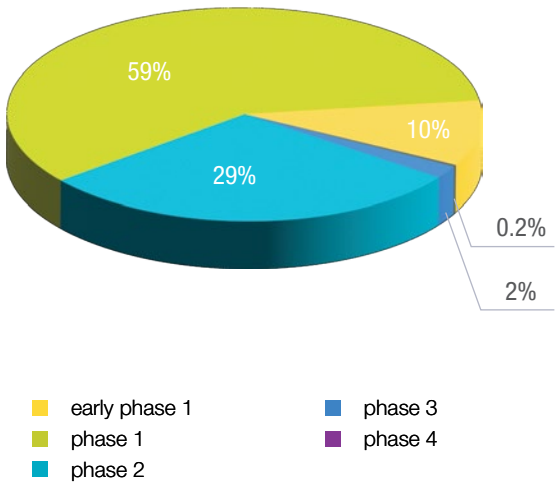


Figure 15b | Clinical Phase of current CAR-T cell trials (Source: clinicaltrials.gov 2/2023)

Table 2 | Number of clinical studies on treatment of non-malignant diseases with CAR-T cells (Source: clinicaltrials.gov 2/2023)

Condition	Studies
Vascular diseases	171
Virus diseases	26
Autoimmune diseases	15

3.6.4 Outlooks

The numerous promising results of CAR-T cell applications indicate an increasing role of cell therapy for a wide range of diseases. By expanding the scope of CAR-T cell therapy to non-malignant diseases, the current challenges in treating autoimmune diseases, as well as many other diseases that currently have limited treatment options, may be overcome.

3.6.5 Existing standardization

3.6.5.1 Standardization by SDOs

a) ISO

ISO/TC 276, in particular its WG 3 and WG 4, are developing standards related to CAR-T cell production, while not explicitly addressing CAR-T cells but cell therapeutics in general. Standards applicable to CAR-T cell production are:

- Published standards
  - ISO/TS 20399 series Biotechnology – Ancillary materials present during the production of cellular therapeutic products
  - ISO 21973 Biotechnology – General requirements for transportation of cells for therapeutic use
  - ISO 23033 Biotechnology – Analytical methods – General requirements and considerations for the testing and characterization of cellular therapeutic products
  - ISO/TS 23565 Biotechnology – Bioprocessing – General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use
  - ISO/DIS 20404:2023 Biotechnology – Bioprocessing – General requirements for the design of packaging to contain cells for therapeutic use
- Standards under development
  - ISO/CD 8934 Biotechnology – General considerations and requirements for cell viability analytical methods – Part 1: Mammalian cells
- Standards in preparation

  Currently a set of standards pertaining to the design, production, handling and use of viral vectors is in preparation at ISO/TC 276/WG 3. It can be expected that the standards will address all of the issues related to viral vectors used in cell therapy.

b) Standardization by non-SDOs

Standardization in CAR-T cell applications is required in three important areas:

- Manufacturing

  The standardization is currently focused on the production of CAR-T cells and mainly based on established guidelines, such as: good laboratory practice (GLP), good manufacturing practice (GMP), good clinical practice (GCP).
- Approval

  For the clinical application, aspects such as clinical safety and efficacy are fundamental. The standardization in this respect is assumed by national or transnational regulatory bodies, such as the US Food and Drug Administration (FDA), Health Canada or the European Medicines Agency (EMA).

- Administration

  The administration to the patient and the collection of data is covered by clinical standards, national regulations and guidelines from professional societies. Institutions that use CAR-T cells on patients require accreditation by official accreditation bodies such as FACT (Foundation for Accreditation of Cellular Therapy) or the Joint Accreditation Committee of ISCT (International Society for Cell & Gene Therapy) and EBMT /European Society for Blood and Marrow Transplantation)

3.6.6 Standardization needs

- Open issues

  Despite the existing guidelines for standardization, many aspects are not yet fully covered. These include:

  – the still high manufacturing failure rates

  – the quality of the viral vectors used, in particular the reliability or non-replicability of the vectors

  – reliable characterization of the T-cells

- Potential standardization targets

  – Pre-commercial development/pre-clinical phase not covered

  – Standardization needs notwithstanding extensive regulation

  – Safety of viral products, quality of viral vectors

  – Handling in the lab

  – Data standards

3.7 CRISPR

3.7.1 Description

The CRISPR/CAS9 (Clustered Regularly Interspaced Short Palindromic Repeats/Cas-9 nuclease) technique is an innovative technique in genetic engineering. Even though the technique is still very new, it has already gained a great deal of significance [87].

Originally, CRISPS/Cas is a method used by bacteria to defend themselves against phages [88]. Parts of the viral DNA are incorporated into the CRISPR region of the bacterial DNA and transcribed into RNA. The RNA molecules are acting as “guide” for the Cas endonuclease by binding to the target sequence on the invaded virus DNA, thus showing the Cas enzyme where to cut the foreign DNA. The viral genome is thus rendered harmless and the infection is averted. Thus bacteria can build up a library of virus DNA and pass these traits also to following generations.

The ability of CRISPR/Cas to recognize a particular locus with high precision and remove a defined sequence without side effects has made this technique highly attractive for genetic engineering. Especially in the treatment of genetic defects, CRISPR/Cas has already proven itself as a tool for removing defective genes in human DNA. The range of applications, however, is much broader and also covers applications in green and white biotechnology.

3.7.2 How the convergence of bio and digital technologies is affecting this domain

The design of suitable sequences for CRISPR/Cas is a key challenge. Accordingly, in the basic data used, the bioinformatics tools and algorithms are of particular importance for the design of the guide sequence. Insufficient specificity of the guide sequence for the intended target can cause off-target effects which consequently lead to unanticipated, often deleterious mutations.

3.7.3 Technology and market trends

Next 5 to 10 years

Future developments in CRISPR technology aim to improve the specificity and efficiency of the technique, enable more targeted and limited

modification of genes, expand the scope of application, and simplify practical use.

- **Specificity**

Although CRISPR technology is far superior to existing methods in terms of specificity and avoidance of side effects, non-specific, unintended changes to genes still occasionally occur. Approaches to make the technology more precise and specific, for example by using smaller CRISPR proteins or developing new delivery systems that can target specific cells or tissues more precisely, are already under development.

- **Efficiency**

Currently, the number of genes that can be edited in one approach using CRISPR technology is very limited. Typically, only a single gene is altered at a time. Initial experience with multiplexed gene editing shows that, in principle, multiple genes can be edited simultaneously with CRISPR technology. In this way, it will be possible to significantly increase the efficiency and performance of the technology.

- **Base targeted editing**

As it stands today, CRISPR allows the insertion or deletion of entire gene segments, but not the more subtle changes that can be achieved by replacing or removing single or several bases. Such point mutations would represent a genetic tool of the highest precision that could be used, for example, to target genetic diseases more precisely. Initial developments in this area are already promising.

- **Epigenetic editing**

Recent work on epigenetics has shown that epigenetic changes in the genome, such as DNA methylation or histone modifications, play a critical role in gene expression and in the development and progression of disease. For this reason, ongoing research is attempting to adapt CRISPR technology for epigenome engineering. Tools that enable the targeted manipulation of the epigenome would also allow the treatment of diseases caused by epigenetic alterations. Furthermore, changes in the epigenome can be used to control or adjust cellular states, which is crucial for cell therapy.

- **In vivo application**

The focus of current research on CRISPR is on in vitro models and in vitro applications. However, for gene therapy applications, it would be useful to edit the genome directly in the living organism (in vivo). The principle possibility of using CRISPR technology in vivo has already been demonstrated in animal models. Many fundamental problems, in particular safety, specificity and consistency, have not yet been solved, but if successful, CRISPR could constitute a promising tool for the treatment of genetic diseases such as muscular dystrophy or cystic fibrosis.

3.7.4 Outlooks

CRISPR technology opens up an immense number of development opportunities in all areas of biotechnology. In gene therapy, CRISPR has already shown promise as an approach to treating inherited diseases such as sickle cell anemia and beta thalassemia. With the current new developments in CRISPR technology, it can be expected that many other genetic disorders, as well as neoplastic diseases [89], can be cured using the technique. In the field of “green biotechnology,” CRISPR will make it possible to modify the genes of plants to develop targeted resistance to plant diseases, drought and pests.

This will help improve the sustainability of agriculture. In industrial biotechnology, CRISPR will enable new and optimized biotechnological processes for the production of biofuels, bioplastics, biomaterials and pharmaceuticals. In this way, it will be possible to increase performance, improve efficiency and reduce waste, leading to more sustainable and environmentally friendly production.

3.7.5 Standardization needs

As the importance of CRISPR technology grows and the variety of foreseeable uses increases, so does the need to develop standards for CRISPR. Standardization will ensure the consistency and reproducibility of tools and products developed with and for CRISPR, as well as the comparability of developments across laboratories, thereby accelerating the development of CRISPR-based therapies and applications.

3.7.5.1 Current standardization by SDOs

- **ISO/TC 276 Standards**
  - ISO 5058-1:2021 Biotechnology – Genome editing – Part 1: Vocabulary
  - ISO 20688 series Biotechnology – Nucleic acid synthesis
  - ISO/DIS 24480 Biotechnology – Validation of database used for nucleotide sequence evaluation
- **Standardization targets**
  - Criteria for assessing product performance consistently applicable across products in the gene therapy field.
  - Identification of factors affecting product performance
  - Appropriate thresholds for performance data
  - Guidelines for sample preparation
  - Product performance test selection and requirements
  - Critical quality attributes applied both early and late in development
  - Risk-based framework for assessing comparability to support manufacturing changes

- **Now**

The most pressing challenges with CRISPR relate to improving the quality, reliability and safety of the products developed. The basis for CRISPR specificity is the guide RNAs. Guide RNAs are a critical component of the CRISPR system because they direct the Cas9 enzyme to the target DNA sequence. However, designing guide RNAs can be complex, and there is currently no standardized approach to their design. Another major challenge with CRISPR is the possibility of off-target effects, in which the Cas9 enzyme can inadvertently alter parts of the genome other than the intended target. The unintended alteration of the genome can have harmful side effects that can cause severe chronic or even life-threatening diseases in therapeutic applications. These off-target effects may vary depending on the specific experimental conditions and techniques. Currently, there is no standardized approach to assessing or minimizing off-target effects. However, standards here could help ensure that experiments are conducted in a consistent and controlled manner, identify best practices for minimizing off-target effects, and avoid incalculable patient risks.

- **Next 5 years**

For CRISPR applications two issues will require standardization:

  – Delivery methods

  The method applied to introduce the Cas9 enzyme and guide RNA into cells can significantly affect the efficiency and specificity of gene editing. Currently several different delivery methods are available, including viral vectors, nanoparticles, and electroporation. Standardization in this area could help identify the most effective delivery methods for different cell types and experimental conditions.

  – Data quality and analysis

  Sophisticated bioinformatics techniques are required for the identification of suitable target

sequences and the design of the guide RNA. The data and algorithms used for this purpose have a significant impact on the quality of the product. Similarly, CRISPR experiments generate large amounts of data, mainly sequence data, which are needed to assess the efficiency and specificity of the procedure. When the product is used, functional data is obtained that is important for evaluating the success of genetic editing and for determining effects of gene manipulation on cellular processes. There is still no standardized approach to data analysis in the CRISPR field, which makes it difficult to evaluate and compare the results of CRISPR experiments. Standardization of data and algorithms is therefore essential to have reproducible, comparable and meaningful data available for future developments and to ensure the quality of genetic engineering products.

3.8 Data quality

3.8.1 Description

Any process in the field of bio-digital convergence is based on data and algorithms. Likewise, these processes usually produce large amounts of data that have to be analyzed and evaluated. As a result, the quality of the data and algorithms is of particular importance in all bio-digital convergence technologies [90].

In any data generation process, a careful quality check of the data with respect to all dimensions of data quality is essential to prevent the use of incorrectly matched, distorted, or otherwise erroneous data in subsequent processes. The steps in detail are given in 3.8.1.1 to 3.8.1.7.

3.8.1.1 Data collection

Experiments are often used to test specific hypotheses or to study the properties of biological systems. The accuracy and reliability of experimental results depend heavily on the data collection technique, the experimental setup, and the equipment used. Only if the documentation of the methods used and the metrological traceability are guaranteed can the data be considered reliable.

3.8.1.2 Merging data

When data from different Sources is merged for further analysis, sufficient metadata must be provided to allow evaluation of the comparability and validity of the data. Machine learning techniques in particular require a large amount of data that usually comes from a variety of different Sources. This data was often collected for a different purpose and/or over a longer period of time. Therefore, the different sets of data are not always comparable and compatible with each other and therefore cannot be used unchecked.

3.8.1.3 Data analysis

Data analysis must be performed with state-of-the-art techniques using established and validated algorithms. Appropriate controls and accompanying documentation of the tools used are necessary to allow subsequent evaluation of the usability of the data and traceability of faulty procedures.

3.8.1.4 Modelling and simulation

Models are created based on the analyzed data and simulations are performed using the models. The simulation shall provide evidence of the completeness and correctness of the designed model. Simulation results should allow predictions to be made about the properties and behaviour of a system. Poor quality data can lead to inaccurate or unreliable predictions that result in inefficient designs and can cause unpredictable damage when applied in the real world.

3.8.1.5 Production and application

During production and subsequent application of products, data is continuously collected for monitoring, control, and documentation. The collected data is of particular importance as it forms the basis for future improvements, error correction and error detection.

Clinical applications require extensive documentation and monitoring of a variety of parameters indicative of the physical condition of the subjects. The quality of data collected during clinical trials or preclinical studies can have a significant impact on the success or failure of efforts to develop and test new diagnostics, therapies, or devices. Poor quality data can lead to inaccurate or unreliable assessments of the safety and efficacy of new therapies, resulting in delays, abandonment of promising treatments, as well as patient harm.

3.8.1.6 Regulatory issues

In many cases, developments in the field of bio-digital convergence in life systems are subject to regulatory oversight by government agencies such as the FDA or EPA. These agencies often require detailed documentation and data to ensure that new products or technologies are safe and effective. Poor quality data can make it difficult to meet these regulatory requirements, which can lead to delays or even rejection of regulatory submissions.

3.8.1.7 Reliability and accountability

For all levels of data generation and processing, it is essential to ensure the reliability of the data and to preclude accidental alteration, intentional manipulation or corruption of the data. Furthermore, the origin and integrity of the data must be ensured by technical measures. Users of the data must also be able to identify who was involved in generating and processing it.

Many of these aspects are already covered by the FAIR principle (findable, accessible, interoperable, reusable), which has already been adopted by many stakeholders.

3.8.2 How the convergence of bio and digital technologies is affecting this domain

Typical use cases for data quality in the field of bio-digital convergence are:

- Big data

  Projects in this field are generating larger and more complex datasets than ever before, which can be difficult to manage and analyze effectively. Ensuring the quality of big data is a significant challenge, as it requires robust data management and processing systems, as well as sophisticated statistical and machine learning techniques (see Figure 16).

- Data integration

  The technologies emerging from bio-digital convergence often involve multiple Sources of data, including genomics, proteomics, metabolomics, and clinical data. Integrating these different types of data can be challenging, as they may be generated using different platforms, protocols, and standards. Ensuring the quality of integrated data requires careful attention to data normalization, validation, and quality control.

- Data sharing

  Sharing data and resources across the life science community is becoming increasingly important for fostering collaboration and accelerating progress. This is also particularly true for developments in bio-digital convergence, which are only possible through joint, coordinated efforts between different disciplines. However, data sharing brings new challenges for ensuring data quality, as data must be properly curated, annotated, and formatted for reuse. To ensure the quality of shared data, standard protocols and policies for data sharing must be developed, along with robust data quality control measures.

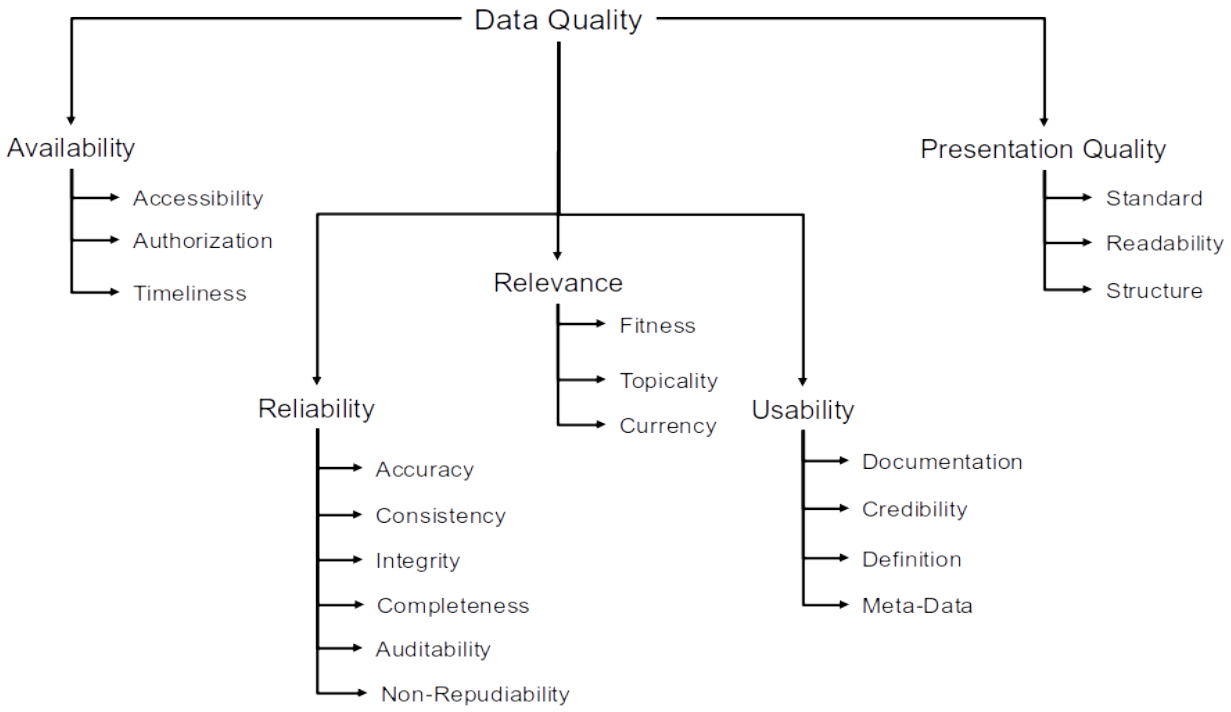


Figure 16 | The dimensions of data quality

- Data privacy and security

  Bio-digital convergence technologies, particularly in the health sector often require sensitive data, including personal health information, genomic data, and other sensitive information. Ensuring the privacy and security of this data is critical, as breaches can have significant legal and ethical implications. To ensure quality data privacy and security, robust data security protocols and technologies must be developed, as well as policies and regulations that promote responsible data management and sharing.

3.8.3 Technology and market trends

The steadily increasing demand for high-quality data is beyond question. Analysts see data and thus data quality as the central element and driver of future developments. Gartner analysts have identified 12 major trends in data and analytics for the near future:

- Adaptive AI systems
- Data-centric AI
- Metadata-driven data fabric
- The need to always share data
- Context-enriched analysis
- Business-composed data and analytics
- Decision-centric data and analytics
- Skills and literacy shortfall
- Connected governance
- AI risk management
- Vendor and region ecosystems
- Expansion to the edge

These trends point to a further increase in the importance of data quality, comprehensive and meaningful metadata, and data interoperability.

3.8.4 Standardization needs

- Existing standards and current standards development
  - SDOs
    - ISO/TC 276/WG 5 Data processing and integration
      - ISO 20691:2022 Biotechnology – Requirements for data formatting and description in the life sciences
      - ISO/ 23494 series: Biotechnology – Provenance information model for biological material and data
    - ISO/IEC JTC 1/SC 7 Software and systems engineering
      - ISO/IEC 25000 series
      - ISO/IEC 25012:2008 Software engineering – Software product Quality Requirements and Evaluation (SQuaRE) – Data quality model
    - ISO/IEC JTC 1/SC 42 Artificial intelligence
      - ISO/IEC CD 5259 series: Artificial intelligence – Data quality for analytics and machine learning (ML)
    - ISO/TC 184/SC 4 Industrial data
      - ISO 8000 series Data quality
  - Non-SDOs
    - FAIR-initiative
- Standardization needs and gaps fundamental to any application
  - Implementation of FAIR-principles to ensure reusability and verifiability
  - Additional quality dimensions
  - Metrological traceability
  - Comparability
  - Validity
  - Generic specifications mostly insufficient, domain-specific requirements needed

3.9 Conclusions and recommendations

3.9.1 Biosensors

- **Now**
  - Olfactory receptors: Manufacturing, stability, cost efficiency, uniform and consistent quality
  - Transducer: Standardized high sensitivity and selectivity, standardized protocol for interfacing receptors to sensor platform, sensor systems with uniform quality
  - Signal processing: Standardization of measurement protocols, systematic protocols for generating smell signal patterns
  - Pattern analysis: Standard algorithm for identifying and predicting smells
- **Next 5 years**
  - Assistive devices for loss of smell: Standardization of integration in multifunctional devices, such as wearables, smartphones
  - Technical/industrial applications: Standardization of smell

3.9.2 Human digital twins

- **For the creation of valid predictive computational models in personalized medicine two major requirements are to be fulfilled:**
  - Data integration – Harmonized strategies and methods for integration of data
  - Model validation – Validation of models and simulations through the underlying clinical question

- **Big data in health demands for**
  - Data-driven computational approaches tailored to individual or stratified patient groups
  - Harnessing, utilizing and understanding large-volume, highly diverse biological, clinical, and exosomal data
  - Developing harmonized guidelines for data integration strategies.
  - Ensuring legally compliant, ethical and fair procedures for the integration of personal data with full respect for personal rights
- **Next 5 years**

For many data types, appropriate standard formats are already in place. In particular for clinical and health data, international consortia and organizations have specified standard formats which have been widely adopted and implemented. Yet several challenges remain to be overcome.

- Harmonized access to data across resources
- Data preparation
- Standards for metadata of data and models
- Minimum reporting guidelines for clinical decision support systems
- Terminologies and ontologies for the description and annotation of data, models and their components
- Model quality and validation
- Data provenance
- Interoperability
- Phenotypic data exchange
- Merging of heterogeneous data

3.9.3 Synthetic biology

- **Now**
  - Fundamental needs
    - Terminology
    - General technical requirements
  - Open issues
    - Standardization of biological parts
    - Quality control and evaluation of fundamental raw materials
    - Design requirements of software
    - Data format and processing standardizations for interoperability.
- **Next 5 years**
  - Application standards
  - Healthcare and clinical service and productions
  - Applications in agriculture

3.9.4 Artificial organs and organoids

- **Now**
  - Harmonized terminology for organoids, organs-on-a-chip, and related models;
  - Quality control and validation of organoids and organs-on-a-chip;
  - Characterization of organoid and organ-on-a-chip models;
  - Standardization of culture conditions for organoids and organs-on-a-chip;
  - Standardized data sharing platform for organoids and organ-on-a-chip models;
- **Next 5 years**
  - Establishing reference materials for benchmarking and comparing organoid and organ-on-a-chip models;

- Standardized protocols for the production and maintenance of organoids and organ-on-a-chip devices;
- Standardization of methods used for analyzing and characterizing organoid and organ-on-a-chip models;

3.9.5 CAR-T cells

- Standardization of methods and material in the pre-commercial development and in the pre-clinical phase
- Standards for viral product safety and the quality of viral vectors
- Data standards

3.9.6 CRISPR

- Product performance criteria applicable across products in the gene therapy field.
- Guidelines for sample preparation
- Critical quality attributes applied both early and late in development
- Risk-based framework for assessing comparability to support manufacturing changes

3.9.7 Data quality

- Implementation of FAIR-principles (findable, accessible, interoperable, reusable) to ensure reusability and verifiability
- Metrological traceability
- Metadata standards for provenance, comparability and validity

3.10 Summary

Standardization needs in the bio-digital convergence of life systems span a broad spectrum that includes the quality of biological material used, the production and processing of biological material, bioelectronic interfaces, the acquisition and analysis of data collected from biological entities, and machine learning algorithms. Some of these requirements are already covered by existing standards, but only at a generic level that is not always sufficient for the specific requirements of the applications.

3.10.1 Terminology

In all the areas considered, there is a lack of standardized, generally accepted terminology. While ISO vocabularies are already available for some specific areas, in many cases different terms are used interchangeably or identical terms are used with different meanings. The creation of a common understanding of the terms used in this field is therefore imperative.

3.10.2 Biological techniques

Standards for the Source, processing, and handling of the biological material or excipients used, the laboratory procedures employed, and the tests used to qualify the product are generally very specific, so that a committee with appropriate expertise is best suited to set standards for these issues.

However, there are also issues of a more general nature that touch on different areas with sometimes overlapping but also different requirements. Here, meaningful and useful standards can only be developed through the combined efforts of experts from the relevant fields. A systemic approach will therefore clearly yield more relevant and better results. Typical technologies in this context are, for example, gene design or gene delivery methods.

3.10.3 Electronics

The electronic interfaces that couple the biological entity to a computer system are usually designed for a very specific environment and are therefore

well served by a committee with precise objectives. When it comes to requirements at a more general level, again a systems approach will be more advantageous.

3.10.4 Data and informatics

Since the techniques used here, such as machine learning or deep learning, inferential statistics, and signal analysis, are relevant to all different domains, standardization must also occur at a more general level. The same applies to specifications for quality, comparability, and usability of the data. Despite some specifics in certain areas, a general, system-based approach should be taken here as well.

3.11 Recommendation

In light of the above, it seems most advisable to analyze standardization needs at a general level, with a systems approach, identifying which topics require narrow technical consideration and which topics need input from many different areas to enable generic solutions. A systems approach is therefore most appropriate, and the establishment of a systems committee is likely to be the best choice.

Section 4

Human augmentation technologies

4.1 Introduction

4.1.1 Terminology

Human augmentation is an emerging and thriving field that focused on replicating, recovering, supplementing, amplifying, or enhancing human abilities for both healthy users and people with disabilities (Boeck & Vaes, 2021 [91]; Daily et al., 2017 [92]; Guerrero et al., 2022 [93]; Ho et al., 2022 [94]; Kazerooni, 2009 [95]). However, the definition of human augmentation is rather obscure. There are several related concepts in and beyond human augmentation. It is necessary to clarify the concept and use a unified terminology framework to facilitate the discussion and future development of the technology (see Figure 17).

Assistive augmentation, human augmentation, and human enhancement are technologies focusing on different levels and user communities. The word assistive augmentation is defined as “any item, piece of equipment, or product system, whether acquired commercially off the shelf, modified, or customized, that is used to increase, maintain, or improve functional capabilities of individuals with disabilities” in the US Technology-Related Assistance for Individuals With Disabilities Act of 1988 and the Assistive Technology Act of 2004, where the later version excludes surgical implants. As the keyword “assistive” goes, the assistive augmentation refers to rehabilitating the lost or impaired functionality for disabled or elder people, whereas human augmentation refers to a broader user community including healthy people, which brings a much wider collection of application scenarios.

