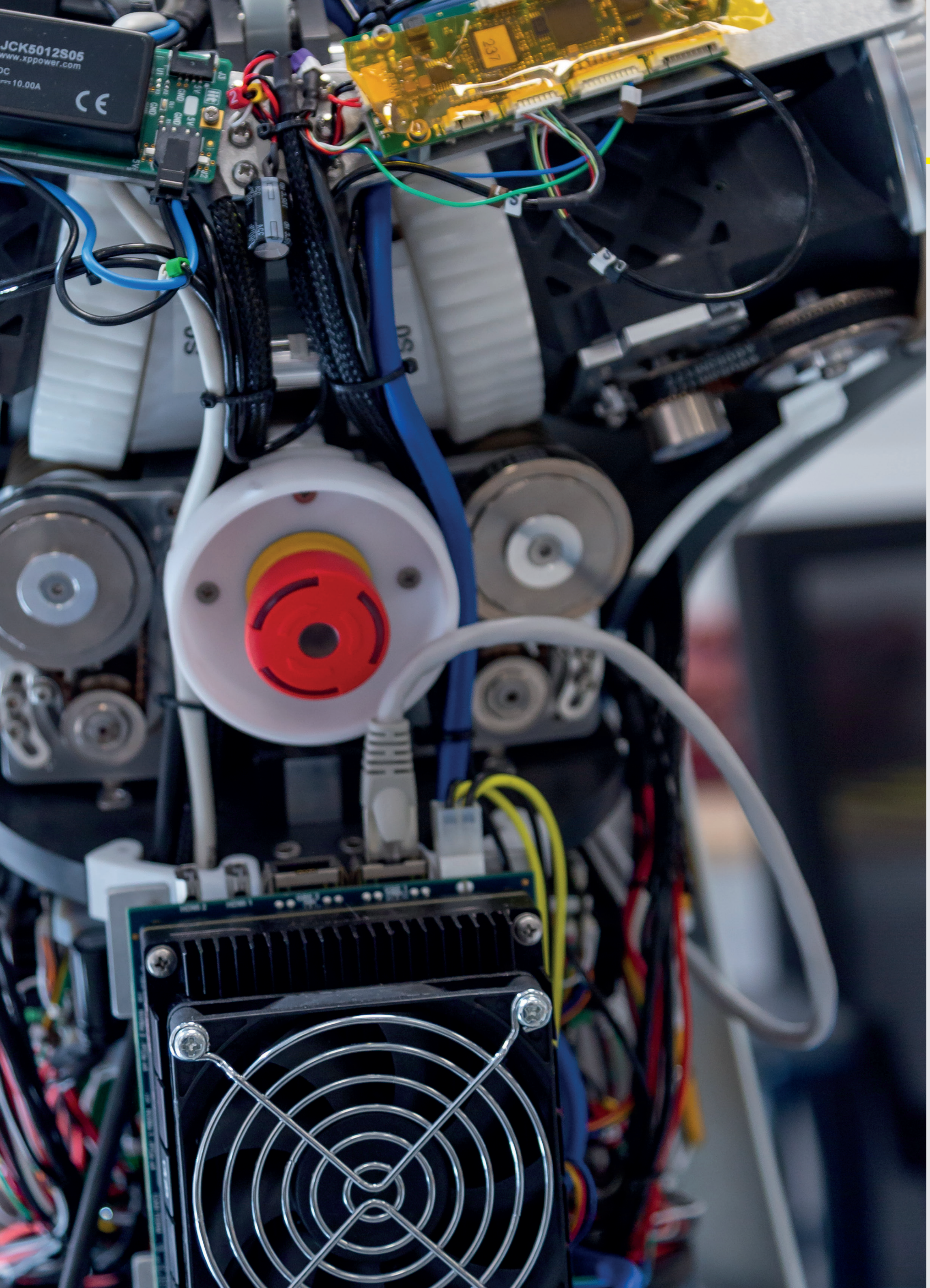

STRATEGIC PLAN TECHNICAL ANNEX 2018-2023

INTERIM UPDATE 2020

ISTITUTO ITALIANO DI TECNOLOGIA

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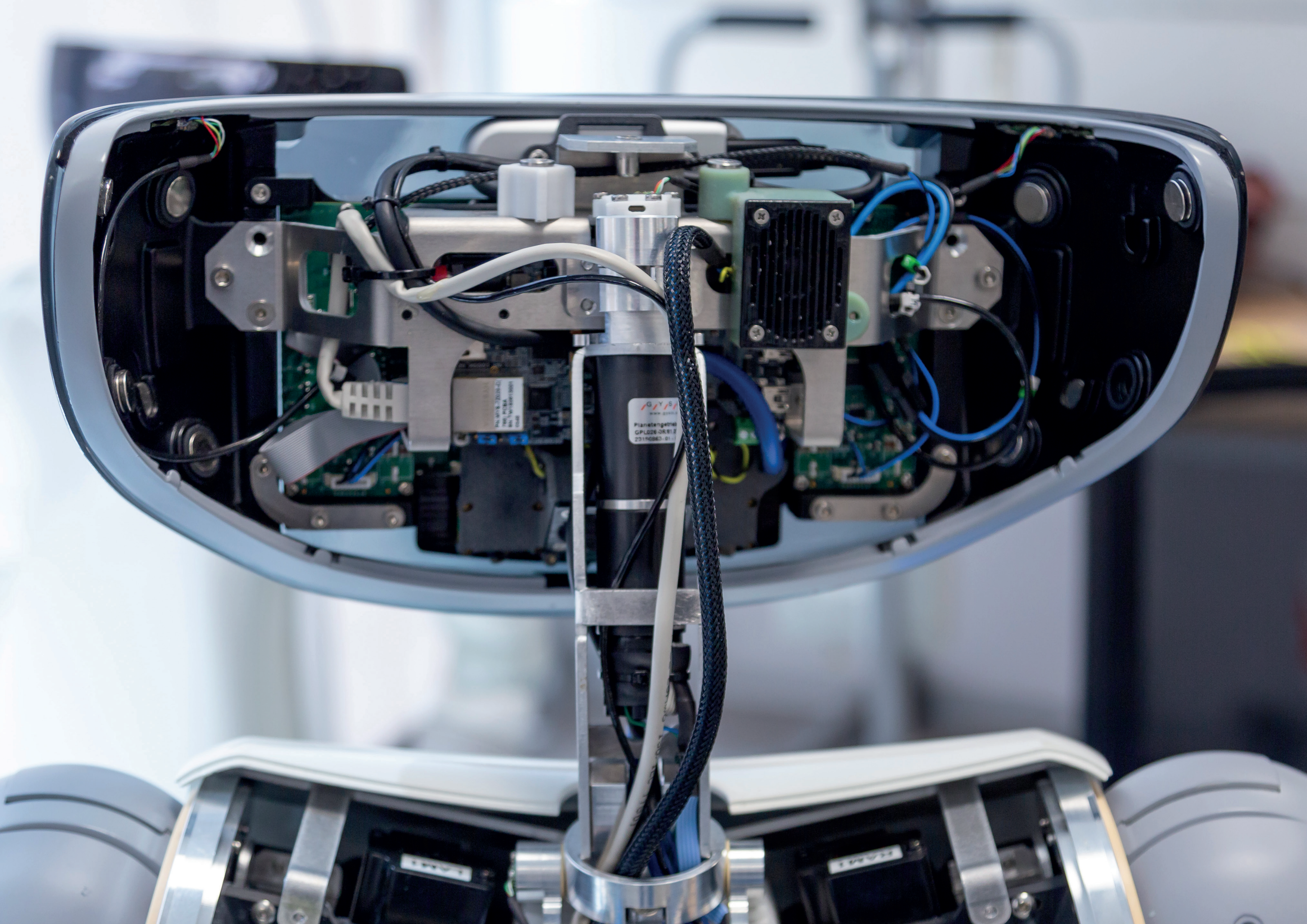


The Robotics Research Domain

Globally aging populations and demographic changes will require new, innovative, and sympathetic approaches to all aspects of human life. Within this context, robotics and artificial intelligence (AI) have great potential to assist, augment, and empower humans. Advanced robots will not be confined to factories and manufacturing tasks. Rather, they will leave the laboratories and the factory floor to help us in daily life. In addition to improving industrial production, AI-enabled robots will assist us in our personal lives (assistive technologies for the elderly and in healthcare), manage and improve safety in hazardous environments (safeguarding human life), and enhance medical treatment (improving quality of life).