The term human enhancement, which may often be mixed up with human augmentation, similarity refers to technologies that can enhance human capability but rather emphasizes the permanent altering of human existing capabilities by biologically related modifications including surgical operations and even genetic engineering methods,

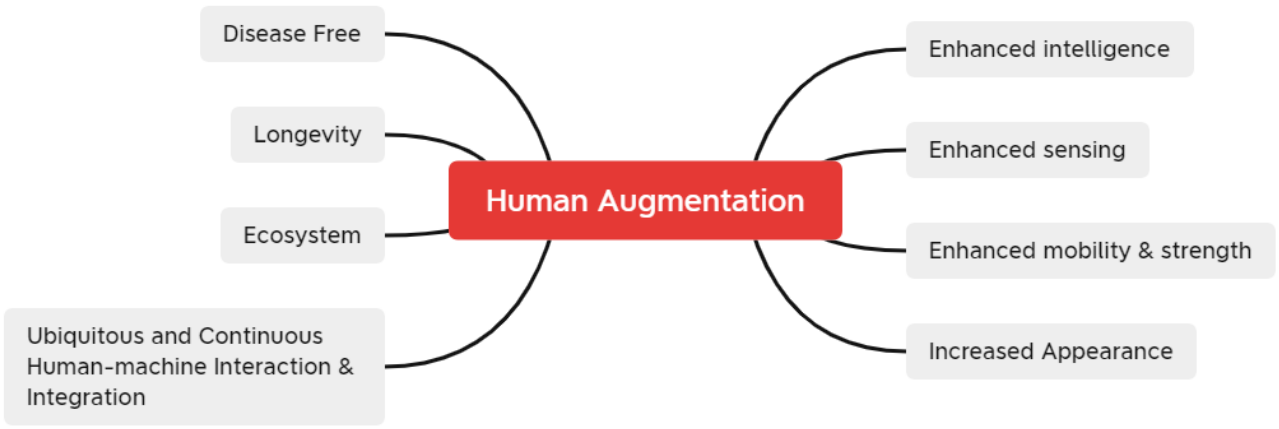


Figure 17 | Human augmentation applications and aims

whereas human augmentation usually refers to device-based technologies which can temporarily profound and strengthen human capabilities.

A typical use case to differentiate the three terms could be presented in Table 3. All the examples are used in the field of human visual sense. Traditional glasses could be categorized in assistive augmentation. Virtual reality (VR) glasses temporarily enhance the human vision by a device, while retinal prosthesis permanently replaces the original human sensing component by surgical implants.

4.1.2 How the convergence of bio and digital technologies is affecting this domain

Human augmentation shall greatly impact human society and the world, where the term transhumanism refers to how humans will experience, react, and perform in the future. In a consulting report from Frost and Sullivan (Transhumanism, n.d.) [96], human augmentation was discussed in three evolutions: biological evolution, human-machine evolution, and behavioural evolution, which could reshape the human experience, refine, and even redefine humanity (see Figure 18).

Table 3 | Examples of assistive augmentation, human augmentation, and human enhancement

Assistive augmentation	Assistive augmentation	Human enhancement
Glasses / Contact lens	Augmented reality (AR), virtual reality (VR), and extended reality (XR)	Retinal prosthesis, intraocular lens

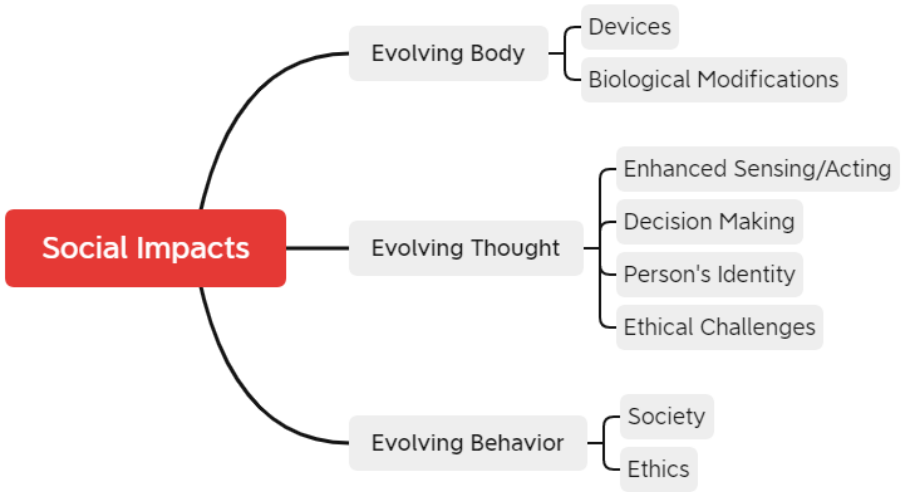


Figure 18 | The social impacts of evolving human body, thought, and behaviour

For an evolving body, human augmentation could enhance human capabilities by additional hardware (wearables, implants, etc.) or biological modifications (surgical, genetic, reproductive, etc.). For an evolving thinking capacity, brain-computer interface, neurostimulation, wearable devices, and other human augmentation technologies could not only enhance physical capabilities throughout the human body, but also lead to an in-depth change of definition of humanity and society. Societal questions are raised, for example, how human beings interact, and society runs following the intervention of the next level human-machine interface in which artificial components could be involved in sensing, decision making, and acting.

We also face ethical problems and risks, especially in the fields of neuroscience and neuroengineering. As brain implants and neurostimulation could alter the existing brain circuits, ethical concerns about personal identity, privacy leaking, and unwanted mind controlling are drawing public attention. For evolving behaviours, the increasing use of artificial intelligence, robots, implants, and wearables may propel humans to behave differently in both positive and negative ways. For example, continuous and ubiquitous monitoring, enhanced human-machine interfacing, and speeded human-human communication could form a more collaborative world or one facing diversity challenges.

4.1.2.1 The United Nations Sustainable Development Goals (UN SDGs)

The goals and technologies related to human augmentation exactly fit into the scope of Sustainable Development Goals proposed by the United Nations. Various types and product categories in this field, such as VR and AR glasses, wearable devices, and exoskeletons enhance mental and/or physical interactions between people. Certain applications, e.g. brain-computer interfaces, may even change the mode of communication in society.

To explore the connection between technologies in WG4 and the UNSDGs would be meaningful in two ways: (1) To understand how the related technologies would impact society, especially in building greener, more inclusive economies, and a stronger, more resilient society. (2) To propose/initiate a standardization framework aligned with the UNSDGs.

SDG 3: Good health and well-being: Brain-computer interfaces for medical and clinical usage. Wearable devices for sports and personal healthcare. Exoskeletons for rehabilitations, etc.

SDG 4: Quality education: Brain-computer interfaces for schools and classes. VR, AR, and XR tools for education, etc.

SDG 9: Industry, innovation and infrastructure: Power suit (powered exoskeletons and robots for enhancing strength). Industrial scenarios involving brain-computer interfaces, wearable devices, and VR/AR/XR, etc.

Filling the gaps from innovation chain to industry chain, the implementation of UNSDGs in the process of designing, manufacturing and applicating human augmentation technologies would not be possible without continued support from international standardization. See 4.4.1 Outlooks.

4.2 Technology and market trends

4.2.1 State-of-the-art technologies

Augmentation categories

Brain-computer interfaces, wearable devices, brain implants, exoskeletons, and many more technologies have been applied in the human augmentation scenario, and various classifications have been proposed (see Table 4). Sensing, actuating, thinking, communicating among human-human and human-machine are common taxonomy and categories in recent literatures. Each augmented capability is mapped into relevant existing human organs, such as the sensory and

Table 4 | Augmentation categories in recent review articles

Review article	Categories			
	1	2	3	4
(Guerrero et al., 2022)	/	Physical Capabilities	Intellectual Capabilities	Social Capabilities
(Boeck & Vaes, 2021)	Sensory Augmentation			
(Valeriani et al., 2021 [97])	Human Performance		Mental Workload	
(Raisman et al., 2019 [98])	Augmented Senses	Augmented Action	Augmented Cognition	/
(Paragoned & Koucheryavy, 2021 [99])	Augmented Sensor Abilities	Augmented Physical Abilities	Augmented Mental Abilities	/
(Lee et al., 2018 [100])	/	Body Augmentation	Brain Augmentation	Social Augmentation
(Daily et al., 2017)	Advanced Sensory Capabilities	Enhanced Muscle Capabilities	Improved Brain Function	Novel Communication Channel

motor system, or high-level human behaviours, such as the mind, communication, and sociality. In the present study, we considered all possible aspects to conclude with four categories: sensory, motor, mental, and social (see Figure 19).

Sensory. Sensing is the most common human augmentation technology and widely mentioned in the literature. Through advanced sensors and sensing technologies, biophysical, biochemical, and environmental signals can be captured and transformed into information and commands in the augmented system, enabling the human sensory system to be restored, substituted, and enhanced.

Motor. Physical actuators, which are usually the output of human augmentation systems, execute the commands like the original human motor system does. Robots and exoskeletons are the major players in this category.

Mental. Restored and augmented abilities related to the central nervous system are considered in this category, including decision making, learning and memory, etc. Cognition and mental/psychological/mood states are the most common examples and cases.

Social. A relatively novel sector of human augmentation refers to enhanced abilities in communications (including both human-human and human-machine interactions), collaboration, empathic and mutual understanding. Though it is not thoroughly studied, intensive ethical concerns and risk management challenges have been raised.

Augmentation phases

According to functioning levels, different phases could be defined in human augmentation from recovering the original abilities to substituting the human organs and functions, up to enhancing and empowering new abilities (see Figure 20).

Phase 1. Recovering, repairing the existing impaired human physiological functions. Most assistive technologies in this phase, e.g., rehabilitation exoskeletons, focus on rehabilitation scenarios in hospitals and at home.

Phase 2. Replicating, substituting human functions and organs. Power augmentation exoskeletons (rehabilitation exoskeletons excluded) and artificial organs are common examples at Phase 2. External devices that supplement daily living capacities, e.g., smart watches and VR glasses, are also considered as typical use cases.

Phase 3. Enhancing, outperforming human capabilities. Applications aiming at exceeding human abilities are performed using emerging technologies from mechanical engineering to genetic engineering. # Examples.

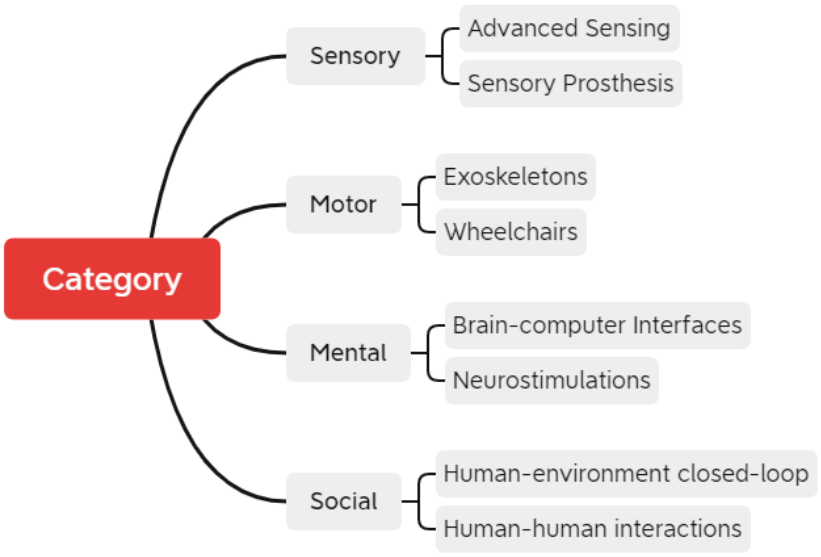


Figure 19 | Four categories of human augmentation

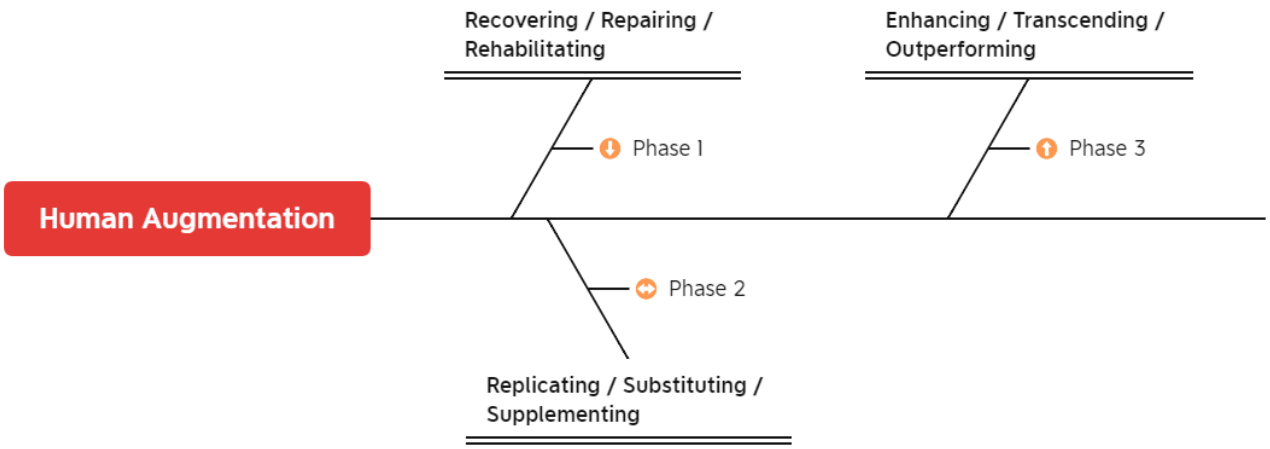


Figure 20 | Augmentation phases

Current statistics

Graciela Guerrero et al., carried out a comprehensive literature review published in January 2022 [101]. A total of 16,914 publications ranging from 2009 to 2020 were covered in the review, which drew on the Association for Computing Machinery (ACM), Institute of Electrical and Electronics Engineers (IEEE), and Scopus databases. Clearly, the topic of human augmentation continues to undergo rapid development, with a peak in 2017 (see Figures 21 and 22).

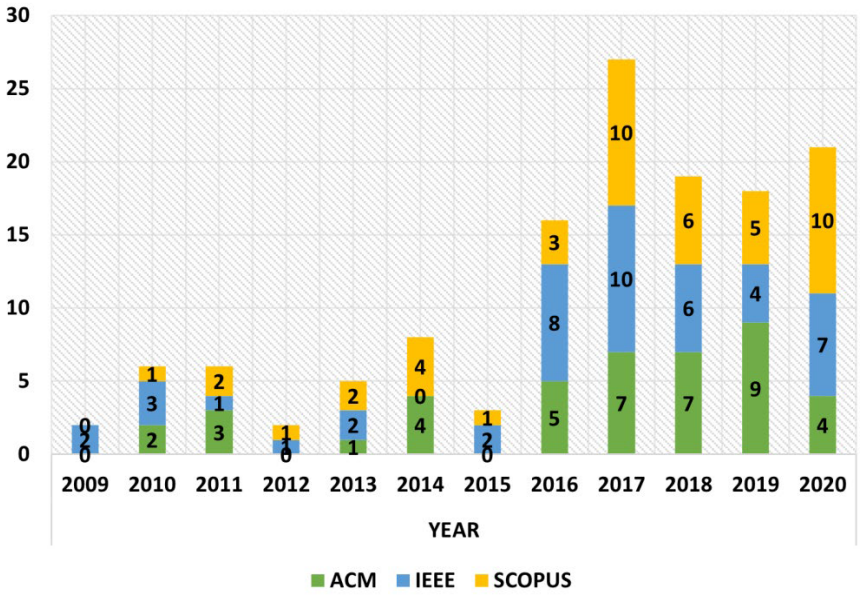


Figure 21 | Research articles mentioning human augmentation

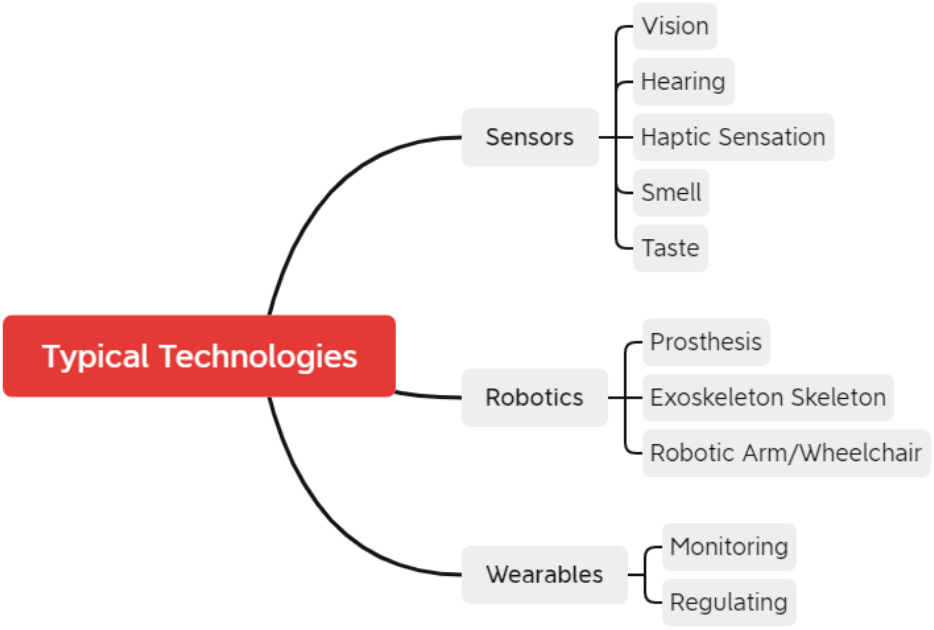


Figure 22 | Typical technologies

4.2.2 Market trends

"Augmentation" is generally a broad concept that can be ambiguous. Academically, human augmentation technologies refer to two general types of technologies: rehabilitative technologies, which work as therapeutic measures to help people recover from certain serious health incidents, and assistive technologies, which aim at improving human performance in certain areas or aid people with specific disabilities.

In this report, we preliminarily surveyed 35 existing products involving human augmentation technologies The detailed categorizations are listed in Figure 23.

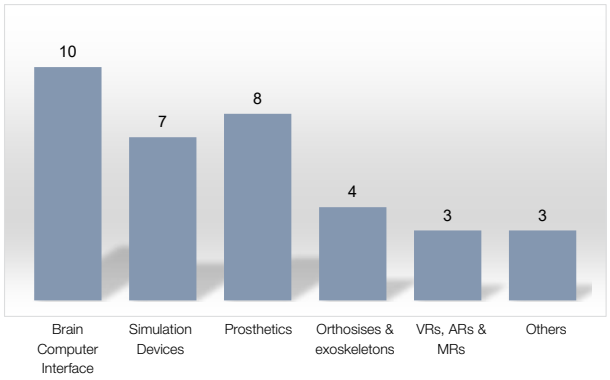


Figure 23 | Categorization of technologies surveyed in this report

We noticed that brain-computer interfaces (BCI) involved the greatest number of human augmentation technology applications, containing both invasive interfaces that require surgical procedures in order to be implanted and non-invasive interfaces that suffer from performance and stability issues with non-stationary signals such as scalp EEG. The majority of BCI products, electrical/magnetic stimulation devices, prosthetics as well as orthosis & exoskeletons are generally used for specialized medical conditions. Therefore, human augmentation technologies with specific medical applications produced the majority of human augmentation technology products. There exist only a few consumer level products designed for entertainment applications, which focus on wearable display products. Other forms of products are scarce, for example, external control devices utilizing surface EMG signals or other biomedical measures, such as body movement monitors.

4.3 Brain-computer interfaces

Brain-computer interfaces are typical human augmentation products, which enable direct connections between the user and external environment. Such direct connections can be used either for human ability restoration in people with various types and levels of disabilities, or for human performance improvement by controlling external devices.

BCIs can generally be categorized into invasive (which requires surgery to implant electrodes) and non-invasive (which mounts devices on the scalp).

(A) Invasive BCI products

Invasive BCI products usually require surgery in order to be implanted into designated recording/stimulation sites. Benefitting from less physical distance and body tissue/structure barriers, invasive BCIs generally have good signal-to-noise ratio and spatial resolution, compared to non-invasive ones. However, surgical implantation may raise medical and ethical issues due to the unclear long-term implantation and immune reaction.

The Link

Neuralink [102] is a startup company founded by Elon Musk in 2016. Their product, the Link (see Figure 24), is now probably the most famous BCI product known to the general public. With sparse updates prior to the unveiling of the Neuralink devices unveiling in 2019, Neuralink allows the brain to interface directly with a computer. In 2020, Neuralink published a YouTube video of a

macaque monkey called “Pager” playing the video game Pong with its mind.

According to the narrator of the video, the nine-year-old monkey, which had two Neuralink devices put on each side of his brain about six weeks before the video recording, learned how to use a joystick to move a cursor to targets on a screen in exchange for a banana smoothie delivered through a straw. Based on the recent announcement, Neuralink is preparing to start human clinical trials with the Link device.

Existing standards foundation: wireless data transmission is used, possibly the IEEE 802.x series may apply, but as yet this is not specified on the product webpage.

BrainGate

BrainGate [103] creates and tests devices utilizing an array of micro-electrodes implanted in the brain. Their research level product (see Figure 25) has shown that the neural signals associated with intentional complex limb movements can be “decoded” in real-time and used to operate external devices with sensory feedbacks. Their investigational system, called BrainGate (an “investigational device limited by federal law to investigational use) has been tested on people with spinal cord injuries, brainstem strokes, and amyotrophic lateral sclerosis (ALS) to control a computer cursor simply by thinking about the movement of their own paralyzed hand and arm. In

Figure 24 | The link product from Neuralink (Source: https://neuralink.com)

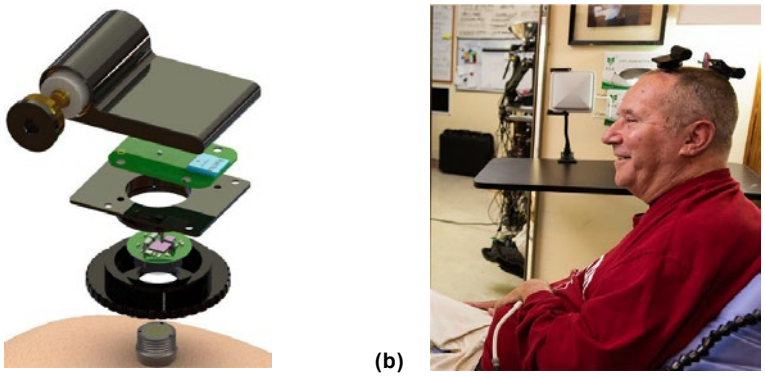


Figure 25 | The BrainGate system, (a) system configuration, (b) participant with system implanted (Source: BrainGate/Nurmikko Lab / Brown University

early clinical research, the BrainGate has provided intuitive control over advanced prosthetic limbs, and provided people suffering from paralysis with easy control over powerful assistive movement and communication devices. An exciting goal is to enable naturally-controlled movements of paralyzed limbs. In addition, a new generation of wireless medical neuro-technologies are under-investigation which are intended to be used in recording and monitoring neural activities and assisting the diagnosis and management of neurologic disease.

Existing standards foundation: wireless power transmission is used, possibly the IEEE 802.x series may apply, but as yet this is not specified on the product webpage nor in their publications.

Synchron

Synchron [104] has developed an endovascular brain computer interface that can access every corner of the brain using its natural highways, the blood vessels. The device's breakthrough platform launches a new frontier for the treatment of neurological diseases: neurointerventional electrophysiology (Neuro EP). Their technology mainly targets three medical verticals: neuroprosthetics (see Figure 26), neuromodulation, and neurodiagnostics. The Neuro EP platform is built on the stentrode™, an endovascular electrode array designed to record or stimulate the brain or nerves from within the blood vessels. The device is designed to be incorporated into the wall of the blood vessel like a tattoo. Similar to a stent, it is designed not to cause long term inflammation or trauma to the brain.

Figure 26 | The brain.io™ motor neuroprosthesis product (Source: https://synchron.com/technology/brain-io)

Existing standards foundation: wireless data and power transmission is used, possibly IEEE 802.x series may apply, but as yet this is not specified on the product webpage.

Medtronic

Medtronic Inc. [105] is one of the world's leading medical technology companies, controlling more than half of the $8 billion global heart-pacing market, which includes pacemakers and defibrillators. The company's products and services also include implantable neurological pain, tremor, spasticity, and incontinence management systems; heart valves; catheters and stents for angioplasty; implantable drug administration systems; hydrocephalic shunts; autotransfusion equipment; disposable devices for handling and monitoring blood during surgery; and instruments and devices used in surgical procedures of the head and spine and by ear, nose, and throat physicians.

Medtronic Inc. is also very famous for its deep brain stimulation (DBS) products (see, for example, Figure 27. By channelling electrical stimulation to designated brain regions, neurological disorders such as Parkinson's Disease, tremors, dystonia, obsessive-compulsive disorders, and epilepsy can be alleviated. These devices are usually designed to work autonomously after implant surgery, detecting signatured early-stage irregular neurological signals and applying pre-programmed electrical stimulation to alleviate the onset of neurological episodes.

Figure 27 | The Percept™ PC DBS system is one of the DBS products developed by Medtronic (Source: https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/deep-brain-stimulation-systems/percept-pc.html)

Existing standards foundation: wireless data and power transmission is used, possibly the IEEE 802.x series may apply, but as yet this is not specified on the product webpage.

NeuroPace

Founded in California US, NeuroPace [106] is a commercial-stage medical device company focused on transforming the lives of people suffering from epilepsy by reducing or eliminating the occurrence of debilitating seizures. According to their website, the RNS® System (see Figure 28) is the only FDA-approved epilepsy device that delivers personalized treatment by responding to abnormal brain activity and provides EEG data that can help improve patient care.

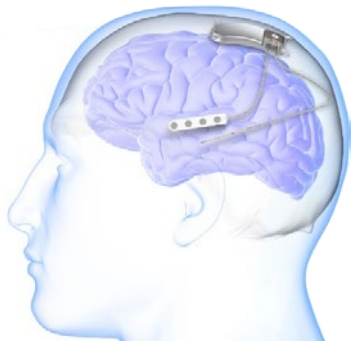


Figure 28 | The RNS® system developed by NeuroPace (Source: https://neuropace.com/patients/neuropace-rns-system)

Existing standards foundation: wireless data and power transmission is used, possibly IEEE 802.x series may apply, but as yet this is not specified on the product webpage.

(B) Non-invasive BCI products

Emotiv

Founded in 2011 and headquartered in San Francisco, EMOTIV [107] is a bioinformatics company advancing understanding of the human brain using electroencephalography (EEG). Products aim to track cognitive performance, monitor emotions, and control both virtual and physical objects via machine learning of trained mental commands. Applications for the EMOTIV technology and interface span an extensive variety of potential industries and applications – from gaming to interactive television, everyday computer interactions, hands-free control systems, smart adaptive environments, art, accessibility design, market research, psychology, learning, medicine, robotics, automotive, transport safety, defense and security (see, for example, Figure 29).

Figure 29 | EMOTIV EPOC X product, with 14 channel saline-based electrodes (Source: https://www.emotiv.com/epoc-x/)

Existing standards foundation: Bluetooth data transmission is used, possibly Bluetooth standards may apply, but as yet this is not specified on the product webpage.

g.tec

g.tec [108] medical engineering was founded in 1999, Austria. Following presentation of the first portable BCI system in 1999 at the BCI Meeting in Rensselaerville, New York, g.tec's products have been internationally used in clinical environments or for research purposes such as analysis of brain, heart or muscle activity, assessment of severe brain injuries and disorders of consciousness, motor rehabilitation after stroke, neuromarketing, deep brain stimulation, brain mapping, neuro prosthesis control, communication, painting and closed-loop invasive and non-invasive BCI experiments. g.tec develops and produces high-performance brain-computer interfaces and neuro-technologies for invasive and non-invasive recordings for research or clinical purposes.

In addition to biosignal amplifiers, invasive/non-invasive stimulators and wearable EEG headsets, g.tec offers CE-certified and FDA-cleared user-ready applications which are used in hospitals and rehabilitation centers for rehabilitation after stroke, brain assessment and communication of coma/ locked-in patients or for brain mappings before and during neurosurgery (see Figure 30).

Figure 30 | The g.Nautilus EEG amplifier developed by g.tec (Source: g.tec)

Existing standards foundation: wireless data (WIFI) and power transmission is used, possibly IEEE 802.11 standards may apply, but as yet this is not specified on the product webpage.

Neurosky

Founded in 2004, NeuroSky [109] is a privately held, Silicon Valley-based company with offices throughout Asia and Europe. NeuroSky aims to break the boundaries of health and wellness tracking and analysis by enabling a new generation of consumer wearables and mobile devices. Their products include biosensors, biometric algorithms, reference designs, and big data analytics enabling leading-edge innovation in mHealth products and services for measuring body and mind performance (see Figure 31).

Figure 31 | The Neurosky, a consumption level electronics (Source: http://neurosky.com/ biosensors/eeg-sensor/biosensors/)

Existing standards foundation: wireless data transmission is used, possibly IEEE 802.11 or Bluetooth standard data communication may apply, but as yet this is not specified on the product webpage.

Muse (InteraXon)

InteraXon is a company based in Toronto. In 2014, InteraXon launched their first product, Muse: a brain-sensing headband (see Figure 32). Muse is a brain fitness tool that senses the brain like a

heart monitor reads a person's heart rate. Muse uses short, fun sessions to help calm the mind, increase focus and composure and reduce stress. In fact, the Muse band constitutes a compact electroencephalography (EEG) system. By leveraging improvements in dry sensor technology, Bluetooth and battery life, as well as significant advances in digital signal processing, Muse enables users to easily access and use EEG data, inside and outside the laboratory and in real-world environments. The latest Muse 2 band focuses on meditation applications which provide real-time feedback on the users' brain activity, heart rate, breathing, and body movements to help build a consistent meditation practice.

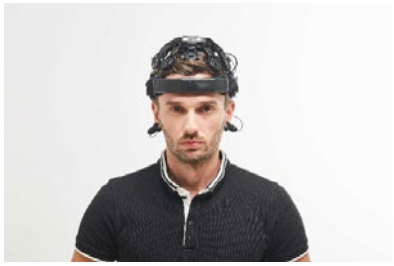
Figure 32 | The Muse 2 band developed by InteraXon (Source: https://choosemuse.com/muse-2/)

Existing standards foundation: wireless data transmission is used, possibly IEEE 802.11 or Bluetooth standards may apply, but as yet this is not specified on the product webpage.

Neuracle (Borui Kang Technology (Changzhou) Co., Ltd)

Neuracle [110] Technology (Changzhou) Co., Ltd. was founded in November 2011 and headquartered in Changzhou, China. The core team is from Tsinghua University Neural Engineering Laboratory. Neuracle develops, produces, sells and provides technical services for brain-computer interface (BCI) system-related equipment with its own innovative technology, specialized in the research and development, production, sales and technical services of related equipment of brain-computer interface systems (see Figure 33). The company provides professional and complete solutions for neuroscience innovation research and clinical neurological diagnosis, treatment and rehabilitation. Up to now, Neuracle has become a leading company in the field of brain-computer interface in China.

(a)



(b)

Figure 33 | Neuracle EEG acquisition system products, (a) gel-based EEG wireless acquisition system; (b) dry electrode EEG wireless acquisition system (Source: http://www.neuracle.cn/nkxxl)

Existing standards foundation: wireless data transmission is used, possibly IEEE 802.11 and Bluetooth standards may apply, but as yet this is not specified on the product webpage.

OpenBCI

OpenBCI [111] is a cost-effective open-Source brain-computer interface platform, following a successful Kickstarter campaign in late 2013. OpenBCI boards (see Figure 34) can be used to measure and record electrical activity produced by the brain (EEG), muscles (electromyography: EMG), and heart (ECG), and is compatible with standard EEG electrodes. The OpenBCI boards

can be used with the open Source OpenBCI GUI, or they can be integrated with other open-Source EEG signal processing tools. OpenBCI has been used to control a HexBug robot using SSVEPs (Steady State Visually Evoked Potentials). Locked-in graffiti artist Tempt One has used the OpenBCI and the low-cost Eyewriter eye-tracking system to continue to draw after being diagnosed with the degenerative nerve disorder ALS.

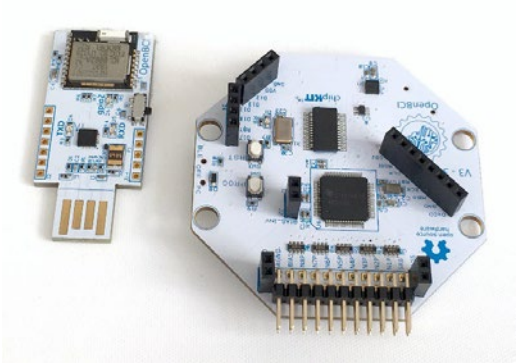


Figure 34 | The OpenBCI system (Source: https://shop.openbci.com/products/cyton-biosensing-board-8-channel)

Existing standards foundation: wireless data transmission is used, a standard Bluetooth 4.n (BLE) connection is used when utilizing Bluetooth module, and IEEE 802.1 b/g/n is used when utilizing WIFI Shield module.

Brain Talker

China Electronics Cloud Brain (Tianjin) Technology Co Ltd. and Tianjin University [112] worked together on the Brain Computer Code Chip (BC3) and assert it is a fully independent intellectual property (see Figure 35). The purpose of the chip, and its design brief, is to improve brain-computer interface technology. Devices powered by the BC3 will thus be able to process electrical signals from a human brain and decode user-intent. The chip does this without the use of the human body's natural neuromuscular pathways. The practical use cases for a dedicated accurate brain reading chip could be rather wide-ranging. The Tianjin University blog reckons the BC3 will be used in portable devices, and even wearables. Some obvious uses would be in devices and gadgets that are designed for those with limited mobility, in medical devices, as well as in games and entertainment devices.

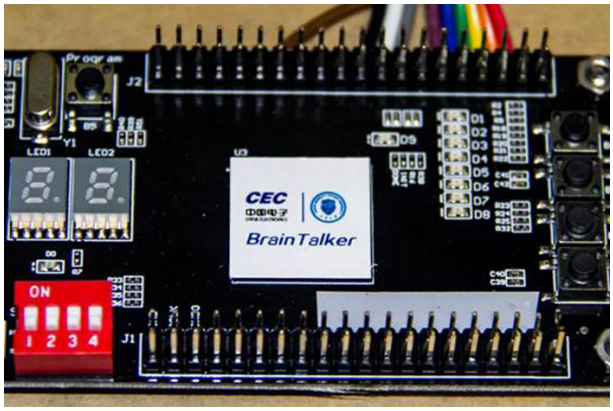


Figure 35 | BrainTalker chip, fully integrated BCI in one chip (Source: http://www.tju.edu.cn/english/info/1010/4245.htm)

Existing standards foundation: RISC-V standard instruction set architecture (ISA) is used, additional standards like IEEE Std 1241-2000 may apply.

NIRx

It is worth mentioning that not all BCI applications are based on EEG. Brain hemodynamic or brain blood oxygen consumption can be also used as an indirect imaging technique for neuroscience research, and both are also very important methods for diagnosing brain hemodynamic dysfunction such as stroke risk level etc. Considering the portability of functional magnetic resonance imaging (fMRI) and traditional functional near-infrared spectroscopy (fNIRS) systems, the author only presented NIRx as an example of brain hemodynamic-related products.

Founders of NIRx [113] started their research on fNIRS in 1988, in New York . Twelve years after their initial scientific discovery in 2000,

the research group formed NIRx to focus and promote the group's instrumentation and software advancements (see Figure 36). Today, NIRx offers a host of integrated technology solutions that support a wide range of investigative aims. Whether the goal is to explore early language acquisition in infants, motor movements in the natural environment, BCI applications or new understandings involving coordinated actions between sensory systems, NIRS imaging solutions from NIRx constitute a comprehensive resource that meet the most demanding applications.

Figure 36 | The NIRSports device developed by NIRX, which can be scaled to high-density arrangement with 48 Sources and 48 detector arrangement with 3 connected fNIRS NIRSport2 devices (Source: NIRSports)

Existing standards foundation: wireless data transmission is used, a standard IEEE 802.1 b/g/n may be used in the product.

Stimulation devices

Commercially available stimulation devices are nowadays quite common to assist users with certain function impairments or to improve human abilities. Most of these consumer level devices deliver magneto-electrical fields to designated areas of the brain, which leads to activation or inhibition of the neurons. Some other devices exploit other physical stimulations such as temperature, sound or light.

(C) Functional electrical stimulations (FES)

The functional electrical stimulation (FES) or transcutaneous electrical nerve stimulation (TENS) or neural muscular electrical stimulation (NMES) is one type of technology that applies small electrical current to the user's muscle (or a group of muscles) via electrodes, which causes the muscles to contract without voluntary intention.

In addition, some devices use very low intensity electrical current for pain relief therapy. Those devices are more commercially available for customers, ranging from USD 30-100.

Hasomed

Hasomed [114] is a company located in Germany. Hasomed develops, produces and markets solutions for neurological rehabilitation and for the prevention and therapy of neurodegenerative diseases. Their main product is RehaMove, a FES system for gait analysis and gait therapy, which makes Hasomed one of the leading companies on the market (see Figure 37).

Figure 37 | The RehaMove device used in cycling training (Source: https://www.optimalmedical.com.sg/product/rehamove-rehabilitation-system/)

Training with RehaMove is an effective method for relieving muscle spasms, preventing or avoiding atrophy due to immobilization, increasing the local blood flow or increasing or maintaining the range of motion. Therapy with functional electrical stimulation is for example recommended in Germany and part of the evidence-based S2 guideline “Rehabilitation of the lower extremities, standing and walking function in people with paraplegia”.

Existing standards foundation: USB is used for data communication and control, additional standards may apply.

(D) Transcranial Magnetic Stimulation (TMS)

Neuronetics

Founded in 2013, US, Neuronetics [115] has pioneered and refined the NeuroStar TMS Therapy system (see Figure 38). This non-invasive, non-systemic treatment for depression uses a highly focused, pulsed magnetic field to stimulate function in targeted brain regions. NeuroStar TMS Therapy is a safe and effective outpatient procedure, performed in a physician's office with each treatment lasting about 37 minutes daily for four to six weeks.

Figure 38 | The NeuroStar device developed by Neuronetics (Source: https://neurostar.com/neuronetics/how-it-works/)

Existing standards foundation: not clear. No such information is provided on their website.

eNeura

eNeura [116] is a privately held medical technology company, which is pioneering the use of portable, non-invasive transcranial magnetic stimulation (TMS) devices for treatment of migraine. Prescribed by physicians but designed for patient use, it is the first truly portable, convenient TMS product that will allow migraine patients to administer treatment as needed at home, in the office or on the go. The sTMS mini is placed at the back of the head for less than a minute, generating a focused, single magnetic pulse that induces a mild electric current in the back of the brain (see Figure 39). Leaders in the field of headache medicine believe this targeted signal depolarizes – or short circuits – the hyperexcitability in areas of the brain associated with migraine and the abnormal brainwaves typical in cortical spreading depression (CSD), which is associated with migraine aura.

Existing standards foundation: not clear. No such information is provided on their website.

Figure 39 | The sTMS mini device developed by eNeura (Source: https://www.eneura.co.uk/getting-started-with-the-stms-mini/)

(E) tDCS/tACS

Some studies suggest that transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) can be used to modulate cortical excitability, producing facilitatory or inhibitory/excitation effects upon a variety of behaviours.

tDCS uses constant, low direct current delivered via electrodes on the head. It was originally developed to help patients with brain injuries or neuropsychiatric conditions such as major depressive disorder.

tACS is expected to synchronize (by one single resonance frequency) or desynchronize (e.g., by the application of several frequencies) cortical oscillations. If applied long enough it may cause neuroplastic effects. In the theta range it may improve cognition when applied in phase. Alpha rhythms could improve motor performance, whereas beta intrusion may deteriorate them. TACS with both alpha and beta frequencies have a high likelihood to induce retinal phosphenes. Gamma intrusion can possibly interfere with attention. Stimulation in the “ripple” range induces intensity dependent inhibition or excitation in the motor cortex (M1) most likely by entrainment of neuronal networks, whereas stimulation in the low kHz range induces excitation by neuronal membrane interference. tACS in the 200 kHz range may have a potential in oncology.

Neurocare

Neurocare [117] is active in the fast-growing market for neurotherapy, which is a non-invasive option for mental health, pain and rehabilitation using neuromodulation technologies integrated with psychotherapy. Neurocare is specialized in applying neuromodulation techniques (such as quantitative electroencephalography (QEEG) assessments) to improve diagnostics for choosing the right therapy (prognostics), as well as treatment for psychiatric disorders, pain management and rehabilitation via its international network of Neurocare clinics. They also offer training for healthcare professionals, researchers and clinicians in the area of neuromodulation techniques supported by industry-leading technology.

Neurocare’s technology brand Neurocare has long been a leader in EEG, neurostimulation and neurofeedback technology. Its approach and implementation of slow cortical potentials (SCP) in the treatment of attention deficit hyperactivity disorder ADHD and epilepsy is considered the world standard in SCP-neurofeedback. Moreover, neuroConn is the leading technology brand in transcranial electric stimulation, co-determining the research in tDCS, tACS and transcranial random noise stimulation (tRNS). In addition, as an original equipment manufacturer (OEM), its technology is commercially used in pain and rehabilitation management (see Figure 40).

Figure 40 | DC-STIMULATOR, a device developed by neurocare for tDCS applications (Source: https://www.omnia-health.com/)

Existing standards foundation: Basic electrical/electronic standards may apply. No such information is provided on their website.

Neuroelectrics

Neuroelectrics [118] was founded in Barcelona in 2011 and opened another office in Boston in 2014. The company is privately held and is now selling in more than 45 countries with an ISO 13485 manufacturing site. Nowadays, Neuroelectrics is a high-tech company offering the best in class non-invasive and high-definition electrical brain stimulation technology for personalized neuromodulation. By measuring and modifying brain function, it aims to restore brain health, minimize disabilities and create a better life for patients.

Based on the leading clinical evidence, Starstim is a renowned and trusted solution for pioneers in pain, epilepsy, Alzheimer's, stroke, rehabilitation, depression and addictive disorders research with numerous publications every year. With the ability to integrate with all-in-one combined transcranial electric stimulation and electrocardiography (tES-EEG), Starstim (see Figure 41) can produce freely customizable tES waveforms and montages allow for advanced investigations with simultaneous monitoring as well as closed-loop applications, with exclusive model-driven tES protocol optimization and personalization to maximize the effects of stimulation and produce accurate results for research level experiments.

Figure 41 | The Starstim device produced by Neuroelectrics (Source: https://www.neuroelectrics.com/solutions/starstim)

Existing standards foundation: Basic electrical/electronic standards may apply. No such information is provided on their website.

tVNS

tVNS (transcutaneous Vagal Nerve Stimulation) is a general term that refers to the use of a small electrical current (applied to the skin) to stimulate the vagus nerve, which runs between the brain and the internal organs of the body. Stimulation of the vagus nerve has been shown to increase parasympathetic activity and decrease sympathetic activity. Vagal nerve regulation of metabolic homeostasis (balance) can be appreciated via its control of heart rate; increasing vagal activity has been associated with decreases in heart rate. This is significant in autonomic dysfunction, which is characterized by an overactive sympathetic response.

However, the industry for tVNS seem still unmature, multiple companies have produced similar devices for the same application. The author presents NEMOS developed by NEUROPIX [119] as one example for treatment of epilepsy and migraine (see Figure 42).

Figure 42 | The NEMOS device developed by NEUROPIX (Source: https://www.neuropix.asia/tvns)

Existing standards foundation: Basic electrical/electronic standards may apply. No such information is provided on their website.

PoNS

PoNS™ [120] (short for Portable Neuromodulation Stimulator) is an innovative medical device, inclusive of a controller and mouthpiece, which delivers mild electrical stimulation to the surface of the tongue. Previously only available in Canada, PoNS™ is now authorized in the US for the treatment of gait deficit due to mild-to-moderate symptoms of multiple sclerosis. The device is non-pharmaceutical, is safe and well tolerated and used in conjunction with a supervised therapeutic exercise program (see Figure 43). PoNS™ works to improve gait deficiency.

PoNS was developed by Helius Medical Technologies, Inc., ("Helius"), which is a neurotech company in the medical device industry, focused on neurological wellness. Helius' origin stems from the early 1990s, and the pioneering work in neuroplasticity at the Tactile Communication and Neurorehabilitation Laboratory, ("TCNL"), at the University of Wisconsin-Madison. The company became public in June 2014 and raised money to perform formal registrational clinical trials and other scientific activities to support regulatory clearance in the US, Canada, Europe and Australia. Helius achieved clearance for PoNS™ in Canada in Q4 2018.

Figure 43 | A participant using the PoNS device produced by Helius Medical Technologies, Inc (Source: https://heliusmedical.com/index.php/divisions/heliusmedical/the-pons-device)

Existing standards foundation: Basic electrical/electronic standards may apply. No such information is provided on their website.

4.3.1 Prosthesis

Prosthetics refers to the field of research and expertise in the production of artificial limbs (protheses) that replace or enhance the function of persons with limb loss. Limb prosthetics covers both upper- and lower-limb prostheses, which can provide replacement due to various levels of amputation.

(A) Upper limb

Upper-limb prostheses can be categorized into three main types: passive, body powered and myoelectric devices, in which body-powered and myoelectric devices are more well developed in recent years.

Body-powered prostheses are controlled with the power of an individual's residual limb, shoulder girdle, and upper-body muscles (see Figure 44). The prostheses work by attaching a harness and cable around the opposite shoulder or hands, enabling the individual to meet the needs of social activities, sports, intricate tasks, or heavy-duty labour and helping the wearer regain their independence.

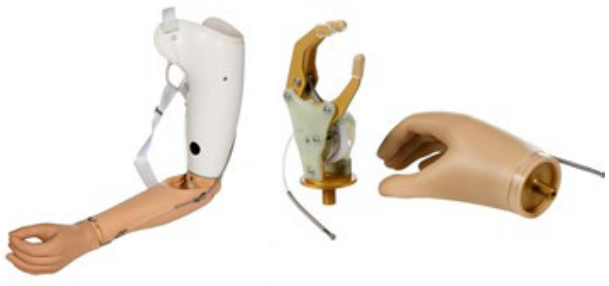


Figure 44 | Body-powered arm and hand (Source: https://www.ottobockus.com/prosthetics/upper-limb-prosthetics/solution-overview/body-powered-prosthetic-solutions/)

Ottobock

Ranking first in global orthopedic prosthetics market, Ottobock Healthcare provides intelligent design option for people with upper limb loss. As shown in Figure 45, the enhanced Bebionic hand by Ottobock with 14 different grip patterns and hand positions can perform daily functional activities easily. Individual motors in each finger allow the wearer to use natural, coordinated grasp patterns. These movements are further enhanced by proportional control, which enables you to adjust the speed and grip force of the hand during daily tasks. Producing softer muscle signals will result in slower movement of the hand and less grip force over an object, whereas stronger signals will produce faster movement and higher grip force.

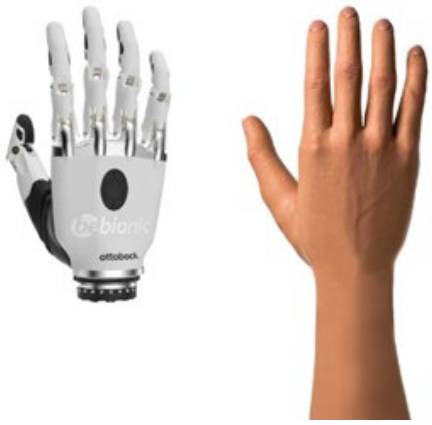


Figure 45 | The Bebionic Hand [121] (Source: https://www.ottobock.com/en-us/product/8E70)

Existing standards foundation: No such information is provided on their website.

(B) Lower limb

Ottobock

Ottobock [122] provides a series of prosthetic legs for various levels of need of amputees and other users. Above-knee prosthesis with: C-Leg 4, X3 waterproof prosthesis, below-knee prosthesis, above-knee water resistant prosthesis, above-knee fitness prosthesis.

The Ottobock C-Leg (see Figure 46) is the world-leading microprocessor knee launched in 1997. Intuitive stance automatically activates to fully block the C-Leg from bending or buckling while standing in order to allow persons to distribute the weight evenly between both legs. The patented inertial measurement unit (IMU) provides stability control when taking steps backwards. The sensors detect motion patterns and actively control and adjust resistance during swing phase. The benefits of microprocessor-controlled prosthetic knees (MPK) have been well established in scientific studies that indicate the use of MPKs may significantly reduce uncontrolled falls by up to 80% and assist persons to walk approximately 14% to 30% faster on different terrains.

Figure 46 | The Ottobock C-Leg (Source: https://www.ottobock.com/en-us/product/3C88-3~23C98-3)

Existing standards foundation: No such information is provided on their website.

(C) Retina implants

Argus II

Argus II[3] was approved by the FDA in 2013, providing rudimentary vision for blind patients and the hope that future advances in the technology will help even more patients.

The approved device was manufactured by Second Sight Medical Products, and uses a small electronic chip surgically implanted onto the surface of the retina. The patient wears glasses containing a small video camera that wirelessly transmits images to the chip. The images look like multiple white spots of light.

In the Argus II (see Figure 47), the resolution is limited, as the device has 60 pixels. It can enable patients with the progressive, hereditary disease retinitis pigmentosa, who previously could see little or no light, to read large letters, determine the location of moving objects or people, and detect street curbs.

Figure 47 | The Argus II system (Source: https://chicago.medicine.uic.edu/argus-ii-retinal-prosthesis-system-on-trial-at-the-ieei/)

Existing standards foundation: Basic electrical/electronic standards may apply. No such information is provided on their website.

(D) Hearing aids

Hearing aids can also be categorized into non-invasive and invasive depending on the level and type of the hearing impairment. Basic hearing problems can be treated with a hearing aid mounted on the ear, which works like a pair of small speakers in the external auditory canals. However, for patients experiencing a more severe hearing impairment, for which amplification of sound volume may not be effective, a cochlear implant that translates sound into an electrical stimulation sequence is the common clinical treatment.

Non-invasive hearing aid

Oticon

Oticon [124] is a renowned Danish company founded in 1904, which focuses on hearing aid technologies. From the onset of the company, its core aim was to assist those experiencing hearing loss. By the early 1970s, Oticon had become the world's leading manufacturer of the "Behind the ear" (BTE) hearing aid (see Figure 48).

Figure 48 | MiniRITE T style hearing aid, one device from Oticon More product series (Source: https://www.hearingsolutions.philips.com/en-ca/hearing-aids/hearing-aids/minirite)

3 Second Sight Medical Products has been reissued as Cortigent, which has discontinued the Argus II. https://www.cortigent.com/ [123].

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

Phonak

Foundation of the “AG für Elektroakustik” with corporate headquarters in Zurich, Switzerland in 1947 is the start point of Phonak [125]. Since then, Phonak has been committed to developing, producing, and distributing hearing solutions for more than 70 years (see Figure 49).

Figure 49 | Phonak Virto™ V produced by Phonak (Source: https://www.phonak.com/us/en/hearing-aids/phonak-virto-v.html)

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

Invasive

A cochlear implant (CI) is a surgically implanted neuro-prosthesis that provides a person who has bilateral moderate-to-profound sensorineural hearing loss with sound perception and the opportunity of therapy for improved speech understanding in both quiet and noisy environments. A CI bypasses acoustic hearing by direct electrical stimulation of the auditory nerve. Through everyday listening and auditory training, cochlear implants allow both children and adults to learn to interpret those signals as speech and sound.

Cochlear Limited

Cochlear Limited [126] is a company that provides hearing implant solutions for those with hearing deficiencies. The Cochlear range of hearing devices includes:

Cochlear Implants – Offers Nucleus 7 sound processor to aid moderate to profound hearing loss, along with the Nucleus Kanso Sound Processor (see Figure 50).

Baha Bone Conduction Implants – Offers a wide range of bone conduction implants including the Baha Attract System, Baha Connect System, Baha 5 Power and Baha Softband.

Cochlear True Wireless – Devices designed to assist in difficult hearing situations. The wireless range includes mini microphones, tv streamers, and phone clips.

Carina Middle-Ear Implants – Offers Cochlear Carina System that is implanted under the skin without any external devices.

Figure 50 | CochlearTM Nucleus® 7 developed by Cochlear (Source: CochlearTM)

Existing standards foundation: Basic electrical/ electronic and data transmission standards may apply. No such information is provided on their website.

MED-EL

MED-EL [127] is one of the global innovation leaders in hearing loss solutions. Founded in 1975 in Austria, its systems have helped restore hearing to more than 200,000 individuals worldwide. From its implants to its audio processors and beyond, MED-EL aims to provide a custom-fit solution for each patient. MED-EL offers five hearing systems to provide effective treatment for specific types of hearing loss, with multiple options existing for each system, which are designed for various customers' needs. Similar to Cochlear Limited, MED-EL also categorize its products as cochlear implants, Electric Acoustic Stimulation (EAS) systems (see Figure 51), Vibrant Soundbridge (middle ear implants), BONEBRIDGE (bone conduction implants) and ADHEAR (bone conduction system).

Figure 51 | The EAS system developed by MED-EL (Source: https://www.medel.com/hearing-solutions/electric-acoustic-stimulation)

Existing standards foundation: Basic electrical/ electronic and data transmission standards may apply. No such information is provided on their website.

(E) Orthoses and Exoskeletons and Passive Training Platforms

Burt®

Burt® [128] is the world's first advanced and affordable end-effector robotic manipulator for upper-extremity rehabilitation training and robotics research, which is based on the proven WAM technology developed by Barrett Technology (see Figure 52). With transparent dynamics, low inertia, and mass, Burt® is designed to be a 3D haptic device of choice for those who desire high-fidelity force feedback throughout a human-sized work volume. Burt® supports researchers with new hardware and software modalities necessary for robotics research.

Figure 52 | The Burt® system (Source: https://advanced.barrett.com/burt-research)

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

Kinarm

Kinarm Exoskeleton Lab[4] uses a complex linkage to permit planar movements of the arm in the horizontal plane involving flexion and extension movements at the shoulder and elbow joints. The

4 https://kinarm.com/

Lab was extensively redesigned in 2016 to enhance stiffness and enable full access to the head for TMS, and other neuro-stimulation techniques.