The Robotics Research Domain (RD) has five Priorities: Mechatronics, Soft Robotics, Social Cognition and Human Robot Interaction, Biomedical Robotics, and Intelligent Companion Robots (Figure 1). Some of these Priorities have a thematic character (Social Cognition and Human Robot Interaction, Intelligent Companion Robots), while others are of a more technological nature (Mechatronics, Soft Robotics). However, they are all strongly focused on applications, often in connection with the other RDs (e.g. new materials for robotics, machine learning (ML), biomedical applications).

The translational activities (Technology Transfer Mission) cut across all Priorities, with the twin goals of industrial and clinical translation. To achieve industrial translation, we will link our research to industry to create new products and innovative industrial processes. To achieve clinical translation, we will create a national clinical network with top clinical research institutions to transfer medical robotics research to the clinic (in close connection with the Technologies for Life Science (LifeTech) RD). Robotics will thus positively impact sustainability, healthcare, and aging society.

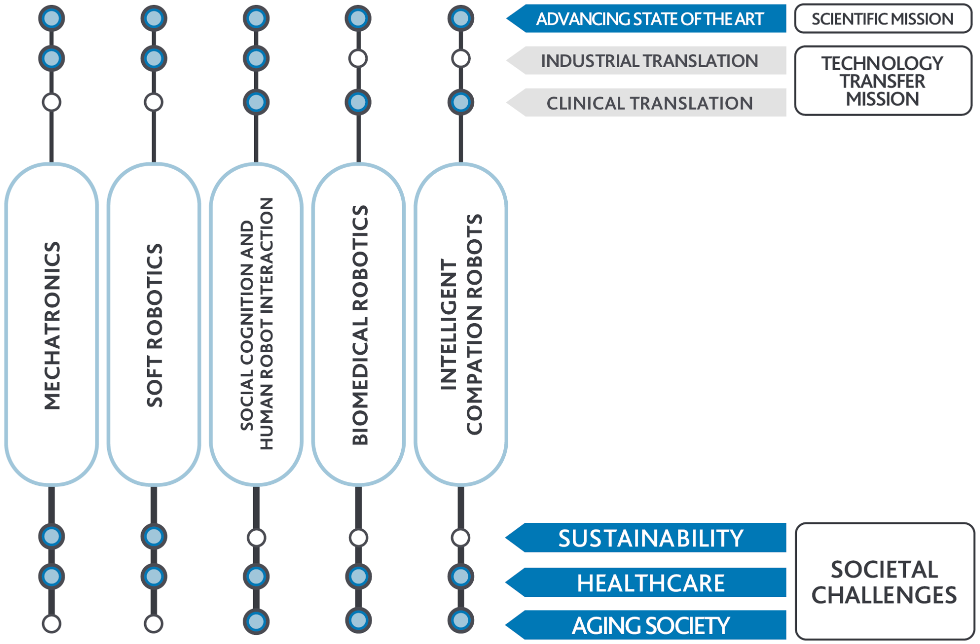


Figure 1: Priorities of the Robotics RD, contribution to IIT's mission, and impact on the Challenges.

Scientific Mission

To fulfill IIT's Scientific Mission, the Robotics RD will continue to pursue and expand the successful research lines established in the Institute's first 10 years of operation. The Robotics RD will advance the state of the art by developing new robotic platforms in hardware and software. To effect pivotal changes in a sympathetic, sustainable, and human-centered manner, robotics must integrate many complementary scientific and technological activities relating to the broad concepts of bodyware (mechanical structures, electronics, sensors, actuators, computers, and batteries) and mindware (soft systems for computation, control, reasoning, learning, perception, and cognition in general). In particular, our research program will focus on designing novel "bodies" with new materials carefully engineered to improve performance, efficiency, reliability, and safety. The future "mind" of the robots will include many AI techniques to achieve adaptability, friendliness, and ease of use in the most disparate environments with increased autonomy. IIT's research laboratories, organization, and infrastructure encourage a close integration of bodyware and mindware. As a result, IIT is in an almost unique position to develop the most advanced robotic platforms and, simultaneously, to create software to fully exploit the platforms' hardware. Extending this bodyware/mindware paradigm, social interaction studies will identify problems and provide unique information, guidance, and understanding of what humans require from the next generation of hardware platforms.