Torque motors record the motion of the arm in the horizontal plane and apply loads to each joint independently. The design provides feedback from, and control of, the shoulder and elbow joints thus permitting loads to be applied to the shoulder and/or elbow joints. Patterns of joint motion are recorded; muscular torques are computed by the system. The hand is free to interact with objects in the environment. One or two robot configurations are available. The use of two Kinarm robots enables comparison of inter-arm performance as well as the study of bimanual coordination.

The application of loads directly to the upper arm and forearm is unique and resulted in issued US, Canadian and European Patents. (US Patent No. 6,155,993; 8,347,710 & 8,800,366; Canadian Patent No. 2,267,821; EP No. 2,150,175).

Kinarm is a solution to the lack of precision and consistency in neurological assessment (see Figure 53). The Kinarm Labs give neuroscientists and clinician-scientists a “window” on brain function that is both objective and quantitative. This allows them to study, with exquisite precision, the sensory, motor and cognitive impact of a wide range of injuries and diseases, such as: stroke, cardiac arrest, cerebral palsy, traumatic brain injury, and Parkinson’s disease.

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

Figure 53 | The Kinarm rehabilitation training platform (Source: https://kinarm.com/kinarm-products/kinarm-exoskeleton-lab/)

Locomat

The system was developed by Hocoma AG [129] and has been reported to be beneficial to post-stroke patients by strengthening their muscles compared to those of a control group. The basic version of the Locomat consists of the Lokomat (Robotic gait orthosis, (see Figure 54 below) and the Lokobasis (body weight support system). It is used in combination with a Woodway treadmill, while the orthosis uses a position-controlled model. The patient’s legs are guided according to a pre-programmed physiological gait pattern.

The Lokomat System utilizes high quality computer-controlled motors (drives) which are integrated in the gait orthosis at each hip and knee joint. Force transducers at the joints accurately measure the interaction between the patient and the Lokomat. The drives are precisely synchronized with the speed of the treadmill. This sensitive system assures a precise match between the speed of the gait orthosis and the treadmill. Moreover, LocomatPro provides an intelligent sensation function where intelligent algorithms adapt robotic assistance in order to create maximum challenge and allow patients to feel their performance.

Figure 54 | The Kinarm rehabilitation training platform (Source: https://kinarm.com/kinarm-products/kinarm-exoskeleton-lab/)

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

SaeboStretch

The SaeboStretch dynamic resting hand split (see Figure 55) helps neurologically impaired clients maintain or improve motion while minimizing joint damage and pain. Its energy-storing technology allows individuals suffering spasticity to stretch comfortably and safely. The company provides three dynamic handpieces for various levels of spasticity and five sizes for adults and children.

Figure 55 | The SaeboStretch orthosis (Source: https://www.saebo.com/shop/pediatric-saebostretch/)

Existing standards foundation: Basic electrical/ electronic standards may apply. No such information is provided on their website.

(F) Miscellaneous technologies for human-machine interaction

EMG

Electromyography (EMG) is a type of compound signal generated from muscle motor unit and nerve cells activation. EMG technology can serve as a diagnostic procedure to assess the health of muscles and the nerve cells that control them (motor neurons). EMG results can reveal nerve dysfunction, muscle dysfunction or problems with nerve-to-muscle signal transmission. With the development of electronics, the possibility of using EMG as a human-machine interaction method is also being investigated.

MYO Armband

The MYO Armband uses EMG sensors to measure and record electrical impulses from a person's muscles. It then interprets this information and allows the person to control various devices based on the gestures. The MYO armband is good for presentations and allows you to communicate with users' hands using MYO's Gesture control. The MYO Armband was developed by Thalmic Labs (founded in 2012) (see Figure 56) and was acquired by Google in June 2020. It is now called North. Since then, the MYO Arm band is no longer commercially available.

Existing standards foundation: wireless data transmission is used, possibly IEEE 802.11 or Bluetooth standards with other basic electronic/ electrical standards may apply, but as yet this is not specified on the product webpage.

Figure 56 | The Myo band developed by Thalmic Labs (Source: https://wearabletech.io/myo-bracelet/)

Figure 57 | Joy-Con controller for Nintendo Switch (Source: https://www.turbosquid.com/3d-models/nintendo-joycon-grip-3d-model-1170254)

Somatic controllers

Cameras, gyros, IMUs and accelerometers can also be integrated into controllers for human machine interfaces. These controllers are now very popular in video gaming devices.

Joy-Con

Joy-Con [130] is a line of controllers for use with the Nintendo Switch system. Two Joy-Con devices can be used independently in each hand, or together as one game Controller when attached to the Joy-Con grip. They can also attach to the main Console for use in handheld mode or be shared with friends to enjoy two- Existing standards foundation: wireless data transmission is used, possibly IEEE 802.11 or Bluetooth standards with other basic electronic/electrical standards may apply, but as yet this is not specified on the product webpage.

player action in supported games. Each Joy-Con device has a full set of buttons and can act as a standalone controller, and each includes an accelerometer and gyro-sensor, making independent left and right motion control possible (see Figure 57).

Existing standards foundation: wireless data transmission is used, possibly Bluetooth standards with other basic electronic/electrical standards may apply, but this is not yet specified on the product webpage.

Kinetic

Kinect [131] is a line of motion sensing input devices produced by Microsoft and first released in 2010 (see Figure 58). The devices generally contain RGB cameras, and infrared projectors and detectors that map depth through either structured light or time of flight calculations, which can in turn be used to perform real-time gesture recognition and body skeletal detection, among other capabilities. They also contain microphones that can be used for speech recognition and voice control. However, Microsoft stopped manufacturing Kinetic in 2017, which makes it unavailable on the market.

Figure 58 | The Kinect device manufactured by Microsoft (Source: https://www.amazon.com/Kinect-Sensor-Adventures-xbox-360/)

Existing standards foundation: Basic electronic/ electrical standards may apply, but as yet this is not specified on the product webpage.

VR/MRs

Virtual reality (VR) is a simulated experience that can be similar to or completely different from the real world. Applications of virtual reality include entertainment (particularly video games), education (such as medical or military training) and business (such as virtual meetings). Other distinct types of VR-style technology include augmented reality and mixed reality, sometimes referred to as extended reality or XR.

HoloLens

HoloLens [132] is a mixed reality headset from Microsoft that allows people to visualize and manipulate objects in holographic form (see Figure 59). Microsoft HoloLens is the first fully self-contained holographic computer to run Windows 10. HoloLens device provides commercial ready management capabilities that are enhanced by the reliability, security, and scalability of cloud and AI services from Microsoft. The device has many commercial and industrial uses, such as 3D computer-aided design and design collaboration, employee training and virtual instruction, and gaming.

Figure 59 | The HoloLens 2 developed by Microsoft (Source: https://www.microsoft.com/en-us/hololens/apps)

Existing standards foundation: Basic electronic/ electrical standards may apply, but as yet this is not specified on the product webpage.

HTC Vive

The HTC Vive [133] is a VR headset and controller suite developed by HTC in collaboration with Valve Corporation. It was released on April 5th, 2016, after initially being unveiled during HTC's Mobile World Congress keynote in March of 2015. The device use“ several “lighthouse” trackers positioned around the room to generate a “zoom scale” VR experience, allowing users to traverse physical space in a 1:1 virtual correlation. The newest Vive Pro 2 device (see Figure 60) is able to visualize virtual environments with 5K fidelity and a wide 120° field of view (FOV). The system can operate at 120Hz refresh rate, which minimizes eye fatigue as well as improves visual fluidity.

Figure 60 | The Vive Pro 2 system

Existing standards foundation: Basic electronic/ electrical standards may apply, but as yet this is not specified on the product webpage.

Oculus

Oculus Quest (now rebranded as Meta Quest [134] is a head-mounted device (HMD) for people who love to enjoy immersive experiences of the world of VR. Oculus Quest is a standalone device; therefore, it does not need any expensive, powerful PC to enjoy the immersive experience (see Figure 61). It was the first multi-purpose

headset specifically built for VR. The system has a fast-switch LCD, with a refresh rate of 90Hz and resolution of 1832×1920 pixels per eye. The processor used in this device is Qualcomm Snapdragon XR2 with 6GB RAM. The operating system is android based. The users can download apps, games, and movies from the Oculus store. It has Wi-Fi, a headphone jack, USB Type-C, an audio sound system, and a microphone. Headset dimensions are 191.5x102x142.5mm and weigh only 503 grams. The controller's dimensions are 90x120mm. And it weighs 126 grams without a battery.

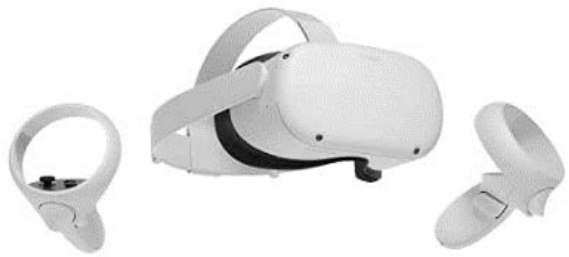


Figure 61 | The Oculus Quest 2 system (Source: https://www.amazon.com/Oculus-Quest-Advanced-All-One-Virtual/)

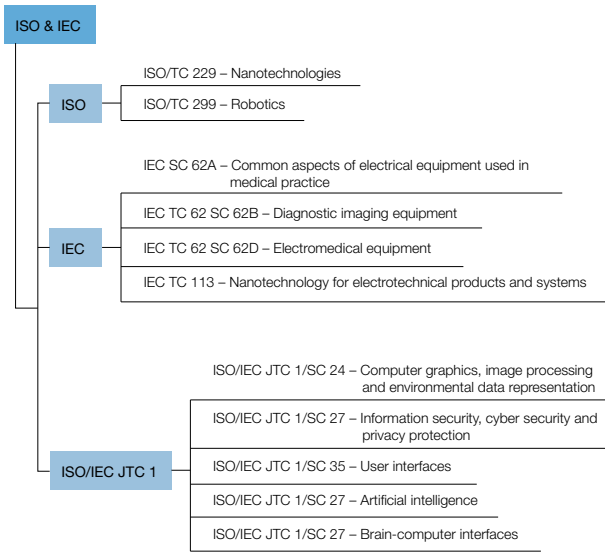
Existing standards foundation: Basic electronic/electrical standards may apply, yet not specified on the product webpage.

4.3.2 Next 5-10 years

It is believed that human augmentation technologies will undoubtedly gain huge development in the next 5 years, especially considering the current popularity of brain computer interface in the capital market. Developments in human augmentation technologies have the potential to profoundly change the daily life of human beings. It is expected that with successful application in medical/assistive applications, human augmentation technology will be included more often in entertainment applications. Consumer level products for general everyday usage may emerge in the next 10 years.

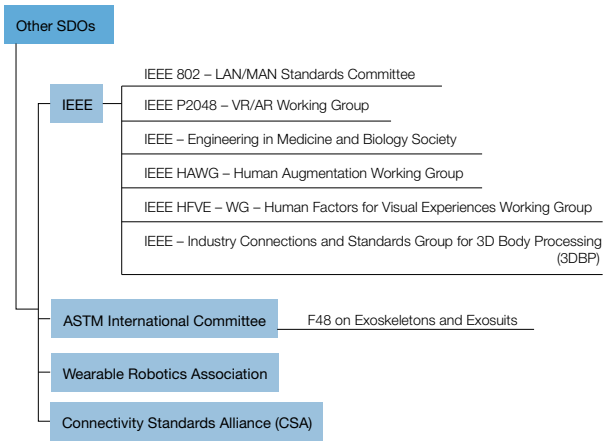
4.4 Current standardization situation

ISO and IEC



Many standardization organizations have carried out standardization research about human augmentation technologies or have published relevant standards. More than 10 ISO or IEC TCs or SCs have published approximately 190 relevant standards. Moreover, approximately 90 further standards are currently under development (See Annex A for the complete list). These standards cover electrical equipment, signal transmission, Bluetooth, cybersecurity, robotics, brain-computer interfaces, and more.

Other SDOs



Many other SDOs besides ISO and IEC have been developing or have published relevant standards, such as IEEE, ASTM International Committee, Wearable Robotics Association and the CSA. IEEE has established several working groups like IEEE 802 LAN/MAN standards committee, IEEE P2048 VR/AR working group, IEEE HAWG working group, IEEE HFVE working group and IEEE Engineering in medicine and biology society. A few IEEE standards, like 802.15.3 IEEE Standard for High Data Rate Wireless Multi-Media Networks mentioned above, could make some assistance of human augmentation technologies. What's more, CSA, ASTM F48, and WRA, are also developing locally applicable standards.

4.4.1 Standardization needs – Outlook

4.4.1.1 Currently

Existing standards: Various products involved in human augmentation have been standardized by IEC/ISO. For example, IEC 60601, IEC 62368, IEC 62368 under TC 108, IEC 60601 for medical devices, TC 106 for electromagnetic radiation exposure, and IEC 63203-406-1(under IEC TC124) for measuring the surface temperature of wrist-worn wearable electronic devices while in contact with human skin all fall into the scope of application safety standardization. However, companies generally do not explicitly label the names of corresponding standards in their product descriptions. Due to the nature of risks and complicity of human augmentation products, it could be considered that manufacturers should be required or recommended to explicitly write all standards' names related to the product, including communication protocol standards, safety requirement standards, etc.

APIs and interfaces: There already exist a variety of products on the market that function similarly but are not compatible. For example, information stored in smartwatches from different manufacturers generally cannot be synchronized, or the synchronization results are unpredictable. Similar things have occurred with brain-computer interface devices. Data formats and communication protocols are usually proprietary and not open to the public. However, the design, development, and implementation of human augmentation technologies rely heavily on a standardized protocol in communication, storage, and representation, especially for mechanical/industrial design of prosthetics and exoskeletons (e.g. ISO/TC 299: Robotics). Therefore, standardization in the general framework of data interfaces and APIs should be considered.

Terminology: The confusion of terminology still poses a great barrier in the field of human augmentation technologies, which is a foundational standardization work for WG 4 of SEG 12. For example, whether we should define a rehabilitation device with a training function as human augmentation is questionable. A clear boundary for terms such as rehabilitative, assistive, or therapeutic applications should be explored.

Recommended practice: Due to the uncertainty of the effectivity and the balance between safety and risks, the optimal timing and frequency for the intervention of human augmentation technologies is still unclear. The collaboration between international standardization organizations and medical societies is expected, and the outcome could be a guideline and/or best practices with a reachable consensus among various stakeholders.

4.4.1.2 Next 5 years

Ethics and risks: As human augmentation would infer a close interaction between devices and the human body, it would have potential impacts on society. Ethical issues and risk management should always be considered before and during the development of related devices. Further, the monitoring of products on the market is also crucial for life cycle regulation. A standardized risk evaluation and management framework are recommended with multiple dimensions, including safety and ethical issues.

4.4.1.3 Scenarios and typical applications

Brain-computer interface and stimulation devices: Devices used in the brain-computer interface are involved in multiple usage scenarios. For most applications including deep brain stimulations, it is crucial for the contacting parts of the devices to be waterproofed. Water-resistant packaging of electrodes and related chips opens a window for standardization. Additionally, power supply and safety concerns regarding both electrodes and other parts of the devices should be taken into consideration, as well as experiment guidelines and quality control of both data and results.

Prosthesis, orthosis, and exoskeleton: The integration and interaction between these devices and the human body can be beneficial, if everything works as expected, or harmful, if there are any flaws in the design, development, or manufacturing process. An emerging type of prosthesis and exoskeletons controlled by both human and artificial intelligence calls for more collaboration among stakeholders. Both mechanical design guidelines and human factors would be recommended to be enlisted in the standardization agenda.

Virtual reality, augmented reality, and mixed reality: Varied concerns and evaluation dimensions exist regarding the near-eye light field display technology as opposed to traditional displays. Not only the human factors arising during the wearing of such devices, but also the ophthalmological issues and requirements should be considered. Meanwhile, the near-eye display would call for different design guidelines in visualization.

4.5 Conclusions and recommendations

Many SDOs have been involved in developing or have developed relevant standards. However, there is no specific TC/SC/WG directly responsible for human argumentation technical standards. Human augmentation terminology poses foundational needs, and (wired/wireless) data communication, technical effectivity, safety, security, and ethics also should be the subject of standardization requirements.

It is recommended that a new integrated TC or SC be established for the human augmentation standardization work.

Section 5

Agricultural bioengineering

5.1 Introduction

Scientific and technical knowledge is increasingly affecting agriculture, and digitalization is a key part of that ongoing evolution. The key areas that are affected include:

- DNA sequencing and sequences, where connection of the biological and digital is particularly evident in plant genomics, molecular modification of plants, animals and microorganisms and breeding techniques. Standardization is developing in this topic area.
- The automation of certain aspects of farming via robots is emerging as an important technology.
- Remote sensing including use of drones and satellite data – little standardization is occurring in this area
- Data communication and operability is key, and standards are being developed in some areas, but not others.
- Modelling of supply chains is inconsistent, and standardization is poor, such that promises of traceability of the food, feed and fibre have yet to deliver.

Overall, data integration is the key step and requires interdisciplinary teams.

Opportunities for standardization to build a more secure and resilient agricultural system for the future that can deliver improved nutrition and also be more sustainable are not consistent, and opportunities for standardization are difficult to pinpoint in such a diverse global industry.

Gap analysis carried out by our team established that there are not a significant number of existing standards that cover all topic/scope areas. Fifty-five possible scope ideas were generated and consolidated into six scope groups. These are Biology/breeding, Agricultural ecosystem, Engineering, Remote and local sensing, Impact of agriculture on the environment, and Supply chains. Further discussion led to clearer definitions of how these areas relate to Agricultural bioengineering.

Sources of existing standards were identified as Codex Alimentarius, ISO, Breeding, and grading standards (e.g., cattle, apples, etc.), and USDA initiatives including the USDA FACT initiative.

The *Codex Alimentarius* international food standards, guidelines and codes of practice contribute to the safety, quality, and fairness of this international food trade. ISO has undertaken significant standardization activity in multiple committees, including the London Declaration – ISO's commitment to combat climate change through standardization. This initiative seeks to prioritize those standards that contribute to countering climate change. The NetZero initiative provides guidance on what governance organizations and other organizations can do to contribute effectively to global efforts to limit warming – and what on the contrary would contribute to further warming. Both are in the early stages of development.

USDA Food and Agriculture Cyberinformatics and Tools (FACT) aims to examine the value of data for small and large farmers, agricultural and food industries, and gain an understanding of how data can impact the agricultural supply chain, reduce

food waste and loss, improve consumer health and environmental and natural resource management, affect the structure of US food and agriculture sectors, and increase US competition.

These three initiatives have the potential to impact the bio-digital revolution in farming in multiple ways.

ISO performed a Standards Advisory Group (SAG) study on smart farming simultaneously with this SEG. Many of the areas studied overlap, and consequently the number of experts available to work on SEG/WG5 was limited. We undertook a study to determine areas of overlap between the topics we had identified and those which are covered in the SAG.

The SAG had a large number of working groups significant in size that overlap with our efforts. Figure 62 shows the areas that are common to both initiatives, and those that are covered uniquely. The smart farming topics are shown in red, bio-digital agriculture in dark blue, with the overlapping topics shown as purple.

For example, the SAG focus in the crop production WG was focused more on the mechanics of crop production than on genomics and biotechnology. The report of IEC/SEG12/WG5 should be combined with that of the ISO SAG on smart farming to get a true picture of the opportunities for standardization in the agriculture field.

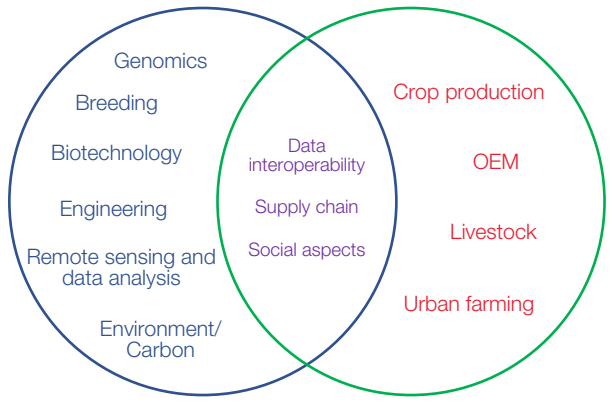


Figure 62 | Scope areas that are unique and common to the IEC SEG and ISO SAG

5.2 Biology/breeding

This scope group includes the steps that lead to the improvement of organisms for employment in the agricultural system. It includes genomic sequence information, biotechnology, breeding, seed, or animal production (including fish for example), understanding disease processes, and the biology of the agriculture system in general. The digital transformation of biological information and breeding techniques including biotechnology are transforming agriculture.

The digital component of breeding is predictive software, and the biological/agricultural component is the actual crop, plant, animal, or other organism. The same concepts can also be applied to fermentation to produce food, feed, or fuel. The digital component is provided by data which is gathered from a single Source (e.g. sequencing) and added preferably to a large number of other Sources, which are integrated in a knowledge system. Sources of data include cameras, temperature, humidity, and a wide range of other sensors, as well as data inputted as a result of human observation. Data such as DNA sequence and physiological measurements is data critical to success in breeding and in assessing agricultural systems. A critical step in any bio-digital system is to decide what data to collect, and therefore what sensors to deploy. This step is confounded by a lack of understanding of the importance of metadata that may not appear important at the time of acquisition but is critical to interpreting the data at a later date, or for another purpose.

Once data is gathered the bio-digital part of the equation becomes predominant. DNA sequence or expression information, paired with knowledge of biology can be used to design or identify organisms with desirable characteristics. Growth of organisms can be monitored and correlated with data gathered using other means.

Standards in this area are well developed: a number of standards cover the acquisition of

sequence data, data publication, databases, and data compression[5], and analytical methods used in the biotechnology field. Standards also cover the production of synthetic DNA used for engineering or diagnostic use[6]. However, many of these standards are not focused on agriculture, and are thus difficult or impractical to apply in the agriculture field.

The value of the information in agriculture is its use in increasing predictability. Predictability allows us to increase efficiency of processes, understand their efficacy as well as forecast their safety.

While ISO/TC 276: Biotechnology has been established, its main focus is the use of biotechnology in a clinical area, as evidenced by the standards it has developed. There is a need for a focus on agriculture, as its needs are different. Thus, we recommend a horizontal SC be established under ISO/TC 34: Food and food products, to focus on the application of biotechnology and breeding techniques in agriculture. This SC would liaise with TC 276, and TC 34/SC 16: Horizontal methods for molecular biomarkers, to ensure consistency and development of agriculture-focused standards.

5.3 Agricultural ecosystem

There are many different ways to practice agriculture, encompassing small plots, small acre farms, large acre, and very large concerns. They depend on the local conditions. Farming practices also vary greatly both with regard to location and approach, ranging from allotments, urban and rooftop, and intensive high output farming up to an including range and extensive farming, and forestry. In addition, there are various types of indoor agriculture, such as greenhouses, (including vertical farms), enclosed animal farming, and hybrids where part of the system is enclosed. In addition, there are agricultural technologies such as aquatic and tank farming and cellular agriculture in which fermentation is used. There are increasingly different forms of input for farming.

It is not possible to cover all approaches to the ecosystem of agriculture. Certain areas such as organic farming already have their own local standards.

5.4 Engineering (equipment)

Engineering of digital systems will strongly influence robotic systems, radio frequency identification (RFID) tracking, and management of agriculture. The question is whether standards can influence the way that engineering affects the biology.

Where digital transformation most impacts agricultural ecosystems is in robotic systems, tracking of animals (e.g. via RFID) or produce including via blockchain systems, and use of information to manage agricultural operations. Data interoperability is once again a critical factor. Data for management of operations will be gathered both within the operation, and from external Sources (weather, prices, etc.).

The working group did not address the standardization of robotic systems. However, the application of such systems will depend strongly

5 For example, ISO/TR 3985:2021 – *Biotechnology – Data publication – Preliminary considerations and concepts*, ISO 20397-1:2022 – *Biotechnology – Massively parallel sequencing – Part 1: Nucleic acid and library preparation*, ISO 20397-2:2021 – *Biotechnology – Massively parallel sequencing – Part 2: Quality evaluation of sequencing data*, ISO PWI 24480 – *Biotechnology – Validation of Database used for nucleotide sequence evaluation*, VOGES et al. Introduction to MPEG-G – *PROCEEDINGS OF THE IEEE* | Vol. 109, No. 9, September 2021

6 For example, ISO 20688-1:2020: *Biotechnology – Nucleic acid synthesis – Part 1: Requirements for the production and quality control of synthesized oligonucleotides.* ISO/DIS 20688-2: *Biotechnology – Nucleic acid synthesis – Part 2: General definitions and requirements for the production and quality control of synthesized gene fragments, genes, and genomes*

on interoperability and access to rural broadband. The latter is a large effector but not within the scope of this study, as it requires the construction of infrastructure.

Once again, the value of the information is to make the system more efficient and more effective. A challenge for this topic area is to make digital systems scalable: how do we make digital transformation available at all scales? That may be the area where standards could contribute.

5.5 Remote and local sensing

Data acquisition is a key area that is undergoing digitalization in agriculture. It is the critical element in the construction of crop models. Historical data that may be useful in this field has to a certain extent been unstructured, and manual, automatic, or semiautomatic techniques have been used to extract knowledge from the data and store it. Programmes to extract data are available and in use.

The core element in digitalization, modelling, and implementation of this technology to impact agriculture is the automatic acquisition of structured information, including the relationship of data sets. These data sets may be acquired variously from satellites, aircraft, drones, and in-field ground stations. For example, pattern recognition in cameras using different wavelengths/ colours can contribute to gathering yield data about crop health and growth, and can also be used to recognize individual animals, along with tagging systems.

Establishing the relationships between data acquired via these disparate methods could benefit from standardization. In the remote sensing area, there does not appear to be significant cooperation between entities involved in this activity to move towards a standardized model.

The definition of the data to be acquired is critical from the point of its present use and future use. Without agreement on the metadata to be acquired, there is little hope of being able to cross reference datasets. Their future use is also compromised. The lack of metadata means that the data has only transient utility, as the knowledge base expands, and it is realized that critical metadata is crucial to model building. Thus, due to its very nature there will be iterative attempts to acquire data, build models and learn from them what metadata is critical to using the data. Standardization of the types of data to be acquired would contribute to better models across the field. The knowledge base is being developed in a fragmented fashion – the industry is in a competitive phase without a base pre-competitive stage.

One critical component that we identified is that of accessing and preserving all available data and metadata. Although such data may not be immediately useful, it is not known what data will be relevant in the future. In addition, it is important that data can be used in different contexts and that interoperability exists. To achieve this the data should adhere to the FAIR and other standards (e.g. ISO 20691, ISO 3985,). Storage of remote sensing, and other relevant data (such as locally acquired data, e.g., weather) is another area that could benefit from standardization. Because of the international study of weather and climate by governments, a base of standardization exists. However, we believe that the interface of this with the remote sensing industry is not standardized, and the data is much better in some geographies than others, depending on resources.

- We support the smart farming conclusions of the ISO Standing Advisory Group regarding data and data standards, that there be an initiative to standardize data and metadata acquisition and storage formats, and in particular recommendation 3.1.2 of the SAG study on smart farming [135]. This would facilitate the application of remote sensing and other data to aid farmers in the decisions made to plant, grow and harvest crops.

5.6 Impact of farming/agriculture on the environment

Agriculture has an enormous effect on the environment and can contribute to reducing the effects of climate change. The question is how standards can contribute.

On the other hand, agriculture is a huge contributor to SDG 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture.

Some areas that were identified as having a possible effect are carbon sequestration by changing farming practices. Possible effectors include increased sequestration by no-till practices, to replacement of animal with plant protein, production of protein and other food and feed components via fermentation. In addition, farming practices that reduce land use or increase biodiversity on farms may have a positive effect on the natural environment. Carbon offset calculations and the business model surrounding them have recently come under criticism, and a major operator has ceased carbon offset operations while they reexamine their calculations.

In order to determine whether such practices have a positive or negative effect, there need to be standardized valid and trusted measurement systems. These systems also need to take into account the need for agriculture as a system for achieving food security and improved nutrition.

Can standards be developed that help assess such factors, and do they fit into the bio-digital conversion space?

Recommendations

- The efforts of ISO to standardize carbon accounting should be strongly supported. There are many gaps in collecting representative data and in standardizing inputs on a per unit of production basis. IEC should support ISO/SAG smart farming recommendation 3.4.20, to enhance the capacity to make informed comparisons regarding true carbon impact.
- In addition to upstream carbon accounting, standards should be developed for measuring downstream carbon accounting – i.e., beyond the farm, including provision of the product to the end consumer and the prevention of waste. There presently exists a gap in carbon accounting which puts all the burden of sustainability on agriculture.

5.7 Supply chain

Food traceability is becoming an integral part of our food supply chain. It comprises all the actors involved in the production, processing, storage, and distribution of food, from the farmer to the consumer. Historically, traceability has been performed using paper records, usually within a contract system. This has now been transformed in many cases to an electronic system. However, it has relied on one forward/one back traceability. An entity will keep records of where they Sourced their materials, and where they were further sold into the food chain. The potential of using a blockchain (distributed ledger) electronic system for this purpose is paradigm- changing. However, the complication of implementing this throughout food chains is underestimated, and the value of blockchain technology is overestimated – the question is what level of implementation is cost effective? The three attributes of a blockchain approach are value, trust, and reliability; without value a blockchain process will not be implemented.

In a post in LinkedIn published November 24, 2022, Kamlesh Tyagi examined the application of blockchain to agriculture. She concluded that such systems would be beneficial for food security, safety, integrity, and waste reduction. While these are important, whether they can be implemented remains a result of cost versus benefit.

As stated by the FAO [136], blockchain is still in its infancy and faces its own challenges, not least in terms of the vast amounts of energy consumed

by the computing power required to operate the underlying technology.

A few large entities have implemented blockchain technology within their organizations to a certain extent for limited applications. Examples are Wal-Mart, and Cargill (reference south America soybean), and in the late 2010s there was a great deal of interest in these approaches [137]. Standardization has the potential to enable smaller entities to use blockchain technologies in their operations. ISO in its 2022 trend report identified blockchain as a key trend [138]. The report further identifies interoperability, governance, common identity frameworks, security, and smart contracts as areas for emphasis, and ISO/TC 307 Blockchain as a key standardization body. However, there is no in-depth consideration of the complications that application to agriculture will pose. Agricultural and food blockchains consist of multiple supply chains that are intertwined as a single product that may contain hundreds of inputs, and these inputs are also used in other products in the food chain. Examples of such products are starch, vitamins, and rising agents. For example, applying the blockchain approaches to just one apple pie product will be complex. Min et al [139] showed the complexity of the relations among food Sources, products, and related food processes of apples that contribute to an apple pie, not even including the non-apple components.

While the ISO smart farming report includes reference to blockchain (ISO/TC 307: Blockchain) no recommendations were made regarding its application to agriculture.

In addition to the digital/operation standards, this technology is in need of ethical standards. As yet there has not been (to our knowledge) a study or standardization attempt to deal with the asymmetric power situation posed by large commercial entities implementing blockchain in their supply chain to the possible detriment of small farmers that supply agricultural products to these entities.

Recommendations

- Consideration of the level of complexity of food feed and fibre supply chains in agriculture with an emphasis of when and how to implement blockchain processes in a size-neutral way.
- Ethical standards for operation of blockchains with particular emphasis on how to protect the interests of small farmers and entities within blockchain systems.

5.8 General recommendations/ coordination with ISO smart farming

- As stated in the smart farming report, the bio-digital transformation of agriculture requires precise coordination among a diverse set of stakeholders and in particular standardization bodies. For this reason, we support General Recommendation 3.1.5: External coordination, which recommends that the ISO Technical Management Board (TMB) work together with the IEC and the ITU-T to establish a Joint Smart Farming Landscape Group (JSFLG).
- The SAG report failed to address agricultural biotechnology. We believe that the digital transformation of biological information and breeding techniques including biotechnology is transforming agriculture, is an integral part of smart farming and should be included in the scope of the JSFLG, and that a Subcommittee on Biotechnology in Agriculture should be established within ISO/TC34.

Section 6

Environmental bioengineering

Working Group 6 was given the mandate to explore bio-digital standardization opportunities in the area of environmental systems of systems. This included geoengineering, sustainability, and the following UN sustainable development goals: climate action, life below water and life on land.

WG 6 had few participating members, thus limiting the depth of its assessment. Nevertheless, it was able to come up with some key findings.

One of the main information technology (IT) enablers in the environmental domains of information and communications technology (ICT) is the Internet of Things (IoT) and its associated technologies (big data, analytics, machine learning, digital twin, etc.). Sensor-provided data enables or can enable the real time monitoring of built environments, human activities and the natural world, both on land and underwater (using underwater sensor networks). This data can be analyzed and used to build and update dynamic models (digital twins) that can be used for predictive analysis. This concept is illustrated in Figure 63.

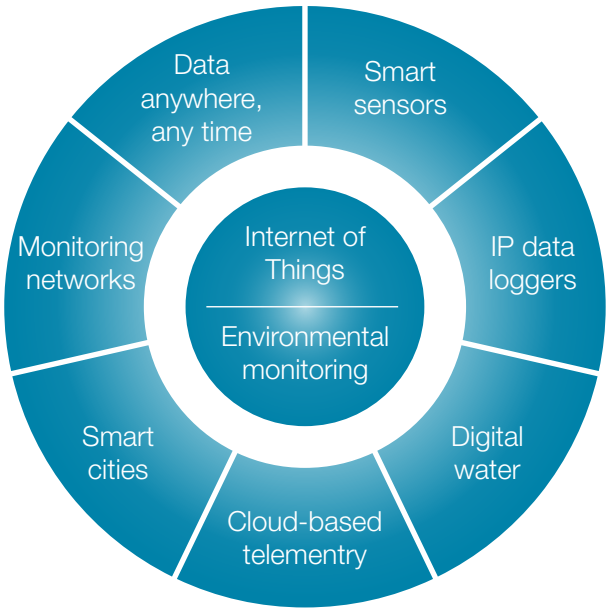


Figure 63 | IT-enabled environmental monitoring [140]

IoT, underwater IoT and digital twin standards are developed by ISO/IEC JTC 1/SC 41. Noteworthy is the recent publication by this committee of the ISO/IEC 30179 standard entitled "*Internet of Things (IoT) – Overview and general requirements of IoT system for ecological environment monitoring*" that specifies IoT systems for "ecological environment monitoring for natural entities such as air, water, soil, living organisms".

Enhanced cooperation between ISO/IEC JTC 1/SC 41 and ISO/TC 8, ISO/TC 207 and ISO/TC 331 would thus be helpful in further pursuing standardization work in this area.

Wastewater monitoring was a very useful public health tool during the recent Covid19 pandemic. With the help of biosensors, it could evolve into a more real-time and automated process to monitor public health.

Another noteworthy bio-digital convergence application in the environmental field is the utilization of shotgun metagenomics to profile entire ecosystems.

Metagenomics is the "study of the structure and function of entire nucleotide sequences isolated and analyzed from all the organisms (3.2.86) in a bulk sample" (see entry 3.2.77 in the glossary of the ISO SAG study on smart farming). Shotgun metagenomics is untargeted and uncultured

metagenomic (3.2.77) analysis of all organisms (3.2.86) in a complex sample by sequencing random DNA strands.

This sample can be from any body of water, sediment, or soil. This type of analysis can not only give an overview of all the types of microbial organisms in the sample, but also of more complex lifeforms, thus measuring the biodiversity of these environments. The analysis process is IT-intensive. For instance, the analysis of a soil sample requires between 500 GB to 1 TB of RAM for metagenomic assembly [141].

Section 7

Bio-digital social risks and ethical aspects

With all new technologies come opportunities, challenges and, in some case, risks. This is the case with the technologies arising from bio-digital convergence. Ethical questions raised by many of these technologies are not only associated with their use, but also, given the current challenges of our global society, their non-use.

SEG 12 mandated its WG 7 to explore these issues, specifically social, ethical, risk, resilience, and safety management issues, including data governance and related issues.

The WG has found that the potential impacts of bio-digital convergence must be assessed from the principles and values described in Table 5.

Numerous studies on ethical aspects of bio-digital convergence have been published in the last 20 years.

For instance, we can quote the "Human Genome Editing Recommendations" [142] from the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, published by the World Health Organization in 2021 as well as the numerous publications about the ethics of genetically modified organisms (GMO).

There is also an extensive literature on the ethics of human augmentation dating back more than a decade. Noteworthy in the standardization areas is

Table 5 | Potential social impacts of bio-digital convergence

Principle	Value
Sovereignty of life	Human-centric; Democracy; Autonomy; Privacy; Knowledge (right to awareness about dual use and impacts)
Human rights	Freedom; Equality; Fraternity and cooperation among people and countries; Human dignity; No torture or inhuman or degrading treatment; To mitigate bias
Social justice	Impact on trust; Fairness, Transparency; Accountability; Control (sovereignty of life and human-centric); Fair cost and fair taxation; Accessibility, Equitable justice, Strong judicial institutions
Professional ethical responsibility	"Do not harm" principle (no lethal machines); Autonomy; Responsibility; Accountability, Trustworthy; Respect for stakeholder interest; Security; Honesty; Equity; Integrity; Respect for international norms of behaviour
To promote planet resilience capability	Sustainability, Well-being; Knowledge (right to receive information about solutions and impacts); Accountability; Beneficence (machines designed to promote active assisted living and health or well-being); Explicability; Security; Innovation through harmony with people, animals and the environment; Respect for rule of law; Democracy

IEEE P2049.4 Standard for Human Augmentation: Methodologies and Processes for Ethical Considerations. As human augmentation would infer a close interaction between devices and the human body, it would have potential impacts on society. Ethical issues and risk management should be always considered before and during the development of related devices.

Bio-digital convergence and its present and potential contributions to the UN sustainability goals have been touched on in 4.1.2.1, and a summary can be found in Figure 64.

While SEG 12 had a working group exploring ethical issues, it believes these should be addressed by the IEC jointly with ISO using other mechanisms than an IEC SyC.

A possible approach could be the creation of a joint SEG specifically on bioethics.

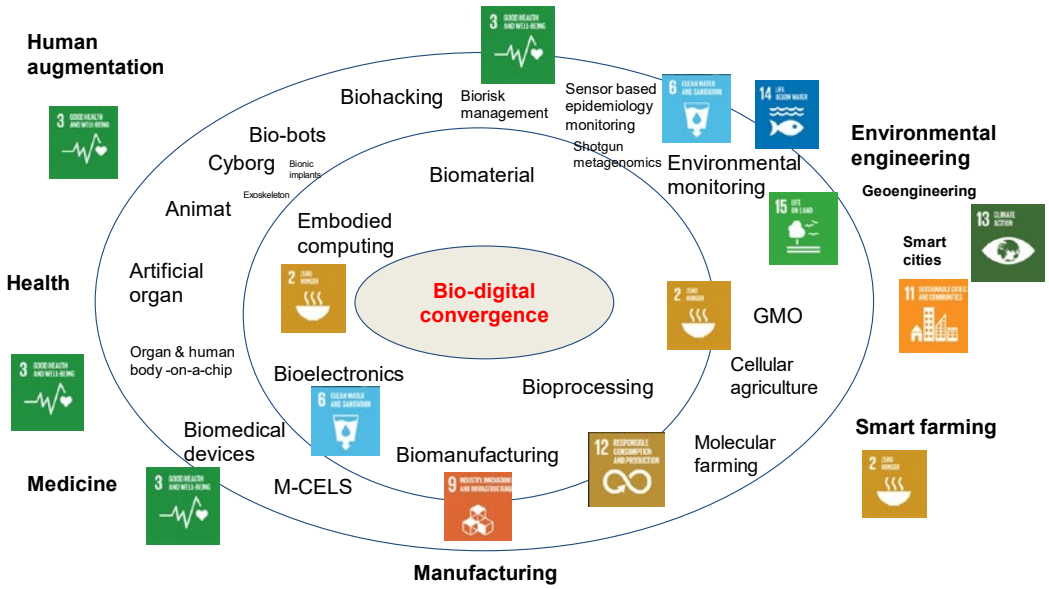


Figure 64 | Bio-digital convergence contributions to sustainability

Section 8

Recommendations to the SMB and the voting results

8.1 Recommendations

Based on the information presented in this technology report, SEG 12 offered the following seven (7) recommendations to the SMB for approval:

ACTION

The SMB is invited to approve the recommendations submitted by SEG 12:

Item A.1: Establish a new Systems Committee (SyC) on Bio-digital convergence.

Item A.2: Approve the initial scope and objectives for the SyC Bio-digital convergence.

Item A.3: Circulate the SEG 12 report to the ISO Technical Management Board (TMB)

Item A.4: Publish Annex 2 as an IEC Technology Report/Brochure, after having Annex 2 go through a final editing process led by the IEC Secretariat.

Item A.5: Recommend that the SMB consider, ideally jointly with ISO, how to address the ethical issues related to bio-digital convergence.

Item A.6: Recommend that the SMB ask ISO to consider the possibility of adopting the concept of SyCs in order to form a Joint SyC for bio-digital convergence (if recommendation A.1 is approved).

Item A.7: Disband SEG 12 at the first meeting of the new SyC Bio-digital convergence.

8.2 Results of voting by the SMB

Decisions of the Standardization Management Board (SMB) taken by correspondence require a two-thirds majority of those voting, abstention is not considered as voting (clause 14.3, Rules of Procedure).

SMB has therefore approved the recommendations from SEG 12:

A.1 Establish a new Systems Committee (SyC) on bio-digital convergence.

A.2 Approve the initial scope and objectives for the SyC Bio-digital convergence.

A.3 Circulate the SEG 12 report to the ISO TMB.

A.4 To publish Annex 2 as an IEC Technology Report/Brochure, after having Annex 2 go through a final editing process led by the IEC Secretariat.

A.5 Recommend that the SMB consider, ideally jointly with ISO, how to address the ethical issues related to bio-digital convergence.

A.6 Recommend that the SMB ask ISO to consider the possibility of adopting the concept of SyCs to form a Joint SyC for bio-digital convergence (if recommendation A.1 is approved).

A.7 Disband SEG 12 at the first meeting of the new SyC Bio-digital convergence.

Annex A

List of identified IEC and ISO technical committees engaged in bio-digital standardization

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 41	Internet of Things and Digital Twin	Published standard: ISO/IEC 30179:2023, *Internet of Things (IoT) – Overview and general requirements of IoT system for ecological environment monitoring*	Ecological monitoring
ISO/TC 207	Environmental management	Standard under development: ISO/AWI TR 14082, *Radiative forcing management – Guidance for the quantification and reporting of radiative forcing-based climate footprints and mitigation efforts*	Geoengineering
IEC SC 62A	Common aspects of medical equipment, software, and systems	Published standards: 1) IEC TR 60513:1994, *Fundamental aspects of safety standards for medical electrical equipment* 2) IEC 60601-1:2005, *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance* 3) IEC 60601-1:2005/AMD1:2012, *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance* 4) IEC 60601-1:2005/AMD2:2020, *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance* 5) IEC TR 60878:2022, *Graphical symbols for electrical equipment in medical practice* 6) IEC 62304:2006, *Medical device software – Software life cycle processes* 7) IEC 62304:2006/AMD1:2015, *Medical device software – Software life cycle processes*	Equipment

TC/SC	Description	Existing standards	Area
IEC SC 62A	Common aspects of medical equipment, software, and systems	8) IEC 62353:2014, *Medical electrical equipment – Recurrent test and test after repair of medical electrical equipment* 9) IEC TR 62354:2014, *General testing procedures for medical electrical equipment* 10) IEC 62366-1:2015, *Medical devices – Part 1: Application of usability engineering to medical devices* 11) IEC 62366-1:2015/AMD1:2020, *Medical devices – Part 1: Application of usability engineering to medical devices* 12) IEC TR 62366-2:2016, *Medical devices – Part 2: Guidance on the application of usability engineering to medical devices* 13) IEC 80001-1:2021, *Application of risk management for IT-networks incorporating medical devices – Part 1: Safety, effectiveness and security in the implementation and use of connected medical devices or connected health software* 14) IEC TR 80001-2-1:2012, *Application of risk management for IT-networks incorporating medical devices – Part 2-1: Step by step risk management of medical IT-networks – Practical applications and examples* 15) IEC TR 80001-2-2:2012, *Application of risk management for IT-networks incorporating medical devices – Part 2-2: Guidance for the disclosure and communication of medical device security needs, risks and controls* 16) IEC TR 80001-2-3:2012, *Application of risk management for IT-networks incorporating medical devices – Part 2-3: Guidance for wireless networks* 17) IEC TR 80001-2-5:2014, *Application of risk management for IT-networks incorporating medical devices – Part 2-5: Application guidance – Guidance on distributed alarm systems*	Equipment

TC/SC	Description	Existing standards	Area
IEC SC 62A	Common aspects of medical equipment, software, and systems	18) IEC TR 80001-2-8:2016, *Application of risk management for IT-networks incorporating medical devices – Part 2-8: Application guidance – Guidance on standards for establishing the security capabilities identified in IEC TR 80001-2-2* 19) IEC TR 80001-2-9:2017, *Application of risk management for IT-networks incorporating medical devices – Part 2-9: Application guidance – Guidance for use of security assurance cases to demonstrate confidence in IEC TR 80001-2-2 security capabilities* 20) IEC TR 80002-1:2009, *Medical device software – Part 1: Guidance on the application of ISO 14971 to medical device software* 21) IEC TR 80002-3:2014, *Medical device software – Part 3: Process reference model of medical device software life cycle processes (IEC 62304)* 22) IEC 81001-5-1:2021, *Health software and health IT systems safety, effectiveness and security – Part 5-1: Security – Activities in the product life cycle* 23) IEC 82304-1:2016, *Health software – Part 1: General requirements for product safety* 24) ISO 14971:2019, *Medical devices – Application of risk management to medical devices* 25) ISO TR 17791:2013, *Health informatics – Guidance on standards for enabling safety in health software* 26) ISO TR 24971:2020, *Medical devices – Guidance on the application of ISO 14971* 27) ISO TR 80001-2-6:2014, *Application of risk management for IT-networks incorporating medical devices – Part 2-6: Application guidance – Guidance for responsibility agreements*	Equipment

TC/SC	Description	Existing standards	Area
IEC SC 62A	Common aspects of medical equipment, software, and systems	28) ISO TR 80001-2-7:2015, *Application of risk management for IT-networks incorporating medical devices – Application guidance – Part 2-7: Guidance for Healthcare Delivery Organizations (HDOs) on how to self-assess their conformance with IEC 80001-1* 29) ISO TR 80002-2:2017, *Medical device software – Part 2: Validation of software for medical device quality systems* 30) ISO 81001-1:2021, *Health software and health IT systems safety, effectiveness and security – Part 1: Principles and concepts* 31) ISO TS 82304-2:2021, *Health software – Part 2: Health and wellness apps – Quality and reliability* Standards under development: 1) IEC TS 60601-4-6 ED1, *Medical electrical equipment – Part 4-6: Guidance and interpretation – Voluntary guidance to help achieve basic safety and essential performance with regard to the possible effects of electromagnetic disturbances* 2) IEC 62304 ED2, *Health software – Software life cycle processes* 3) IEC 63120 ED1, *Refurbishment of medical electrical equipment, medical electrical systems and sub-assemblies and reuse of components as part of the extended life-cycle* 4) IEC TR 80001-2-2 ED2, *Application of risk management for IT-networks incorporating medical devices – Part 2-2: Guidance for the disclosure and communication of medical device security needs, risks and controls*	Equipment

TC/SC	Description	Existing standards	Area
IEC SC 62A	Common aspects of medical equipment, software, and systems	5) IEC TR 80001-2-8 ED2, *Application of risk management for IT-networks incorporating medical devices – Part 2-8: Application guidance – Guidance on standards for establishing the security capabilities identified in IEC TR 80001-2-2* 6) ISO TS 81001-2-1 ED1, *Health software and health IT systems safety, effectiveness and security – Part 2-1: Coordination – Guidance for the use of assurance cases for safety and security*	Equipment
IEC TC 62/SC 62B	Medical imaging equipment, software, and systems	Published standards: 1) IEC 60601-2-33:2022, *Medical electrical equipment – Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis* 2) IEC 60601-2-37:2007, *Medical electrical equipment – Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment* 3) IEC 60601-2-37:2007/AMD1:2015, *Medical electrical equipment – Part 2-37: Particular requirements for the basic safety and essential performance of ultrasonic medical diagnostic and monitoring equipment* 4) IEC 62464-1:2018, *Magnetic resonance equipment for medical imaging – Part 1: Determination of essential image quality parameters*	Equipment
IEC TC 62/SC 62D	Particular medical equipment, software, and systems	Published standards: 1) IEC 60601-2-2:2017, *Medical electrical equipment – Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories*	Equipment

TC/SC	Description	Existing standards	Area
IEC TC 62/SC 62D	Particular medical equipment, software, and systems	2) IEC 60601-2-2:2017/AMD1:2023, *Medical electrical equipment – Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories* 3) IEC 60601-2-3:2012, *Medical electrical equipment – Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment* 4) IEC 60601-2-3:2012/AMD1:2016, *Medical electrical equipment – Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment* 5) IEC 60601-2-3:2012/AMD2:2022, *Medical electrical equipment – Part 2-3: Particular requirements for the basic safety and essential performance of short-wave therapy equipment* 6) IEC 60601-2-5:2009, *Medical electrical equipment – Part 2-5: Particular requirements for the basic safety and essential performance of ultrasonic physiotherapy equipment* 7) IEC 60601-2-6:2012, *Medical electrical equipment – Part 2-6: Particular requirements for the basic safety and essential performance of microwave therapy equipment* 8) IEC 60601-2-6:2012/AMD1:2016, *Medical electrical equipment – Part 2-6: Particular requirements for the basic safety and essential performance of microwave therapy equipment* 9) IEC 60601-2-6:2012/AMD2:2022, *Medical electrical equipment – Part 2-6: Particular requirements for the basic safety and essential performance of microwave therapy equipment* 10) IEC 60601-2-10:2012, *Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators*	Equipment

TC/SC	Description	Existing standards	Area
IEC TC 62/SC 62D	Particular medical equipment, software, and systems	10) IEC 60601-2-10:2012, *Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators* 11) IEC 60601-2-10:2012/AMD1:2016, *Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators* 12) IEC 60601-2-10:2012/AMD2:2023, *Medical electrical equipment – Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators* 13) IEC 60601-2-36:2014, *Medical electrical equipment – Part 2-36: Particular requirements for the basic safety and essential performance of equipment for extracorporeally induced lithotripsy* 14) IEC 60601-2-40:2016, *Medical electrical equipment – Part 2-40: Particular requirements for the basic safety and essential performance of electromyographs and evoked response equipment* 15) IEC 60601-2-46:2023, *Medical electrical equipment – Part 2-46: Particular requirements for the basic safety and essential performance of operating tables* 16) IEC 60601-2-62:2013, *Medical electrical equipment – Part 2-62: Particular requirements for the basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment* 17) IEC 60601-2-75:2017, *Medical electrical equipment – Part 2-75: Particular requirements for the basic safety and essential performance of photodynamic therapy and photodynamic diagnosis equipment*	Equipment

TC/SC	Description	Existing standards	Area
IEC TC 62/SC 62D	Particular medical equipment, software, and systems	18) IEC 60601-2-75:2017/AMD1:2023, *Medical electrical equipment – Part 2-75: Particular requirements for the basic safety and essential performance of photodynamic therapy and photodynamic diagnosis equipment* 19) IEC 60601-2-83:2019, *Medical electrical equipment – Part 2-83: Particular requirements for the basic safety and essential performance of home light therapy equipment* 20) IEC 60601-2-83:2019/AMD1:2022, *Medical electrical equipment – Part 2-83: Particular requirements for the basic safety and essential performance of home light therapy equipment* 21) IEC TR 61289:2019, *High frequency surgical equipment and high frequency surgical accessories – Operation and maintenance* 22) IEC 80601-2-26:2019, *Medical electrical equipment – Part 2-26: Particular requirements for the basic safety and essential performance of electroencephalographs* 23) IEC 80601-2-49:2018, *Medical electrical equipment – Part 2-49: Particular requirements for the basic safety and essential performance of multifunction patient monitors* 24) IEC 80601-2-58:2024, *Medical electrical equipment – Part 2-58: Particular requirements for the basic safety and essential performance of lens removal devices and vitrectomy devices for ophthalmic surgery* 25) IEC 80601-2-71:2015, *Medical electrical equipment – Part 2-71: Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment*	Equipment

TC/SC	Description	Existing standards	Area
IEC TC 62/SC 62D	Particular medical equipment, software, and systems	26) IEC 80601-2-77:2019, *Medical electrical equipment – Part 2-77: Particular requirements for the basic safety and essential performance of robotically assisted surgical equipment* 27) IEC 80601-2-77:2019/AMD1:2023, *Medical electrical equipment – Part 2-77: Particular requirements for the basic safety and essential performance of robotically assisted surgical equipment* 28) IEC 80601-2-78:2019, *Medical electrical equipment – Part 2-78: Particular requirements for basic safety and essential performance of medical robots for rehabilitation, assessment, compensation or alleviation* 29) IEC 80601-2-78:2019/AMD1:2024, *Medical electrical equipment – Part 2-78: Particular requirements for basic safety and essential performance of medical robots for rehabilitation, assessment, compensation or alleviation* Standards under development: 1) IEC 60601-2-40 ED3, *Medical electrical equipment – Part 2-40: Particular requirements for the basic safety and essential performance of electromyographs and evoked response equipment* 2) IEC TR 61289/AMD1 ED2, *High frequency surgical equipment and high frequency surgical accessories – Operation and maintenance* 3) IEC 80601-2-49/AMD1 ED1, *Medical electrical equipment – Part 2-49: Particular requirements for the basic safety and essential performance of multifunction patient monitors* 4) IEC 80601-2-71 ED2, *Medical electrical equipment – Part 2-71: Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment*	Equipment