Technology Transfer Mission

In recent years, the Robotics RD has experienced tremendous growth in its technology transfer (TT) activities. IIT has used a broad spectrum of contractual instruments, including traditional sponsored research agreements, the creation of start-ups, and licensing arrangements through Joint Labs. IIT already collaborates with Leonardo, Ansaldo Energia, and Fameccanica under focused research-driven agreements. Joint Labs are particularly relevant. The Moog@IIT Joint Lab will result in the next generation of hydraulic actuated robots. A Joint Lab with Gruppo Camozzi SpA studies collaborative robots for industry 4.0 and is already delivering high technology readiness level (TRL) results. With Danieli Automation, IIT is developing applications for the steel production industry. IBM has helped develop AI packages for the R1 robot in a healthcare context.

There have been several start-up activities, most notably Movendo Technology in the field of rehabilitation robotics. In the next six years, IIT will likely experience a growing number of opportunities to create start-ups around several existing projects (namely R1, iCub, WalkMan, Centauro, HyQ), either in their current form or following further development. Results from these projects will be expanded to clinical applications in the domain of robotic surgery (IRCCS San Martino-IST and IRCCS G. Gaslini Children's Hospital) and in the theranostic robotics program (IRCCS G. Gaslini Children's Hospital).

In the theranostic robotics program, IIT is developing sensorimotor intervention protocols for children with autism spectrum disorders (ASD) with young patients from the Fondazione Don Orione care service. With INAIL (IIT-INAIL Joint Lab), we will continue and broaden our development of prostheses (hand, leg), exoskeletons (lower limb), and rehabilitation devices (shoulder).

Sustainability Challenge: Safe and clean production

Robots with legs (two or four) are perhaps uniquely suited to working towards sustainability with respect to safe and clean production processes. Robotic vehicles, initially wheeled, but possibly legged, will be able to autonomously assess farmland on a 24/7 basis. Walking will provide greater stability on slopes and hillsides, while feet (as opposed to tires) will reduce soil damage (i.e. compaction). Agricultural vehicles already use GPS to position themselves within a few centimeters of a target. Future work at IIT will address the issue of dosage (fertilizers, pesticides, and water), optimizing their amounts and reducing costs. As part of the Joint Lab with Università Cattolica del Sacro Cuore, IIT is developing robots for automated winter pruning (e.g. of grapevines) by combining ML with advanced locomotion. Harvesting will be product-driven to optimize yield and quality. We will develop vehicles for smaller or less commercial farmland, such as hillsides and remote areas. The robots, initially teleoperated, will eventually become mixed autonomy units. In the longer term, they may have full autonomy. Legged robots are also uniquely suited to working in hazardous areas (e.g. nuclear decommissioning, oil and gas extraction, metal processing).

Our competences in force control, haptics, and teleoperation can effectively remove humans from hazardous environments. Instead, robots can undertake tasks such as waste manipulation, the handling and manipulation of materials, and operations in extreme temperatures. The Robotics RD will develop complete systems that use robots, which can be multiarmed and possibly mobile (wheels or legs), to operate in such hazardous environments. This will improve safety for workers, who will typically control the robots from a distance.

Aging Society Challenge: Intelligent robots

A demographic megatrend will soon affect many developed countries, with 40% of the population aged over 65 by 2050. According to estimates, this demographic imbalance could have an economic impact of over US$10 trillion by 2030. This will affect personal and national wealth, increase the retirement age (people may work well into their 70s), and increase global tensions. A more widespread and diversified use of robotics will be one way to address these problems. Robots can tackle human workforce shortages and maintain the current level of the economy in advanced countries as well as improve working conditions by collaborating with human workers at different levels of autonomy. Increased productivity from greater and better use of robotics and automation will ensure that the retirement age does not spiral out of control. Introducing robots into home and care environments for rehabilitation, assistance, and wellness will help contain the costs of care for the elderly, while maintaining or even improving the quality of this care, thus reducing inequalities while improving wellness. This will require robots that are more autonomous, with advanced AI technologies and cognitive skills supporting more intuitive interfaces. These robots will need to understand the cognitive and social mechanisms involved in human interaction and natural communication, and be able to reason about the outcomes of their own actions and the actions of others. The goal is to create robots that can monitor a patient's condition, survey a hospital ward, and provide useful and safe support and, perhaps, social companionship. Importantly, these robots must be affordable enough for social security systems to subsidize them, perhaps within a "sharing society".