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	Published standards: 1) IEC PAS 62565-2-1:2011, *Nanomanufacturing – Material specifications – Part 2-1: Single-wall carbon nanotubes – Blank detail specification* 2) IEC TS 62565-4-1:2019, *Nanomanufacturing – Key control characteristics – Part 4-1: Luminescent nanomaterials – Blank detail specification* 3) IEC TS 62565-4-2:2018, *Nanomanufacturing – Material specifications – Part 4-2: Luminescent nanomaterials – Detail specification for general lighting and display applications* 4) IEC TS 62607-2-1:2012, *Nanomanufacturing – Key control characteristics – Part 2-1: Carbon nanotube materials – Film resistance* 5) IEC TS 62607-2-4:2020, *Nanomanufacturing – Key control characteristics – Part 2-4: Carbon nanotube materials – Test methods for determination of resistance of individual carbon nanotubes* 6) IEC 62607-3-1:2014, *Nanomanufacturing – Key control characteristics – Part 3-1: Luminescent nanomaterials – Quantum efficiency* 7) IEC TS 62607-3-2:2017, *Nanomanufacturing – Key control characteristics – Part 3-2: Luminescent nanoparticles – Determination of mass of quantum dot dispersion* 8) IEC TS 62607-3-3:2020, *Nanomanufacturing – Key control characteristics – Part 3-3: Luminescent nanomaterials – Determination of fluorescence lifetime of semiconductor quantum dots using time correlated single photon counting (TCSPC)*	Technologies

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	9) IEC TS 62607-4-1:2015, *Nanomanufacturing – Key control characteristics – Part 4-1: Cathode nanomaterials for nano-enabled electrical energy storage – Electrochemical characterization, 2-electrode cell method* 10) IEC TS 62607-4-2:2016, *Nanomanufacturing – Key control characteristics – Part 4-2: Nano-enabled electrical energy storage – Physical characterization of cathode nanomaterials, density measurement* 11) IEC TS 62607-4-3:2015, *Nanomanufacturing – Key control characteristics – Part 4-3: Nano-enabled electrical energy storage – Contact and coating resistivity measurements for nanomaterials* 12) IEC TS 62607-4-4:2016, *Nanomanufacturing – Key control characteristics – Part 4-4: Nano-enabled electrical energy storage – Thermal characterization of nanomaterials, nail penetration method* 13) IEC TS 62607-4-5:2017, *Nanomanufacturing – Key control characteristics – Part 4-5: Cathode nanomaterials for nano-enabled electrical energy storage – Electrochemical characterization, 3-electrode cell method* 14) IEC TS 62607-4-6:2018, *Nanomanufacturing – Key control characteristics – Part 4-6: Nano-enabled electrical energy storage devices – Determination of carbon content for nano electrode materials, infrared absorption method* 15) IEC TS 62607-4-7:2018, *Nanomanufacturing – Key control characteristics – Part 4-7: Nano-enabled electrical energy storage – Determination of magnetic impurities in anode nanomaterials, ICP-OES method*	Technologies

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	16) IEC TS 62607-4-8:2020, *Nanomanufacturing – Key control characteristics – Part 4-8: Nano-enabled electrical energy storage – Determination of water content in electrode nanomaterials, Karl Fischer method* 17) IEC TS 62607-5-1:2014, *Nanomanufacturing – Key control characteristics – Part 5-1: Thin-film organic/nano electronic devices – Carrier transport measurements* 18) IEC TS 62607-5-3:2020, *Nanomanufacturing – Key control characteristics – Part 5-3: Thin-film organic/nano electronic devices – Measurements of charge carrier concentration* 19) IEC TS 62607-6-1:2020, *Nanomanufacturing – Key control characteristics – Part 6-1: Graphene-based material – Volume resistivity: four probe method* 20) IEC TS 62607-6-3:2020, *Nanomanufacturing – Key control characteristics – Part 6-3: Graphene-based material – Domain size: substrate oxidation* 21) IEC TS 62607-6-4:2024, *Nanomanufacturing – Key control characteristics – Part 6-4: Graphene – Surface conductance measurement using resonant cavity* 22) IEC TS 62607-6-6:2021, *Nanomanufacturing – Key control characteristics – Part 6-6: Graphene – Strain uniformity: Raman spectroscopy* 23) IEC TS 62607-6-9:2022, *Nanomanufacturing – Key control characteristics – Part 6-9: Graphene-based material – Sheet resistance: Eddy current method*	Technologies

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	24) IEC TS 62607-6-10:2021, *Nanomanufacturing – Key control characteristics – Part 6-10: Graphene-based material – Sheet resistance: Terahertz time-domain spectroscopy* 25) IEC TS 62607-6-11:2022, *Nanomanufacturing – Key control characteristics – Part 6-11: Graphene – Defect density: Raman spectroscopy* 26) IEC TS 62607-6-13:2020, *Nanomanufacturing – Key control characteristics – Part 6-13: Graphene powder – Oxygen functional group content: Boehm titration method* 27) IEC TS 62607-6-14:2020, *Nanomanufacturing – Key control characteristics – Part 6-14: Graphene-based material – Defect level: Raman spectroscopy* 28) IEC TS 62607-6-19:2021, *Nanomanufacturing – Key control characteristics – Part 6-19: Graphene-based material – Elemental composition: CS analyser, ONH analyser* 29) IEC TS 62607-8-1:2020, *Nanomanufacturing – Key control characteristics – Part 8-1: Nano-enabled metal-oxide interfacial devices – Test method for defect states by thermally stimulated current* Standards under development: 1) IEC 62565-2-1 ED2, *Nanomanufacturing – Material specifications – Part 2-1: Carbon nanotube materials – Blank detail specification: Single-wall carbon nanotubes* 2) IEC TS 62565-3-3 ED1, *Nanomanufacturing – Material specifications – Part 3-3: Graphene-based material – Sectional blank detail specification: Monolayer graphene*	Technologies

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	3) IEC TS 62565-3-6 ED1, *Nanomanufacturing – Material specification – Part 3-6 Graphene-based material – Blank detail specification: Graphene oxide* 4) IEC TS 62565-4-3 ED1, *Nanomanufacturing – Product specifications – Part 4-3: Quantum dots materials – Blank detail specification: Light emitting diodes (QLED)* 5) IEC TS 62565-4-4 ED1, *Nanomanufacturing – Product specifications – Part 4-4: Nanophotonic products – Blank detail specifications: Quantum dot materials in light conversion films* 6) IEC TS 62607-2-1 ED2, *Nanomanufacturing – Key control characteristics – Part 2-1: Carbon nanotube materials – Film resistance: Four terminal method* 7) PWI 113-127 IEC TS 62607-3-x, *Nanomanufacturing – Key control characteristics – Part 3-x: Quantum dot materials used in Q-LCF subassemblies* 8) IEC 62607-3-1 ED2, *Nanomanufacturing – Key control characteristics – Part 3-1: Luminescent nanomaterials – Quantum efficiency* 9) PWI 113-137 IEC TS 62607-3-4, *Nanomanufacturing – Key control characteristics – Part 3-4: Luminescent nanomaterials – Key control characteristics used in QLED products* 10) IEC TS 62607-6-23 ED1, *Nanomanufacturing – Key control characteristics – Part 6-23: Graphene film – Sheet resistance, Carrier density, Carrier mobility: Hall bar* 11) IEC TS 62607-6-28 ED1, *Nanomanufacturing – Key control characteristics – Part 6-28: Graphene-based material – Number of layers: Raman spectroscopy*	Technologies

TC/SC	Description	Existing standards	Area
IEC TC 113	Nanotechnology for electrotechnical products and systems	12) IEC TS 62607-6-32 ED1, *Nanomanufacturing – Key control characteristics – Part 6-32: Two-dimensional materials – Charge carrier mobility, contact resistance, sheet resistance, doping, and hysteresis: Gated transfer length method* 13) PWI 113-78 ED1 IEC TS 62607-7-1, *Nanomanufacturing – Key control characteristics – Part 7-1: Nano-enabled photovoltaics measurement of the electrical performance and spectral response of tandem cells* 14) IEC TS 62607-9-2 ED1, *Nanomanufacturing – Key control characteristics – Part 9-2: Traceable spatially resolved nano-scale magnetic field measurements – Magneto-optical indicator film technique* 15) PWI 113-135 IEC TS 62876-3-3, *Nanomanufacturing – Reliability assessment – Part 3-3: 2D materials – Stability test: Density of interface defects* 16) IEC TS 62876-4-1 ED1, *Nanomanufacturing – Reliability assessments – Part 4-1: Quantum dots light conversion film (QLCF) – Test: Temperature, humidity and light exposure* 17) PWI 113-138, *Nanomanufacturing – Key control characteristics – Quantification of Functional Groups and Ligands at the Surface of Nanomaterials* 18) PWI 113-139, *Nanomanufacturing – Key control characteristics – Quantification of Hansen parameters to characterize surface properties of Carbon Black materials*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 229	Nanotechnologies	Published standards: 1) ISO/TS 4958:2024, *Nanotechnologies – Vocabularies – Liposomes* 2) ISO/TS 4988:2022, *Nanotechnologies – Toxicity assessment and bioassimilation of manufactured nano-objects in suspension using the unicellular organism Tetrahymena sp.* 3) ISO/TS 10797:2012, *Nanotechnologie – Characterization of single-wall carbon nanotubes using transmission electron microscopy* 4) ISO/TS 10798:2011, *Nanotechnologies – Characterization of single-wall carbon nanotubes using scanning electron microscopy and energy dispersive X-ray spectrometry analysis* 5) ISO/TS 10867:2019, *Nanotechnologies – Characterization of single-wall carbon nanotubes using near infrared photoluminescence spectroscopy* 6) ISO/TS 10868:2017, *Nanotechnologies – Characterization of single-wall carbon nanotubes using ultraviolet-visible-near infrared (UV-Vis-NIR) absorption spectroscopy* 7) ISO/TR 10929:2012, *Nanotechnologies – Characterization of multiwall carbon nanotube (MWCNT) samples* 8) ISO/TS 11251:2019, *Nanotechnologie – Characterization of volatile components in single-wall carbon nanotube samples using evolved gas analysis/gas chromatograph-mass spectrometry* 9) ISO/TS 11308:2020, *Nanotechnologies – Characterization of carbon nanotube samples using thermogravimetric analysis* 10) ISO/TR 11360:2010, *Nanotechnologies – Methodology for the classification and categorization of nanomaterials*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 229	Nanotechnologies	11) ISO/TR 11811:2012, *Nanotechnologies – Guidance on methods for nano- and microbiology measurements* 12) ISO/TS 11888:2017, *Nanotechnologies – Characterization of multiwall carbon nanotubes – Mesoscopic shape factors* 13) ISO/TR 12802:2010, *Nanotechnologies – Model taxonomic framework for use in developing vocabularies – Core concepts* 14) ISO/TS 12805:2011, *Nanotechnologies – Materials specifications – Guidance on specifying nano-objects* 15) ISO/TR 12885:2018, *Nanotechnologies – Health and safety practices in occupational settings* 16) ISO/TS 12901-1:2012, *Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 1: Principles and approaches* 17) ISO/TS 12901-2:2014, *Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 2: Use of the control banding approach* 18) ISO/TR 13121:2011, *Nanotechnologies – Nanomaterial risk evaluation* 19) ISO/TR 13329:2012, *Nanomaterials – Preparation of material safety data sheet (MSDS)* 20) ISO/TS 13830:2013, *Nanotechnologies – Guidance on voluntary labelling for consumer products containing manufactured nano-objects* 21) ISO/TS 14101:2012, *Surface characterization of gold nanoparticles for nanomaterial specific toxicity screening: FT-IR method*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 229	Nanotechnologies	22) ISO/TR 14786:2014, *Nanotechnologies – Considerations for the development of chemical nomenclature for selected nano-objects* 23) ISO/TR 16197:2014, *Nanotechnologies – Compilation and description of toxicological screening methods for manufactured nanomaterials* 24) ISO/TR 17302:2015, *Nanotechnologies – Framework for identifying vocabulary development for nanotechnology applications in human healthcare* 25) ISO/TS 18110:2015, *Nanotechnologies – Vocabularies for science, technology and innovation indicators* 26) ISO/TR 18196:2016, *Nanotechnologies – Measurement technique matrix for the characterization of nano-objects* 27) ISO/TR 18401:2017, *Nanotechnologies – Plain language explanation of selected terms from the ISO/IEC 80004 series* 28) ISO/TR 18637:2016, *Nanotechnologies – Overview of available frameworks for the development of occupational exposure limits and bands for nano-objects and their aggregates and agglomerates (NOAAs)* 29) ISO/TR 19057:2017, *Nanotechnologies – Use and application of acellular in vitro tests and methodologies to assess nanomaterial biodurability* 30) ISO/TR 19716:2016, *Nanotechnologies – Characterization of cellulose nanocrystals* 31) ISO/TR 19733:2019, *Nanotechnologies – Matrix of properties and measurement techniques for graphene and related two-dimensional (2D) materials*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 229	Nanotechnologies	32) ISO TS 23366:2023, *Nanotechnologies – Performance evaluation requirements for quantifying biomolecules using fluorescent nanoparticles in immunohistochemistry* 33) ISO/TS 23367-1:2022, *Nanotechnologies – Performance characteristics of nanosensors for chemical and biomolecule detection – Part 1: Detection performance* 34) ISO 80004-1:2023, *Nanotechnologies – Vocabulary – Part 1: Core vocabulary* 35) ISO/TS 80004-5:2011, *Nanotechnologies – Vocabulary – Part 5: Nano/bio interface* Standards under development: 1) ISO/DTS 12901-1 ED2, *Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 1: Principles and approaches* 2) ISO/WD TS 12901-2, *Nanotechnologies – Occupational risk management applied to engineered nanomaterials – Part 2: Use of the control banding approach* 3) ISO/DTS 13329 ED2, *Nanomaterials – Preparation of material safety data sheet (MSDS)* 4) ISO/AWI TS 18196 Ed1, *Nanotechnologies – Measurement technique matrix for the characterization of nano-objects* 5) ISO/AWI TS 20477, *Nanotechnologies – Standard terms and their definition for cellulose nanomaterial* 6) ISO/CD TS 23361.2 ED1, *Nanotechnologies – Crystallinity of cellulose nanomaterials by powder X-ray diffraction (Ruland-Rietveld analysis)* 7) ISO/DTS 80004-13 ED2, *Nanotechnologies – Vocabulary – Part 13: Graphene and related two-dimensional (2D) materials*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 299	Robotics	Published standards: 1) ISO/PAS 5672:2023, *Robotics – Collaborative applications – Test methods for measuring forces and pressures in human-robot contacts* 2) ISO 8373:2021, *Robotics – Vocabulary* 3) ISO 9283:1998, *Manipulating industrial robots – Performance criteria and related test methods* 4) ISO 9409-1:2004, *Manipulating industrial robots – Mechanical interfaces – Part 1: Plates* 5) ISO 9409-2:2002, *Manipulating industrial robots – Mechanical interfaces – Part 2: Shafts* 6) ISO 9787:2013, *Robots and robotic devices – Coordinate systems and motion nomenclatures* 7) ISO 9946:1999, *Manipulating industrial robots – Presentation of characteristics* 8) ISO 10218-1:2011, *Robots and robotic devices – Safety requirements for industrial robots – Part 1: Robots* 9) ISO 10218-2:2011, *Robots and robotic devices – Safety requirements for industrial robots – Part 2: Robot systems and integration* 10) ISO 11593:2022, *Robots for industrial environments – Automatic end effector exchange systems – Vocabulary* 11) ISO/TR 13309:1995, *Manipulating industrial robots – Informative guide on test equipment and metrology methods of operation for robot performance evaluation in accordance with ISO 9283* 12) ISO 13482:2014, *Robots and robotic devices – Safety requirements for personal care robots* 13) ISO 14539:2000, *Manipulating industrial robots – Object handling with grasp-type grippers – Vocabulary and presentation of characteristics*	Products

TC/SC	Description	Existing standards	Area
ISO/TC 299	Robotics	14) ISO/TS 15066:2016, *Robots and robotic devices – Collaborative robots* 15) ISO 18646-1:2016, *Robotics – Performance criteria and related test methods for service robots – Part 1: Locomotion for wheeled robots* 16) ISO 18646-2:2024, *Robotics – Performance criteria and related test methods for service robots – Part 2: Navigation* 17) ISO 18646-3:2021, *Robotics – Performance criteria and related test methods for service robots – Part 3: Manipulation* 18) ISO 18646-4:2021, *Robotics – Performance criteria and related test methods for service robots – Part 4: Lower-back support robots* 19) ISO 19649:2017, *Mobile robots – Vocabulary* 20) ISO/TR 20218-1:2018, *Robotics – Safety design for industrial robot systems – Part 1: End-effectors* 21) ISO/TR 20218-2:2017, *Robotics – Safety design for industrial robot systems – Part 2: Manual load/unload stations* 22) ISO 22166-1:2021, *Robotics – Modularity for service robots – Part 1: General requirements* 23) ISO 22166-201:2024, *Robotics – Modularity for service robots – Part 201: Common information model for modules* 24) ISO/TR 23482-1:2020, *Robotics – Application of ISO 13482 – Part 1: Safety-related test methods* 25) ISO/TR 23482-2:2019, *Robotics – Application of ISO 13482 – Part 2: Application guidelines* 26) ISO 31101:2023, *Robotics – Application services provided by service robots – Safety management systems requirements*	Products

TC/SC	Description	Existing standards	Area
ISO/TC 299	Robotics	Standards under development: 1) ISO/CD 5363, *Robotics – Test methods for exoskeleton-type walking RACA robot* 2) ISO/FDIS 10218-1 ED2, *Robotics – Safety requirements – Part 1: Industrial robots* 3) ISO/CD 13482 ED2, *Robots and robotic devices – Safety requirements for personal care robots* 4) ISO/FDIS 10218-2 ED2, *Robotics – Safety requirements – Part 2: Industrial robot applications and robot cells*	Products
ISO/IEC JTC 1/SC 24	Computer graphics, image processing and environmental data representation	Published standards: 1) ISO/IEC 3721:2023, *Information technology – Computer graphics, image processing and environmental data representation – Information model for mixed and augmented reality content – Core objects and attributes* 2) ISO/IEC 5927:2024, *Computer graphics, image processing and environmental data representation – Augmented and virtual reality safety – Guidance on safe immersion, set up and usage* 3) ISO/IEC 14772-1:1997, *Information technology – Computer graphics and image processing – The Virtual Reality Modeling Language – Part 1: Functional specification and UTF-8 encoding* 4) ISO/IEC 14772-1:1997/AMD 1:2003, *Information technology – Computer graphics and image processing – The Virtual Reality Modeling Language – Part 1: Functional specification and UTF-8 encoding – Amendment 1: Enhanced interoperability* 5) ISO/IEC 14772-2:2004, *Information technology – Computer graphics and image processing – The Virtual Reality Modeling Language (VRML) – Part 2: External authoring interface (EAI)*	Technologies

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 24	Computer graphics, image processing and environmental data representation	6) ISO/IEC 18520:2019, *Information technology – Computer graphics, image processing and environmental data representation – Benchmarking of vision-based spatial registration and tracking methods for mixed and augmented reality (MAR)* 7) ISO/IEC 19775-1:2013, *Information technology – Computer graphics, image processing and environmental data representation – Extensible 3D (X3D) – Part 1: Architecture and base components* 8) ISO/IEC 19775-2:2015, *Information technology – Computer graphics, image processing and environmental data representation – Extensible 3D (X3D) – Part 2: Scene access interface (SAI)* 9) ISO/IEC 19776-1:2015, *Information technology – Computer graphics, image processing and environmental data representation – Extensible 3D (X3D) encodings – Part 1: Extensible Markup Language (XML) encoding* 10) ISO/IEC 19776-2:2015, *Information technology – Computer graphics, image processing and environmental data representation – Extensible 3D (X3D) encodings – Part 2: Classic VRML encoding* 11) ISO/IEC 19776-3:2015, *Information technology – Computer graphics, image processing and environmental data representation – Extensible 3D (X3D) encodings – Part 3: Compressed binary encoding* 12) ISO/IEC 23488:2022, *Information technology – Computer graphics, image processing and environment data representation – Object/ environmental representation for image-based rendering in virtual/mixed and augmented reality (VR/MAR)* 13) ISO/IEC TS 23884:2021, *Information technology – Computer graphics, image processing and environmental data representation – Material property and parameter representation for model-based haptic simulation of objects in virtual, mixed and augmented reality (VR/MAR)*	Technologies

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 24	Computer graphics, image processing and environmental data representation	Standards under development: 1) ISO/IEC CD 9234 ED1, *Information technology – Information modelling for VR/AR/MR based education and training systems* 2) ISO/IEC AWI TR 16088 ED1, *Constructs for visual positioning systems in mixed and augmented reality (MAR)*	Technologies
ISO/IEC JTC 1/SC 27	Information security, cybersecurity and privacy protection	Published standards: 1) ISO/IEC TR 5891:2024, *Information security, cybersecurity and privacy protection – Hardware monitoring technology for hardware security assessment* 2) ISO/IEC TR 14516:2002, *Information technology – Security techniques – Guidelines for the use and management of Trusted Third Party services* 3) ISO/IEC 15408-1:2022, *Information security, cybersecurity and privacy protection – Evaluation criteria for IT security – Part 1: Introduction and general model* 4) ISO/IEC 15408-2:2022, *Information technology – Security techniques – Evaluation criteria for IT security – Part 2: Security functional components* 5) ISO/IEC 15408-3:2022, *Information technology – Security techniques – Evaluation criteria for IT security – Part 3: Security assurance components* 6) ISO/IEC 15408-4:2022, *Information security, cybersecurity and privacy protection – Evaluation criteria for IT security – Part 4: Framework for the specification of evaluation methods and activities* 7) ISO/IEC 15408-5:2022, *Information security, cybersecurity and privacy protection – Evaluation criteria for IT security – Part 5: Pre-defined packages of security requirements*	Security

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 27	Information security, cybersecurity and privacy protection	8) ISO/IEC TR 15443-1:2012, *Information technology – Security techniques – Security assurance framework – Part 1: Introduction and concepts* 9) ISO/IEC TR 15443-2:2012, *Information technology – Security techniques – Security assurance framework – Part 2: Analysis* 10) ISO/IEC TR 15446:2017, *Information technology – Security techniques – Guidance for the production of protection profiles and security targets* 11) ISO/IEC 15816:2002, *Information technology – Security techniques – Security information objects for access control* 12) ISO/IEC 18045:2022, *Information security, cybersecurity and privacy protection – Evaluation criteria for IT security – Methodology for IT security evaluation* 13) ISO/IEC 19792:2009, *Information technology – Security techniques – Security evaluation of biometrics* 14) ISO/IEC 19989-1:2020, *Information security – Criteria and methodology for security evaluation of biometric systems – Part 1: Framework* 15) ISO/IEC 19989-2:2020, *Information security – Criteria and methodology for security evaluation of biometric systems – Part 2: Biometric recognition performance* 16) ISO/IEC 19989-3:2020, *Information security – Criteria and methodology for security evaluation of biometric systems – Part 3: Presentation attack detection* 17) ISO/IEC 27557:2022, *Information security, cybersecurity and privacy protection – Application of ISO 31000:2018 for organizational privacy risk management* 18) ISO/IEC 27563:2023, *Security and privacy in artificial intelligence use cases – Best practices*	Security

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 27	Information security, cybersecurity and privacy protection	Standard under development: 1) ISO/IEC CD 19792 ED2, *Information security, cybersecurity and privacy protection – General principles of security evaluation of biometric systems*	Security
ISO/IEC JTC 1/SC 35	User interfaces	Published standards: 1) ISO/IEC TR 11580:2007, *Information technology – Framework for describing user interface objects, actions, and attributes* 2) ISO/IEC 13066-1:2011, *Information technology – Interoperability with assistive technology (AT) – Part 1: Requirements and recommendations for interoperability* 3) ISO/IEC TR 13066-2:2016, *Information technology – Interoperability with assistive technology (AT) – Part 2: Windows accessibility application programming interface (API)* 4) ISO/IEC TR 13066-3:2012, *Information technology – Interoperability with assistive technology (AT) – Part 3: IAccessible2 accessibility application programming interface (API)* 5) ISO/IEC TR 13066-4:2015, *Information technology – Interoperability with assistive technology (AT) – Part 4: Linux/UNIX graphical environments accessibility API* 6) ISO/IEC TR 13066-6:2014, *Information technology – Interoperability with Assistive Technology (AT) – Part 6: Java accessibility application programming interface (API)* 7) ISO/IEC 20382-1:2017, *Information technology – User interfaces – Face-to-face speech translation – Part 1: User interface* 8) ISO/IEC 20382-2:2017, *Information technology – User interface – Face-to-face speech translation – Part 2: System architecture and functional components*	Technologies

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 35	User interfaces	9) ISO/IEC 23836:2020, *Information technology – User interfaces – Universal interface for human language selection* 10) ISO/IEC TR 29138-2:2009, *Information technology – Accessibility considerations for people with disabilities – Part 2: Standards inventory* 11) ISO/IEC TR 29138-3:2009, *Information technology – Accessibility considerations for people with disabilities – Part 3: Guidance on user needs mapping* 12) ISO/IEC 30122-1:2016, *Information technology – User interfaces – Voice commands – Part 1: Framework and general guidance* 13) ISO/IEC 30122-2:2017, *Information technology – User interfaces – Voice commands – Part 2: Constructing and testing* 14) ISO/IEC 30122-3:2017, *Information technology – User interfaces – Voice commands – Part 3: Translation and localization* 15) ISO/IEC 30122-4:2016, *Information technology – User interfaces – Voice commands – Part 4: Management of voice command registration* Standards under development: 1) ISO/IEC DIS 23773-1 ED1, *User interface – Automatic Simultaneous Interpretation System – Part 1: General* 2) ISO/IEC DIS 23773-2 ED1, *User interface – Automatic Simultaneous Interpretation System – Part 2: Requirements and functional description* 3) ISO/IEC PRF 23773-3 ED1, *User interface – Automatic Simultaneous Interpretation System – Part 3: System architecture*	Technologies

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 42	Artificial intelligence	Published standards: 1) ISO/IEC 5338:2023, *Information technology – Artificial intelligence – AI system life cycle processes* 2) ISO/IEC 5339:2024, *Information technology – Artificial intelligence – Guidance for AI applications* 3) ISO/IEC 5392:2024, *Information technology – Artificial intelligence – Reference architecture of knowledge engineering* 4) ISO/IEC TR 5469:2024, *Artificial intelligence – Functional safety and AI systems* 5) ISO/IEC 8183:2023, *Information technology – Artificial intelligence – Data life cycle framework* 6) ISO/IEC TS 8200:2024, *Information technology – Artificial intelligence – Controllability of automated artificial intelligence systems* 7) ISO/IEC 22989:2022, *Information technology – Artificial intelligence – Artificial intelligence concepts and terminology* 8) ISO/IEC 23053:2022, *Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML)* 9) ISO/IEC 23894:2023, *Information technology – Artificial intelligence – Guidance on risk management* 10) ISO/IEC TR 24029-1:2021, *Artificial intelligence (AI) – Assessment of the robustness of neural networks – Part 1: Overview* 11) ISO/IEC TR 24372:2021, *Information technology – Artificial intelligence (AI) – Overview of computational approaches for AI systems* 12) ISO/IEC TR 24028:2020, *Information technology – Artificial intelligence – Overview of trustworthiness in artificial intelligence*	Technologies

TC/SC	Description	Existing standards	Area
ISO/IEC JTC 1/SC 42	Artificial intelligence	13) ISO/IEC TR 24027:2021, *Information technology – Artificial intelligence (AI) – Bias in AI systems and AI aided decision making* 14) ISO/IEC 24029-2:2023, *Artificial intelligence (AI) – Assessment of the robustness of neural networks – Part 2: Methodology for the use of formal methods* 15) ISO/IEC TR 24030:2021, *Information technology – Artificial intelligence (AI) – Use cases* 16) ISO/IEC TR 24368:2022, *Information technology – Artificial intelligence – Overview of ethical and societal concerns* 17) ISO/IEC 24668:2022, *Information technology – Artificial intelligence – Process management framework for big data analytics* 18) ISO/IEC 25059:2023, *Software engineering – Systems and software Quality Requirements and Evaluation (SQuaRE) – Quality model for AI systems* Standards under development: 1) ISO/IEC CD TS 6254 ED1, *Information technology – Artificial intelligence – Objectives and approaches for explainability of ML models and AI systems* 2) ISO/IEC TS 12791 ED1, *Information technology – Artificial intelligence – Treatment of unwanted bias in classification and regression machine learning tasks*	Technologies
ISO/IEC JTC 1/SC 43	Brain-computer interfaces	Standards under development: 1) ISO/IEC CD 8663 ED1, *Information Technology – Brain-computer Interface – Vocabulary* 2) *Information Technology – Brain-computer Interface – Use Cases*	Technologies

TC/SC	Description	Existing standards	Area
ISO/TC 215	Health informatics	Published standards: 1) ISO 10781:2023, *Health informatics – HL7 Electronic Health Record-System Functional Model, Release 2.1 (EHR FM)* 2) ISO 12052:2017, *Health informatics – Digital imaging and communication in medicine (DICOM) including workflow and data management* 3) ISO/TR 12300:2014, *Health informatics – Principles of mapping between terminological systems* 4) ISO/TR 12309:2009, *Health informatics – Guidelines for terminology development organizations* 5) ISO/TR 12310:2015, *Health informatics – Principles and guidelines for the measurement of conformance in the implementation of terminological systems* 6) ISO 13120:2019, *Health informatics – Syntax to represent the content of healthcare classification systems – Classification Markup Language (ClaML)* 7) ISO 16527:2023, *Health informatics – HL7 Personal Health Record System Functional Model, Release 2 (PHR-S FM)* 8) ISO 18308:2011, *Health informatics – Requirements for an electronic health record architecture* 9) ISO/TR 20514:2005, *Health informatics – Electronic health record – Definition, scope and context* 10) ISO/TS 21547:2010, *Health informatics – Security requirements for archiving of electronic health records – Principles* 11) ISO/TR 21548:2010, *Health informatics – Security requirements for archiving of electronic health records – Guidelines* 12) ISO/HL7 21731:2014, *Health informatics – HL7 version 3 – Reference information model – Release 4*	Life Systems: Human Digital Twins

TC/SC	Description	Existing standards	Area
ISO/TC 215	Health informatics	13) ISO/TR 24291:2021, *Health informatics – Applications of machine learning technologies in imaging and other medical applications* 14) ISO/HL7 27931:2009, *Data Exchange Standards – Health Level Seven Version 2.5 – An application protocol for electronic data exchange in healthcare environments* 15) ISO/HL7 27932:2009, *Data Exchange Standards – HL7 Clinical Document Architecture, Release 2* 16) ISO/IEEE 11073 series, *Health informatics – Device interoperability* Standard under development: 1) ISO CD 12052 ED2, *Health informatics – Digital imaging and communication in medicine (DICOM) including workflow and data management*	Life Systems: Human Digital Twins
ISO/TC 276	Biotechnology	Published standards: 1) ISO 5058-1:2021, *Biotechnology – Genome editing – Part 1: Vocabulary* 2) ISO 5058-1:2021/Amd 1:2022, *Biotechnology – Genome editing – Part 1: Vocabulary – Amendment 1* 3) ISO 20688-1:2020, *Biotechnology – Nucleic acid synthesis – Part 1: Requirements for the production and quality control of synthesized oligonucleotides*	Life Systems: Synthetic Biology Life Systems: CRISPR
ISO/TC 276	Biotechnology	Published standards: 1) ISO 20399:2022, *Biotechnology – Ancillary materials present during the production of cellular therapeutic products and gene therapy products* 2) ISO 21973:2020, *Biotechnology – General requirements for transportation of cells for therapeutic use* 3) ISO/TS 22859:2022, *Biotechnology – Biobanking – Requirements for human mesenchymal stromal cells derived from umbilical cord tissue*	Life Systems: CAR-T cells

TC/SC	Description	Existing standards	Area
ISO/TC 276	Biotechnology	4) ISO 23033:2021, *Biotechnology – Analytical methods – General requirements and considerations for the testing and characterization of cellular therapeutic products* 5) ISO/TS 23565:2021, *Biotechnology – Bioprocessing – General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use*	Life Systems: CAR-T cells
ISO/TC 276	Biotechnology	Published standards: 1) ISO 24603:2022, *Biotechnology – Biobanking – Requirements for human and mouse pluripotent stem cells* 2) ISO 24651:2022, *Biotechnology – Biobanking – Requirements for human mesenchymal stromal cells derived from bone marrow*	Life Systems: Artificial Organs and Organoids Life Systems: CAR-T cells
ISO/TC 276	Biotechnology	Published standard: 1) ISO 20691:2022, *Biotechnology – Requirements for data formatting and description in the life sciences*	Life Systems: Human Digital Twins Life Systems: Data Quality
ISO/IEC JTC 1/SC 7	Software and systems engineering	Published standard: 1) ISO/IEC 25012:2008, *Software engineering – Software product Quality Requirements and evaluation (SQuaRE) – Data quality model*	Life Systems: Data Quality
ISO/IEC JTC 1/SC 42	Artificial intelligence	Standards under development: 1) ISO/IEC 5259 series, *Artificial intelligence – Data quality for analytics and machine learning (ML)*	Life Systems: Human Digital Twins Life Systems: Data Quality
ISO/TC 34/SC 16	Horizontal methods for molecular biomarker analysis	Published standard: 1) ISO 16578:2022, *Molecular biomarker analysis – Requirements for microarray detection of specific nucleic acid sequences*	Life Systems: Synthetic Biology
CEN TC/264 WG 41	Emissions and ambient air – Instrumental odour monitoring		Life Systems: Biosensors – Bio-Electronic Nose

TC/SC	Description	Existing standards	Area
NEN (Dutch SDO)		NTA 9055:2012, *Air quality – Electronic air monitoring – Odour (nuisance) and safety*	Life Systems: Biosensors – Bio-Electronic Nose
UNI (Italian SDO)		UNI 1605848, *Emissions and air quality. Odour determination using IOMS (Instrumental Odour Monitoring Systems) and their qualification*	Life Systems: Biosensors – Bio-Electronic Nose
ASTM		ASTM E3072-22A, *Standard Terminology for Industrial Biotechnology and Synthetic Biology*	Synthetic Biology
VDI (VDI - The Association of German Engineers)		VDI 3518-3:2018, *Multigas sensors – Odour-related measurements with electronic noses and their testing*	Biosensors – Bio-Electronic Nose
IEEE		1) IEEE 1451, *A universal transducer protocol standard* 2) IEEE 2700-2014, *Standard for Sensor Performance Parameter Definitions* 3) P2520, *Guide for Testing Machine Olfaction Devices and Systems*	Biosensors – Bio-Electronic Nose

Annex B

Bio-digital convergence: Other organizations and interests outside of ISO and IEC

Name of organization	Domain					
	Reverse engineering	Bio-engineering	Human augmentation technologies	Agriculture	Environment	Social, risk & ethics
IEEE		x	x			x
Connectivity Standards Alliance (CSA)			x			
ASTM International Committee F48 on Exoskeletons and Exosuits			x			
VDI (VDI – The Association of German Engineers)		x				
Wearable Robotics Association			x			
ASTM		x				

Annex C

Bio-digital convergence – Vocabulary

Disclaimer for Annex C

The rapid development of information technologies in the last twenty years has not only facilitated the development of the biological sciences, but also the convergence and integration of the field of biology and information technologies. This convergence is known as “bio-digital convergence”.

The purpose of this annex is to provide a multi-disciplinary collection of terms to facilitate the comprehension of this area and facilitate communications among stakeholders.

This document is primarily intended for use horizontally.

The terms and definitions in Annex C are either new or, when available and relevant, are extracted from the ISO and the IEC vocabulary repositories. Where multiple definitions are given in the repositories, those that best fit the current context of bio-digital convergence have been selected.

The terms and definitions in Annex C are provided **FOR INFORMATION ONLY** in support of this Technology Report and are not yet endorsed by IEC or ISO.

C.1 Bio-digital convergence

C.1.1 bio-digital convergence
biodigital convergence

convergence of engineering (C.3.23), nanotechnology (C.3.34), biotechnology (C.2.43), information technology (C.3.27) and cognitive science (C.2.49)

Note 1 to entry: Convergence means the creative union of sciences, technologies, engineering and peoples, focused on mutual benefit; this is a process requiring increasing integration across traditionally separate disciplines, areas of relevance, and across multiple levels of abstraction and organization.

[Source: Modified from: M. C. Roco, W. S. Bainbridge, B. Tonn, and G. Whitesides, Eds., *Convergence of Knowledge, Technology and Society: Beyond Convergence of Nano-Bio-Info-Cognitive Technologies*. Cham: Springer International Publishing, 2013. doi: 10.1007/978-3-319-02204-8.]

C.2 Selected bioengineering terms

C.2.1 animat

simulated organism (C.2.86) or robot (C.3.41) the structure and functionalities of which are inspired by current biological knowledge as much as possible, with the intention that it will exhibit at least some of the survival capacities of a real organism

Note 1 to entry: Term includes physical robots and virtual simulations. The animat model includes features of a simple animal capable of interacting with its environment. It is, therefore, designed to simulate the ability to associate certain signals from the environment within a learning phase that indicate a potential for cognitive structure.

Note 2 to entry: Animat research is a subset of artificial life (C.2.2) studies.

[Source: Modified from https://en.wikipedia.org/wiki/Animat, http://www.scholarpedia.org/article/Animat. Accessed on 2022-06-21]

C.2.2 artificial life

synthetic systems that behave like living organisms (C.2.86)

[Source: https://en.wiktionary.org/wiki/arti–icial_life. Accessed on 2022-06-21]

C.2.3 artificial nose
bioelectronic nose
electronic nose
e-nose

device comprising olfactory receptors, transducer, signal processing, and pattern analysis system, capable of recognizing odours

C.2.4 artificial organ

engineered (C.3.23) device or tissue that can be integrated or implanted into an organism (C.2.86) for interfacing with living tissues to replace natural organs

Note 1 to entry: Usually to replace a damaged organ, to duplicate or augment a specific function or functions.

[Source: Modified from https://www.sciencedirect.com/topics/materials-science/artificial-organ, Green Biocomposites for Biomedical Engineering, 2021. The note is from Wikipedia: https://en.wikipedia.org/wiki/Artificial_organ. Accessed on 2022-06-21]

C.2.5 artificial tongue
bioelectronic tongue
electronic tongue
e-tongue

device comprising taste receptors, transducer, signal processing, and pattern analysis system, capable of recognizing tastes

C.2.6 bioactive material

a biomaterial (C.2.24) that is designed to elicit or modulate biological activity

[Source: Williams D.F., Black J., Doherty P.J. In: Biomaterial – Tissue Interfaces. Doherty P.J., Williams R.L., Williams D.F., Lee A.J.C., editors. Elsevier; Amsterdam: 1992. Second consensus conference on definitions in biomaterials; pp. 525–533 as quoted by https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC8636667/#.]

C.2.7 big bio-data
big biological data

bigdata (C.2.11) of bio-data (C.2.10)

[Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4411415/. Accessed on 2022-06-21]

C.2.8 bioanalytics

the field of research in biotechnology (C.2.43) concerned with analytical techniques (C.3.17)

[Source: https://www.definitions.net/definition/BIOANALYTICS. Accessed on 2022-06-21]

C.2.9 bio-bots

robots (C.3.41) built from living tissue

[Source: https://eandt.theiet.org/content/articles/2017/04/bio-bots-the-living-tissue-robots-and-the-future-of-personal-health/. Accessed on 2022-06-21]

C.2.10 bio-data
biodata
bioinformatic data

data (C.3.16) derived from or describing a biological system or biological material (C.2.21)

C.2.11 bio-data mining

data mining (C.3.18) of bio-data (C.2.10)

[Source: modified from https://www.resurchify.com/impact/details/–7300154988. Accessed on 2022-06-21]

C.2.12 bio-data science
BDS

application of data science (C.3.22) principles and associated technologies for deriving insights from bio-data (C.2.10)

[Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7393550/. Accessed on 2022-06-21]

C.2.13 biodegradable electronics
soft electronics
transient electronics

electronics that have the ability to dissolve, resorb, or physically disappear in physiological or natural environments in a controlled manner

[Source: Modified from Rongfeng Li, Liu Wang, Deying Kong, Lan Yin. Recent progress on biodegradable materials and transient electronics. *Bioactive Materials*, Volume 3, Issue 3, 2018, Pages 322-333, ISSN 2452-199X, https://doi.org/10.1016/j.bioactmat.2017.12.001.]

C.2.14 bioelectronics

application of the principles of electronics in the field of biology or medicine

Note 1 to entry: This includes the study of electron transfer reactions as they occur in biological systems as well as the application of electronic devices to living organisms for clinical testing, diagnosis, and therapy.

[Source: Modified from https://www.yourdictionary.com/bioelectronics and https://www.thefreedictionary.com/bioelectronics. Accessed on 2023-03-19]

C.2.15 bioengineering

systematic application of scientific and technological knowledge, methods, and experience to the design, implementation and maintenance of biological systems (C.3.49) and systems of systems (C.3.50).

C.2.16 bioethics

ethics in the field of life sciences (C.2.72) and medicine

Note 1 to entry: Bioethics studies the philosophical, social, and legal issues arising in medicine and the life sciences including but not limited to medical devices and nuances of impact and/or intersection.

Note 2 to entry: Bioethics is chiefly concerned with human life and well-being, though it sometimes also treats ethical questions relating to the nonhuman biological environment. (Such questions are studied primarily in the independent fields of environmental ethics and animal rights.)

C.2.17 biofeedback

process of gaining greater awareness of various physiological functions of the user's own body, with the goal of being able to manipulate the body's functions at will

[Source: ISO/IEC JTC 1 N15401]

C.2.18 biohacking

manipulation of biological functioning including genetic information stored on nucleic acids or other biological material (C.2.21)

Note 1 to entry: as it is for its IT analog, biohacking can be ethical ("white hat") or unethical ("black hat").

Note 2 to entry: “Black Hat” biohacking is the activity of exploiting genetic material experimentally without regard to accepted ethical standards, or for criminal purposes (derived from the Oxford dictionary).

Note 3 to entry: Biohacking is sometime described as citizen or do-it-yourself biology. For many “biohackers,” this consists of making small, incremental diet or lifestyle changes to make small improvements in health and well-being. It is associated with concepts such as nutrigenomics, DIY biology and grinder. (https://www.healthline.com/health/biohacking)

C.2.19 bioinformatics

application of computer technology to the understanding and effective use of bio¬log-ical and biomedical data

Note 1 to entry: It is the discipline that stores, analyses, and interprets the big data (C.3.9) generated by life-sciences (C.2.72) experiments, or collected in a clinical context.

[Source: Modified from https://www.sib.swiss/what-is-bioinformatics. Accessed on 2022-06-21]

C.2.20 bio-inspired nanotechnology
biomimetic nanotechnology

use of principles found in biology for the design and/or fabrication of nanomaterials, nanoscale devices or nanoscale systems

[Source: Modified from ISO/TS80004-5:2011, 3.3 – the example was removed]

C.2.21 biological material

any plants, seeds, microorganisms, cells, parts of cells, DNA, RNA, cDNA, proteins, peptides, enzymes as well as any combination of the foregoing, other organic matter and biologically active compounds

[Source: https://www.lawinsider.com/dictionary/biologic–l-material. Accessed on 2022-06-21]

C.2.22 biological system

coherent group of observable elements originating from the living world spanning from nanoscale to macroscale

[Source: ISO 18548:2015, 2.6]

C.2.23 biomanufacturing

industrial production using scalable, validated processes that use a biological organism, or parts of a biological organism, in an unnatural manner to produce a product, as well as products designed to detect, modify, maintain and study biological organisms for use as new manufacturing agents

Note 1 to entry: Biomanufacturing uses living cells as miniature factories.

[Source: Modified from https://www.pharma-iq.com/glossary/biomanufacturing. Accessed on 2023-03-19]

C.2.24 biomaterial

material intended to interface with biological systems (C.2.22) to evaluate, treat, augment, or replace any tissue, organ or function of the body

[Source: ISO 20579-3:2021(en), 3.1]

C.2.25 biomechanics

study of the structure, function and motion of the mechanical aspects of biological systems, at any level from whole organisms to organs, cells and cell organelles

[Source: Modified from R. McNeill Alexander (2005), Mechanics of animal movement. Current Biology Volume 15, Issue 16, 23 August 2005, Pages R616-R619. doi:10.1016/j.cub.2005.08.016 as quoted in https://en.wikipedia.org/wiki/B–omechanics. Accessed on 2023-03-19]

C.2.26 biomedical device

a medical device (C.2.76) that incorporates at least one biological component

Note 1 to entry: Biomedical devices are the result of the convergence of bioengineering and medical dev ices.

[Source: https://www.biotech-careers.org/articles/what-biomedical-device. Accessed on 2023-04-25]

C.2.27 biomedical engineering
BME
medical engineering

application of engineering (C.3.23) principles and design concepts to medicine and biology for healthcare purposes (e.g., diagnostic or therapeutic)

Note 1 to entry: This field seeks to close the gap between engineering and medicine, combining the design and problem-solving skills of engineering with medical biological sciences to advance health care treatment, including diagnosis, monitoring, and therapy.

[Source: Wikipedia: https://en.wikipedia.org/wiki/Biomedical_engineering, https://www.sciencedirect.com/topics/engineering/biomedical-engineering. Accessed on 2023-03-19]

C.2.28 biomedical (or biological) microelectromechanical systems
Bio-MEMS

science and technology of operating at the microscale for biological and biomedical applications, which may or may not include any electronic or mechanical functions

[Source: https://en.wikipedia.org/wiki/Bio-MEMS. Accessed on 2022-06-21]

C.2.29 biometrics
bio-metrics

automated recognition of individuals based on their behavioural and biological characteristics

Note 1 to entry: include the use of specific attributes that reflect unique personal characteristics, such as a fingerprint, an eye blood-vessel print, or a voice print, to validate the identity of a person.

[Source: ISO/IEC 19784-1:2018, 4.53 – Modified – a synonym was added as well as a note]

C.2.30 biomimetics

interdisciplinary cooperation of biology and technology or other fields of innovation with the goal of solving practical problems through the function analysis of biological systems (C.2.22), their abstraction into models, and the transfer into and application of these models to the solution

[Source: ISO 18458:2015, 2.9]

C.2.31 biomolecular engineering

application of engineering (C.3.23) principles and practices to the purposeful manipulation of molecules of biological origin

[Source: https://en.wikipedia.org/wiki/Biomolecular_engineering. Accessed on 2023-03-19]

C.2.32 biomolecule
biological molecule

any of numerous substances that are produced by cells and living organisms

[Source: https://www.britannica.com/science/biomolecule. Accessed on 2023-03-19]

C.2.33 bionic

biological organism (C.2.86), having been enhanced by electronic or mechanical part

[Source: https://en.wiktionary.org/wiki/bionic. Accessed on 2022-06-21]

C.2.34 bionics

study of electro-mechanical systems (C.3.49) that function like living organisms (C.2.86) or parts of living organisms

[Source: modified from Oxford]

C.2.35 bionics implant

mechanical or electronic implant (C.2.71)

C.2.36 biophysics

interdisciplinary science that applies approaches and methods traditionally used in physics to study biological phenomena

[Source: modified from https://en.wikipedia.org/wiki/Biophysics. Accessed on 2022-03-19]

C.2.37 bioprocess

process that uses complete living cells or their components (e.g., bacteria, enzymes, chloroplasts) to obtain desired products

[Source: modified from https://www.pharma-iq.com/glossary/bioprocessing. Accessed on 2022-06-21]

C.2.38 bioprocessing

production of a value-added material from a living Source

[Source : https ://www.sciencedirect.com/topics/engineering/bioprocessing. Accessed on 2022-06-21]

C.2.39 biorisk
biothreat

effect of uncertainty expressed by the combination of the consequences of an event (including changes in circumstances) and the associated "likelihood" (as defined in ISO Guide 73) of occurrence, where biological material is the Source of harm

Note 1 to entry: The harm can be the consequence of an unintentional exposure, accidental release or loss, theft, misuse, diversion, unauthorized access or intentional unauthorized release.

[Source: Modified from ISO/TS 22859:2022, 3.4 – biothreat was added]

C.2.40 biorisk management

coordinated activities to direct and control an organization with regard to biorisk (C.2.39)

[Source: ISO 35001:2019, 3.6]

C.2.41 biosensing

detection of target molecules by means of biosensors (C.2.42)

[Source: Modified from Hiroki Yasuga, Kan Shoji, Keiichiro Koiwai, Ryuji Kawano. *New Sensing Technologies: Microtas/NEMS/MEMS*, Editor(s): Roger Narayan, Encyclopedia of Sensors and Biosensors (First Edition), Elsevier, 2023, Pages 526-540, ISBN 9780128225493, https://doi.org/10.1016/B978-0-12-822548-6.00046-7]

C.2.42 biosensor

sensor (C.3.43) that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals

[Source: Modified from IUPAC GoldBook (DOI: 10.1351/goldbook.B00663)]

C.2.43 biotechnology

integration of natural sciences and engineering sciences in order to achieve the application of organisms (C.2.86), cells, parts thereof and molecular analogues for products and services

[Source: Modified from IUPAC GoldBook (DOI: 10.1351/goldbook.B00666)]

C.2.44 bioterrorism

the intentional release of biological agents or toxins for the purpose of harming or killing humans, animals or plants with the intent to intimidate or coerce a government or civilian population to further political or social objectives

[Source: INTERPOL Bioterrorism incident pre-planning and response guide, as quoted in https://www.interpol.int/Crimes/Terrorism/Bioterrorism. Accessed on 2022-09-09]

C.2.45 brain implants
neural implants

functional unit that is attached to or inserted through the surface of the central nervous system parts and collects neural activities

Note 1 to entry: Can be temporary or perm anent

[Source: ISO/IEC JTC 1 N15401]

C.2.46 brain-machine interface
BMI
brain-computer interface
BCI

<engineered systems> system (C.3.49) that sends and receives signals between the brain and external devices to enable direct communication

[Source: ISO/IEC JTC 1 N15401]

C.2.47 brain-machine interface enabled crime
BMI enabled crime

computer crime (C.3.12) committed through or facilitated by a brain-machine interface (C.2.46)

C.2.48 cellular agriculture

field of growing animal agricultural products directly from cell cultures

[Source: https://www.cellag.ca/cellagabout. Accessed on 2022-06-21]

C.2.49 cognitive science
cognitivism

interdisciplinary knowledge field, whose stated objective is to discover the representational and computational capacities of the mind and their structural and functional representation in the brain

Note 1 to entry: Cognitive science deals with the symbol-processing nature of cognition and encompasses disciplines as diverse as psychology, computer science, linguistics, anthropology, philosophy, education, mathematics, engineering (C.3.23), physiology, and neuroscience.

[Source: ISO/IEC 2382:2015(–n), 212297– – modified – notes 2 and 3 were removed]

C.2.50 computational biology

development and application of data-analytical and theoretical methods, mathematical modelling and computational simulation techniques to the study of biological, ecological, behavioural, and social system

[Source: Modified from https://en.wikipedia.org/wiki/Computational_biology. Accessed on 2022-06-21]

C.2.51 connectome

comprehensive map of neural connections in a nervous system of a given species

[Source: Modified from Philipp Haueis, Jan Slab– Chapter 7 – Connectomes as constitutively epistemic objects: Critical perspectives on modelling in current neuroanatomy, Editor(s): Tara Mahfoud, Sam McLean, Nikolas Rose, Progress in Brain Research, Elsevier, Volume 233, 2017, Pages 149-177, ISSN 0079-6123, ISBN 9780128042151, https://doi.org/10.1016/bs.pbr.2017.05.002.]

C.2.52 CRISPR Cas
clustered regularly interspaced short palindromic repeats- CRISPR associated system

recombinant DNA technology consisting of a protein and bioactive RNA complex originally Sourced from microbial anti-bacteriophage defence systems and re-engineered to provide a sequence specific recognition, cleavage and excision system

Note 1 to entry: The combination of CRISPR-Cas and native recombination and repair mechanisms in any cell can enable many different types of genetic engineering.

Note 2 to entry: CRISPR-Cas9 was the first of the CRISPR-Cas recombinant technologies; however, Cas12a and Cas13 systems have also been developed.

Note 3 to entry: The bioactive RNA in Cas9 can be reengineered to recognize any cognate target sequence. It is called “single guide” or “sgRNA”.

Note 4 to entry: The Cas9 complex contains a nickase.

[Source: ISO 16577:2022, 3.6.3]

C.2.53 cybernetic

science of communications and automatic control systems in both machines and organisms (C.2.86)

[Source: Derived from Oxford dictionary]

C.2.54 cyborg
cybernetic organism

organism (C.2.86) with both biological and bionics (C.2.34) components

Note 1 to entry: In popular literature, a cyborg is usually referred to as an augmented (C.2.69) human that has superhuman capabilities and retains his free will.

[Source: Derived from https://www.techopedia.com/definition/15651/cyborg. Accessed on 2022-06-21]

C.2.55 developmental biology

science that investigates the processes that control an organism’s (C.2.86) shape, size and structure throughout its life cycle

C.2.56 ecological environmental monitoring
EEM

process or activity that uses physical, chemical, biochemical, ecological and other technologies for the purpose of reflecting accurately, comprehensively, and in a timely manner the various elements of the ecological environment, the relationship between organisms and the environment, and the change trend of the ecosystem (C.2.57)

[Source: ISO/IEC 30179:2023, 3.1]

C.2.57 ecosystem

system (C.3.49) of complex interactions between communities of plants, animals, microorganisms, and their environment, which function as a unit

[Source: ISO 13065:2015, 3.14]

C.2.58 embodied computing
body-centered computing

paradigm on the merging of information technology (C.3.27) and an organism (C.2.86)

Note 1 to entry: Includes wearable, implantable and ingestible devices as well as bionics.

[Source: Multiple references]

C.2.59 environmental monitoring

systematic observation, measurement and calculation of the condition of the environment, emission of pollutants or populations and species, which are necessary for the assessment of the condition of the environment, the development of environment policies and the planning of environmental protection measures, as well as the control of the effectiveness thereof
[Source: ISO 12878;2012, 3.11]

C.2.60 epigenetic

processes that change the phenotype without altering the genotype

[Source: IUPAC GoldBook (DOI: 10.1351/goldbook.E02164)]

C.2.61 evolution

<biology> process by which new species or populations of living things develop from preexisting forms through successive generations

[Source: https://www.merriam-webster.com/dictionary/evolution. Accessed on 2022-06-21]

C.2.62 gaia

hypothesis that the living and non-living components of earth function as a single system (C.3.49) in such a way that the living component regulates and maintains conditions (such as the temperature of the ocean or composition of the atmosphere) so as to be suitable for life

Note 1 to entry: There are various version of the Gaia hypothesis. The least controversial from a scientific perspective is the recognition that "biota minimally influence certain aspects of the abiotic world, e.g. temperature and atmosphere" ("Influential Gaia"). There is also a recognition that Gaia is co-evolutive e.g., "Biota influence their abiotic environment, and that environment in turn influences the biota by Darwinian process." ("Weak Gaia"). See https://courses.seas.harvard.edu/climate/eli/Courses/EPS281r/Sources/Gaia/Gaia-hypothesis-wikipedia. pdf.

[Source: https://www.merriam-webster.com/dictionary/Gaia. Accessed on 2022-06-21]

C.2.63 genetic engineering

selective, deliberate alteration of genes (genetic material) by means of recombinant DNA technology

[Source: ISO 16577:2016, 3.71]

C.2.64 genetically modified organism GMO

organism (C.2.88) in which the genetic material has been changed through modern biotechnology (C.2.43) in a way that does not occur naturally by multiplication and/or natural recombination

[Source: ISO 16577:2016, 3.73]

C.2.65 genome

total genetic material (nucleic acid, DNA or RNA) of a cell that codes genetic information

[Source: ISO 6107:2021, 3.1.6]

C.2.66 genomics

study of the complete genome (C.2.65) of an organism (C.2.86)

[Source: https://en.wiktionary.org/wiki/genomics. Accessed on 2022-06-21]

C.2.67 geoengineering

artificial manipulation of the environments of the earth

[Source: https://en.wiktionary.org/wiki/geoengineering. Accessed on 2022-06-21]

C.2.68 human anatomy

analysis and representation of the structural organization of the human body

Note 1 to entry: Human anatomy thus defined encompasses the material objects from the granularity level of the whole human body to that of cell parts, portions of body substances, and non-material entities such as surfaces, spaces, lines and points, that form the phenotypic organization of the human body. Although encompassed by the definition of anatomical structure, biological macromolecules do not come under the purview of the science of human anatomy.

[Source: ISO 16278:2016(en), 2.1]

C.2.69 human augmentation
human performance enhancement
HPE

technologies that intend to augment the mental and physical capabilities of the human body by using artificial, scientific, and/or natural technology

[Source: Modified from https://cmte.ieee.org/futuredirections/2018/08/09/transhumanism-evolving-the-human-body-ii/. Accessed on 2022-06-21]

C.2.70 human body-on-a-chip

multi-channel 3-D microfluidic cell culture, integrated circuit (chip) that simulates the activities, mechanics and physiological response of an entire human body

[Source: Modified from https://en.wikipedia.org/wiki/Organ-on-a-chip. Accessed on 2022-06-21]

C.2.71 implant

medical device (C.2.76) which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by means of clinical intervention and which is intended to remain in place after the procedure

[Source: ISO 10993-1:2018, 3.10]

C.2.72 life sciences

sciences concerned with the study of living organisms (C.2.86), including biology, botany, zoology, microbiology, physiology (C.2.89), biochemistry, and related subjects

[Source: Oxford dictionary]

C.2.73 M-CELS
multi-cellular engineered living systems

purpose-driven living systems with multiple interacting living components engineered for specific goals or functions but take emergence into account during the design process, allowing the final system to emerge through natural and non-natural biological proc esses

[Source: https://m-cels.mit.edu. Accessed on 2023-04-25]

C.2.74 microbiome

characteristic microbial community occupying a reasonably well-defined habitat which has distinct physio-chemical properties

[Source: https://en.wikipedia.org/wiki/Microbiome. Accessed on 2022-06-21]

C.2.75 microbiomics

scientific study of the microbiome (C.2.74)

[Source: https://www.dictionary.com/browse/microbiomics. Accessed on 2022-06-21]

C.2.76 medical device

instrument, apparatus, appliance, material, or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purpose of

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process, and
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which can be assisted in its function by such means

Note 1 to entry: Devices are different from drugs and their biological evaluation requires a different approach.

Note 2 to entry: Use of “medical device” includes dental devices.

[Source: ISO 20342-1:2022, 3.21]

C.2.77 megagenomics

study of the structure and function of entire nucleotide sequences isolated and analyzed from all the organism (C.2.86) in a bulk s ample

[Source: https://www.genome.gov/genetics-glossary/Metagenomics#. Accessed on 2022-09-09]

Note 1 to entry: Metagenomics is often used to study a specific community of microorganisms, such as those residing on human skin, in the soil or in a water sample. See also shotgun metagenomics.

C.2.78 metabolic engineering

practice of optimizing genetic and regulatory processes within cells to increase the cell's production of a certain substance

Note 1 to entry: These processes are chemical networks that use a series of biochemical reactions and enzymes that allow cells to convert raw materials into molecules necessary for the cell's survival. Metabolic engineering specifically seeks to mathematically model these networks, calculate a yield of useful products, and pin-point parts of the network that constrain the production of these products.

[Source: https://en.wikipedia.org/wiki/Metabolic_engineering#/media/File:Computational_design_and_evaluation_of_DNA_circuits_to_achieve_optimal_perf–rmance.svg. Accessed on 2022-06-21]

C.2.79 metabolome

complete set of metabolites to be found within an organism or a biological sample

[Source: ISO 23118:2021, 3.7]

C.2.80 metabolomics

scientific study of the metabolome (C.2.79)

C.2.81 molecular biophysics

study of the physical principles governing biomolecular systems

Note 1 to entry: Molecular biophysics seeks to explain biological function in terms of molecular structure, dynamics and organization, from single molecules to supramolecular structures.

[Source: https://www.nature.com/subjects/molecular-biophysics. Accessed on 2023-03-19]

C.2.82 molecular farming

production of proteins or other metabolites in vegetable organisms valuable to medicine or industry

[Source: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/molecular-farming]

C.2.83 neurobotics

multidiscipline of neuroscience, robotics (C.3.41), and artificial intelligence (C.3.3), which focuses on building computational models and hardware mimicking the structure, function, and behaviour of the nervous system

Note 1 to entry: Usually including rehabilitation robots and embodied neural robots.

[Source: ISO/IEC JTC 1 N15401]

C.2.84 neuroscience

scientific study of the nervous system.

Note 1 to entry: It is a multidisciplinary science that combines physiology, anatomy, molecular biology, developmental biology, cytology, computer science (C.3.13), and mathematical modelling to understand the fundamental and emergent properties of neurons, glia and neural circuits.

[Source: Wikipedia: https://en.wikipedia.org/wiki/Neuroscience. Accessed on 2022-06-21]

C.2.85 neurostimulation
neuromodulation

technology that modulates neural activities on a specific goal by invasive or non-invasive means

Note 1 to entry: Stimulation may include: electric, magnetic, optic, mechanical, and chemical methods, also the combination of the methods above.

Note 2 to entry: The targeted delivery of neurostimulation usually aims at alternating neural activities.

[Source: ISO/IEC JTC 1 N15401]

C.2.86 organism

individual living entity anatomical origin that can react to stimuli, reproduce, grow, and maintain homeostasis

[Source: ISO 11238:2018, 3.56]

C.2.87 organoid

miniaturized and simplified version of an organ produced in vitro in three dimensions that shows realistic micro-anatomy

Note 1 to entry: Organoids are three-dimensional assemblies that contain multiple cell types, arranged similarly to the cells in a specific tissue, at least at the micro-scale.

[Source: Wikipedia: https://en.wikipedia.org/wiki/Organoid, the Note is from Jamie A. Davies, in Organoids and Mini-Organs, 2018. Accessed on 2022-06-21]

C.2.88 organ-on-chip
OoC

multi-channel 3-D microfluidic cell culture, integrated circuit (chip) that simulates the activities, mechanics and physiological response of an entire organ or an organ system, a type of artificial organ

[Source: https://en.wikipedia.org/wiki/Organ-on-a-chip. Accessed on 2022-06-21]

C.2.89 physiology

way in which an organism (C.2.86) or bodily part functions

[Source: Derived from Oxford Languages]

C.2.90 precision agriculture

farming management strategy based on observing, measuring and responding to temporal and spatial variability to improve agricultural production sustainability

[Source: https://www.ispag.org/about/definition. Accessed on 2022-04-25]

C.2.91 proteome

entire complement of proteins that is or can be expressed by a cell, tissue, or organism

[Source: Oxford Languages]

C.2.92 proteomics

scientific study of the proteome (C.2.91)

[Source: Oxford Languages]

C.2.93 shotgun megagenomics

untargeted and uncultured metagenomic (C.2.77) analysis of all organisms (C.2.86) in a complex sample by sequencing random DNA strands.

[Source: Modified from https://en.wikipedia.org/wiki/Shotgun_sequencing. Accessed on 2022-09-09, and other Sources]

C.2.94 smart farming

agricultural concept of applying advanced sensing (C.3.43), tracking, monitoring, automation, biotechnologies (C.2.43), and information technology (C.3.27) to achieve optimum production with minimal resource input

C.2.95 synthetic biology

area of engineering (C.3.23) and science, which aims at redesigning and creating novel artificial biological pathways or synthetic biomolecules

[Source: https://www.sciencedirect.com/topics/engineering/synthetic-biology. Accessed on 2022-06-21]

C.2.96 systems biology

study of the interactions and behaviour of the components of biological entities, including molecules, cells, organs, and organisms (C.2.86)

[Source: https://www.britannica.com/science/systems-biology. Accessed on 2023-03-19]

C.2.97 transgenic organism

organism (C.2.88) that contains novel genetic material, e.g. originally derived from different species or synthetic, that has been inserted into the genome using recombinant DNA techniques

Note 1 to entry: See genetically modified organism (C.2.64).

[Source: ISO/FDIS 16577-2022, 3.21- – modified – note 1 was added]

C.2.98 transcriptome

set of all RNA molecules in one cell or a population of cells for a specific developmental stage or physiological condition

[Source: ISO/TS 22690:2021, 3.21]

C.2.99 transcriptomics

study of transcriptomes (C.2.98) and their functions

[Source: Oxford Languages]

C.2.100 urban climate informatics
UCI

study of urban climatology through an analysis of the interaction between a city and the overlying atmosphere using a combination of climate science, statistics and digital and information technologies (C.3.27) such as the internet of things (C.3.28), novel sensing approaches, machine learning, big data (C.3.9) and data mining (C.3.18)

[Source: Modified from Middel, Ariane, Nazarian, Negin, Demuzere, Matthias, and Bechtel, Benjamin. Urban Climate Informatics: An Emerging Research Field. Retrieved from https://par.nsf.gov/biblio/10328203. Frontiers in Environmental Science 10. Web. doi:10.3389/fenvs.2022.867434.]

C.2.101 wastewater-based epidemiology
WBE

analysis of wastewater to determine and monitor the consumption of, or exposure to, chemicals or pathogens in a population

Note 1 to entry: Can be done through biosensing (C.2.41).

[Source: Modified from https://en.wikipedia.org/wiki/Wastewater-based_e–idemiology. Accessed on 2022-03-19]

C.2.102 wearable
wearable technology
smart wear

smart wearable devices (C.2.103) that detect, analyze, and transmit information concerning body signals such as vital signs, and/or ambient data (C.3.16) and which allow in some cases immediate biofeedback (C.2.17) to the wearer

Note 1 to entry: See embodied computing (C.2.58).

[Source: Modified from: https://en.wikipedia.org/wiki/Wearable_technology. Accessed on 2022-06-21]

C.2.103 wearable device

electronic device intended to be located near to, on or in a body

Note 1 to entry: Wearable devices often have a variety of sensing abilities, but limited power capacity constraining communication and data processing abilities. As critical devices of the IoT (C.3.28), it is considered that the communication between wearable devices and a network might not require any human intervention. Wearable devices include electronic devices usable by humans, animals, and other organisms.

[Source: ISO/IEC 20924:2021, 3.1.36]

C.3 Selected IT and engineering supporting definitions

C.3.1 3D printing

fabrication of objects through the deposition of a material using a print head, nozzle or another printer technology

[Source: ISO/ASTM 52900, 3.3.1]

C.3.2 actuator

device that provides a physical output in response to an input signal in a predetermine d way

[Source: IS O/IEC 29182-2:2013(en), 2.1.1]

C.3.3 ambient intelligence
AmI
ambient computing

paradigm that refers to electronic environments that are sensitive and responsive to events (such as the presence of people for instance)

[Source: Modified from: https://en.wikipedia.org/wiki/Ambient_intelligence. Accessed on 2022-06-21]

C.3.4 artificial intelligence
AI

<discipline> research and development of mechanisms and applications of AI systems (C.3.5)

Note 1 to entry: Research and development can take place across any number of fields such as computer science, data science (C.3.20), humanities, mathematics and natural sciences.

[Source: ISO/EC 22989, 3.1.3]

C.3.5 artificial intelligence system
AI system

engineered system (C.3.49) that generates outputs such as content, forecasts, recommendations or decisions for a given set of human-defined objectives

Note 1 to entry: The engineered system can use various techniques and approaches related to artificial intelligence (C.3.4) to develop a model to represent data (C.3.16), knowledge (C.3.31), processes, etc. which can be used to conduct tasks (ISO/IEC FDIS 22929, 3.1.35)

Note 2 to entry: AI systems are designed to operate with varying levels of automation (C.3.7).

[Source: ISO/IEC 22929, 3.1.4]

C.3.6 artificial intelligence of things
AIoT

integration of artificial intelligence (C.3.5) technologies within an Internet of Things (C.3.28) infrastructure

Note 1 to entry: This is to achieve more efficient IoT operations, improve human-machine interactions and enhance data management and analytics.

[Source: modified from https://en.wikipedia.org/wiki/Artificial_intelligence_of_things. Accessed on 2022-06-21]

C.3.7 automatic
automation
automated

pertaining to a process or system that, under specified conditions, functions without human intervention

[Source: ISO/IEC 2382:2015, 2121282, modified – In the definition, “a process or equipment” has been replaced by “a process or system” and

preferred terms of “automated and automation” are added.]

[Source: ISO/IEC 22929, 3.1.7]

C.3.8 behavioural interoperability

interoperability (C.3.29) so that the actual result of the exchange achieves the expected outcome

[Source: ISO/IEC 19941:2017 3.1.6]

C.3.9 bigdata

extensive datasets (C.3.21) – primarily in the data (C.3.16) characteristics of volume, variety, velocity, and/or variability – that require a scalable technology for efficient storage, manipulation, management, and analysis

Note 1 to entry: Big data is commonly used in many different ways, for example as the name of the scalable technology used to handle big data extensive datasets.

[Source: ISO/IEC 20546:2019, 3.1.2]

C.3.10 cloud computing

paradigm for enabling network access to a scalable and elastic pool of shareable physical or virtual resources with self-service provisioning and administration-on-demand

Note 1 to entry: Examples of resources include servers, operating systems, networks, software, applications, and storage equipment.

[Source: IS O/IEC 22123-1:2021, 3.2.1]

C.3.11 cloud services

one or more capabilities offered via cloud computing (C.3.10) invoked using a defined interface

[Source: IS O/IEC 22123-1: 2021, 3.2.2]

C.3.12 computer crime

crime committed through the use, modification, or destruction of hardware, software, or data

[Source: ISO/IEC/IEEE 24765:2017, 3.719]

C.3.13 computer science

branch of science and technology that is concerned with information processing by means of computers

[Source: ISO/IEC/IEEE 24765:2017, 3.731]

C.3.14 constituent system

independent system (C.3.49) that forms part of a system of systems (SoS) (C.3.50)

Note 1 to entry: Constituent systems can be part of one or more SoS. Each constituent system is a useful system by itself, having its own development, management, utilization, goals, and resources, but interacts within the SoS to provide the unique capability of the SoS.

[Source: ISO/IEC/IEEE 21839:2019, 3.1.1]

C.3.15 cyber-physical system
CPS

comprise interacting digital, analog, physical, and human components engineered for function through integrated physics and logic

[Source: NIST 2020]

C.3.16 data

representation of facts, concepts, or instructions represented in a digital and formalized manner suitable for communication, interpretation, or processing by human beings or by automatic means

[Source: ISO/IEC 20924: 2021, 3.1.13 and ISO/IEC 20546: 2019, 3.1 – Modified – “information” was removed and replaced by “facts, concepts, or instructions” and note 1 was merged in the definition]

C.3.17 data analytics

composite concept consisting of data (C.3.16) acquisition, data collection, data validation, data processing, including data quantification, data visualization, and data interpretation

Note 1 to entry: Data analytics is used to understand objects represented by data (C.3.16), to make predictions for a given situation, and to recommend on steps to achieve objectives. The insights obtained from analytics are used for various purposes such as decision-making, research, sustainable development, design, planning, etc.

[Source: ISO/IEC 20546:2019, 3.1.6]

C.3.18 data mining

computational search and retrieval process that identifies patterns by analysing quantitative data (C.3.16) from different perspectives and dimensions, categorizing it, and summarizing potential relationships and impacts

[Source: ISO 5127:2017, 3.10.2.05]

C.3.19 data processing

systematic performance of operations upon data (C.3.16)

Note 1 to entry: Example: Arithmetic or logic operations upon data, merging or sorting of data, or operations on text, such as editing, sorting, merging, storing, retrieving, displaying, or printing.

Note 2 to entry: The term data processing should not be used as a synonym for information processing.

[Source: ISO/IEC 2382:2015, 2121276]

C.3.20 data science

extraction of actionable knowledge from data (C.3.16) through a process of discovery, or hypothesis and hypothesis testing

[Source: ISO/IEC 20546:2019, 3.1.10]

C.3.21 data set
dataset

identifiable collection of data (C.3.16) available for access or download in one or more formats

[Source: ISO/IEC 20546: 2019, 3.1.11]

C.3.22 digital twin
DTw

digital representation of a target entity with data (C.3.16) connections that enable convergence between the physical and digital states at an appropriate rate of synchronization

Note 1 to entry: Digital twins have some or all of the capabilities of connection, integration, analysis, simulation, visualization, optimization, etc.

Note 2 to entry: Digital twin may provide an integrated view throughout the lifecycle of the target entity.

[Source: ISO /IEC CD 30173:2021-12-10, 3.1.1]

C.3.23 engineered

anything that benefited from an application of science to analyze, plan, design and implement processes, products or services to meet stakeholders needs and expectations

[Source: modified from ISO/IEC 9092:2019, 3.1.2]

C.3.24 harm

injury or damage to the health of people, or damage to property or the environment

[Source: ISO/IEC Guide 51:2014, 3.1]

C.3.25 informatics

<systems> study of the structure, behaviour, and interactions of natural and engineered computational systems

Note 1 to entry: Informatics studies the representation, processing, and communication of information in natural and engineered systems. It is basically the science of information.

[Source: Modified from https://www.ed.ac.uk/files/atoms/files/what20is20informatics.pdf. Accessed on 2022-06-21]

C.3.26 information

data (C.3.16) in context that enables interpretation with meaning and relevance

[Source: ISO/TR 17119:2005, 2.13]

C.3.27 information technology
IT

resources used to acquire, process, store, and disseminate information (C.3.26)

[Source: ISO/IEC 38500 :2015, 2.12]

C.3.28 internet of things
IoT

infrastructure of interconnected entities, people, systems (C.3.49) and information resources together with services which processes and reacts to information from the physical world and virtual world

[Source: ISO/IEC 20924:2018, 3.2.1]

C.3.29 interoperability

ability for two or more systems (C.3.49) or applications to exchange information (C.3.26) and to mutually use the information that has been exchanged

[Source: ISO/IEC 19941:2017 3.3.1]

C.3.30 knowledge

outcome of the assimilation of information, the body of facts, principles, theories and practices that is related to a field of work, through learning (theoretical and/or factual)

Note 1 to entry: Adapted from European Council Recommendation 2017/C 189/03, Annex I, (f)

[Source: 14731:2019(en), 3.6]

C.3.31 knowledge

<artificial intelligence> abstracted information (C.3.26) about objects, events, concepts or rules, their relationships and properties, organized for goal-oriented systematic use

Note 1 to entry: Knowledge in the AI domain does not imply a cognitive capability, contrary to usage of the term in some other domains. In particular, knowledge does not imply the cognitive act of understanding.

Note 2 to entry: Information (C.3.26) can exist in numeric or symbolic form.

Note 3 to entry: Information (C.3.26) is data (C.3.16) that has been contextualized, so that it is interpretable. Data is created through abstraction or measurement from the world.

[Source: ISO/IEC FDIS 22989, 3.1.21]

C.3.32 metadata
meta data

data (C.3.16) that defines and describe other data

[Source: ISO/TR 3985:2021, 3.10]

C.3.33 model

physical, mathematical or otherwise logical representation of a system, entity, phenomenon, process or data (C.3.16)

[Source: ISO/IEC 18023-1:2006, 3.1.11, modified – Remove comma after “mathematical” in the definition. “or data” is added at the end.]

[Source: ISO/IEC FDIS 22989, 3.1.23]

C.3.34 nanotechnology

application of scientific knowledge to manipulate and control matter predominantly in the nanoscale to make use of size- and structure-dependent properties and phenomena distinct from those associated with individual atoms or molecules, or extrapolation from larger sizes of the same material

[Source: ISO/TR 10993-22:2017, 3.18]

C.3.35 ontology

specification of concrete or abstract things, and the relationships among them, in a prescribed domain of knowledge

[Source: 19763-1:2015, 4.1.20]

C.3.36 policy interoperability

interoperability (C.3.29) while complying with the legal, organizational, and policy frameworks applicable to the participating systems

[Source: ISO/IEC 19941:2017 3.1.7]

C.3.37 privacy

freedom from intrusion into the private life or affairs of an individual

[Source: ISO /IEC DTS 5723:2021, 3.2.9]

C.3.38 quantum sensor

device whose functionality or principle of operation depends essentially on quantum mechanical effects that observes and measures a physical property of a natural phenomenon or man-made process and converts that measurement into a signal

[Source: Modified from ISO/IEC 29182-2:2013(en), 2.1.5 and Encyclopedia of Condensed Matter Physics, 2005, Pages 17-22, https://doi.org/10.1016/B0-12-369401-9/00500-3]

C.3.39 risk

<organization> effect of uncertainty on objectives

Note 1 to entry: An effect is a deviation from the expected – positive or negative.

Note 2 to entry: Uncertainty is the state, even partial, of deficiency of information related to, understanding or knowledge of, an event, its consequence, or likelihood.

Note 3 to entry: Risk is often characterized by reference to potential "events" (as defined in ISO Guide 73:2009, 3.5.1.3) and "consequences" (as defined in ISO Guide 73:2009, 3.6.1.3), or a combination of these.

Note 4 to entry: Risk is often expressed in terms of a combination of the consequences of an event (including changes in circumstances) and the associated "likelihood" (as defined in ISO Guide 73:2009, 3.6.1.1) of occurrence.

Note 5 to entry: This constitutes one of the common terms and core definitions of the high-level structure for ISO management system standards. The original definition has been modified by adding "on objectives" to align with the definition of risk in ISO Guide 73:2009, 1.1.

[Source: Modified from ISO 34101-1:2019, 3.48 – the domain "organization" was added]

C.3.40 risk

<product> combination of the probability of occurrence of harm (C.3.27) and the severity of that harm

Note 1 to entry: The probability of occurrence includes the exposure to a hazardous situation, the occurrence of a hazardous event and the possibility to avoid or limit the harm.

[Source: Modified from ISO/IEC Guide 51:2014 – the domain "product" was added]

C.3.41 robot

automation (C.3.7) system (C.3.49) with actuators (C.3.2) that performs intended tasks in the physical world, by means of sensing (C.3.43) its environment and a software control system

Note 1 to entry: A robot includes the control system and interface of a control system.

Note 2 to entry: The classification of a robot as industrial robot or service robot is done according to its intended application.

Note 3 to entry: In order to properly perform its tasks, a robot makes use of different kinds of sensors (C.3.43) to confirm its current state and perceive the elements composing the environment in which it operates.

[Source: ISO/IEC 22989, 3.1.29]

C.3.42 semantic interoperability
interoperability (C.3.29) so that the meaning of the data model within the context of a subject area is understood by the participating systems

[Source: ISO/IEC 21823-1:2019, 3.9.]

C.3.43 sensor
device that observes and measures a physical property of a natural phenomenon or man-made process and converts that measurement into a signal

Note 1 to entry: Signal can be electrical, chemical, etc.

[Source: IS O/IEC 29182-2:2013(en), 2.1.5]

C.3.44 socio-technical system
system (C.3.49) that includes a combination of technical and human or natural elements

[Source: I SO/IEC DT5723:2022, 3.3.9]

C.3.45 sociotechnological
of, pertaining to, or signifying the combination or interaction of social and technological factors

[Source: https://www.collinsdictionary.com/dictionary/english/sociote–hnological. Accessed on 2022-06-21]

C.3.46 sociotechnology
socio technology
study of processes on the intersection of society and technology

Note 1 to entry: includes a combination of technical and human or natural factors.

[Source: https://en.wikipedia.org/wiki/Sociotechnology. Accessed on 2022-06-21]

C.3.47 sustainability
state of the global system, including environmental, social and economic aspects, in which the needs of the present are met without compromising the ability of future generations to meet their own needs

[Source: ISO 23434-1:2021, 3.1]

C.3.48 syntactic interoperability
interoperability (C.3.29) such that the formats of the exchanged information can be understood by the participating systems

[Source: ISO/IEC 19941:2017 3.1.4]

C.3.49 system
combination of interacting elements organized to achieve one or more stated purposes

[Source: ISO/IEC/IEEE 21840:2019, 3.1.8]

C.3.50 system of systems
set of systems (C.3.49) and system elements that interact to provide a unique capability that none of the constituent systems can accomplish on its own

Note 1 to entry: System elements can be necessary to facilitate interaction of the constituent systems (C.3.14) in the system of systems.

[Source: ISO/IEC/IEEE 21840:2019, 3.1.10]

C.3.51 transport interoperability
interoperability (C.3.29) where information exchange uses an established communication infrastructure between the participating systems

[Source: ISO/IEC 19941:2017 3.1.3]

C.3.52 trustworthiness
ability to meet stakeholders' expectations in a verifiable way

Note 1 to entry: Depending on the context or sector, and also on the specific product or service, data (C.3.16), technology and process used, different

characteristics apply and need verification to ensure stakeholders' expectations are met.

Note 2 to entry: Characteristics of trustworthiness include, for instance, accountability, accuracy, authenticity, availability, controllability, integrity, privacy, quality, reliability, resilience, robustness, safety, security, transparency and usability.

Note 3 to entry: Trustworthiness is an attribute that can be applied to services, products, technology, data (C.3.16) and information as well as to organizations.

Note 4 to entry: Verifiability includes measurability and demonstrability by means of objective evidence.

[Source: ISO /IEC DTS 5723:2022, 3.1.1]

C.3.53 virtual sensor
inferential sensor
logical sensor
soft sensor

software component that uses information available from other measurements and parameters to calculate an estimate of the quantity of interest

Note 1 to entry: Virtual sensors can infer the state of an object without direct access to a specific physical sensor (C.3.43).

Note 2 to entry: Virtual sensors are capable of capturing context data (C.3.16) from software applications or services.

[Source: Modified from https://en.wikipedia.org/wiki/Virtual_sensing, https://www.bluefruit.co.uk/quality/virtual-sensors-for-digital-twins/ and https://www.igi-global.com/dictionary/virtual-sensor/34977. Accessed on 2022-06-21]

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