Healthcare Challenge: Affordable rehabilitation, surgery, and prosthetics

Rehabilitation is the forerunner in robotic applications to healthcare. IIT has invested considerably in research into high-performance prosthetic limbs and rehabilitation systems to alleviate the effects of stroke, paralysis, and physical injury. In the near future, IIT will also research and develop lower limb exoskeletons and limb prosthetics for rehabilitation, and new machines for upper-limb rehabilitation. This will be within the scope of the IIT-INAIL Joint Lab, combining basic robotic research with product-driven development and field tests (with patients) to develop the next generation of rehabilitation devices. In advanced robot-assisted surgery, there is a demand to operate at unimaginable levels of accuracy, well beyond the limits of unaided human perception. When the structures are too delicate, the size too small, the required sensitivity too high, or the operation time too long, robotic systems can augment the skills of the surgeon, providing previously unattainable quality. Micro-interventions (e.g. pediatric, otolaryngology) are a particular strength for medical robotics at IIT (c.f. agreements with IRCCS San Martino-IST and IRCCS G. Gaslini Children's Hospital). Robots can also help improve the quality of life for people with ALS and Alzheimer's disease, and provide therapy for children with ASD. In addition, assistive technologies, such as R1, will result in robots that routinely provide care, companionship, and general assistance in home settings.

Priorities of the Robotics Research Domain

In 2021-2022, the Robotics RD laboratories will move to IIT's new Center for Robotics and Intelligent Systems (CRIS, San Quirico building). CRIS will host a new enlarged mechanical workshop with full CAD design and fabrication support, the IIT-INAIL Joint Lab on robotic rehabilitation, and the Moog@IIT Joint Lab. The recently launched Center for Joint Industrial Research (CJIR) will host the Joint Labs with Danieli Automation, Gruppo Camozzi SpA, the industrial robotics facility, and the nodes of the Italian Competence Center on Industry 4.0 (Artes 4.0, Start 4.0).

Additional activities at the Center will be developed jointly with the Soft Robotics laboratories in the Center for Converging Technologies (CCT) in Genoa Morego (in collaboration with the Nanotech RD), with the new ML and computer vision teams of the Computational Sciences RD, and with the teams of the LifeTech RD in the Center for Human Technologies in the Erzelli building.

In the coming years, we expect the Robotics RD to increase its staff numbers by about 10% (currently more than 200 staff members, including 13 PIs and 6 ERC winners) with the inclusion of new PIs in the fields of locomotion and ML.

Priority 1: Mechatronics Program

The heart of IIT's robotics strategy has always been the development of state-of-the-art mechatronics systems. This has led to the creation of internationally recognized humanoid robots (iCub, COMAN, WalkMan, COMAN+, R1) and pioneering quadrupeds (HyQ, HyQ2Max, HyQReal, Centauro) (Figure 2).

IIT's family of cutting-edge robots is not limited to legged systems. With the Plantoid robots, inspired by the sensing and growth mechanisms of plants, the Mechatronics Program has explored completely new designs and operational paradigms, including materials, compliance, soft bodies, and distributed intelligence.

In addition to our advanced integrated robot platforms, IIT researchers have developed components, including novel patented high-performance actuation systems, variable impedance actuators, advanced fingertip and large-area tactile sensors, exoskeletons (leg, arm, hand), instrumented haptic devices, novel medical systems, a variety of force/torque sensors, dexterous manipulators (e.g. SoftHand), and advanced industrial end-effectors.

To meet the challenges of the 2018-2023 Strategic Plan (and beyond), the Mechatronics Program will continue to develop new body design concepts for our integrated robotic systems, leading to better and more efficient robots, particularly the humanoid and legged kind. In these domains, researchers will focus on combining locomotion, manipulation, whole-body capabilities, new materials, and high-dynamics structures. As in most areas of engineering, it will be crucial to optimize energy use. To achieve this, we will use innovative lightweight materials, improve mechatronics to better use the available power, and develop robots with more natural gaits and locomotion skills, coupled with enhanced actuator design. Improvements in ruggedness, robustness, and reliability will require novel kinematics, shock-absorbing materials, and lightweight designs optimized for indoor and outdoor use in dirty and wet environments.

We will develop highly integrated actuation solutions that offer improved power density and efficiency performance and decentralized diagnostics, inspired by the concept of "smart high-performance mechatronics". Novel actuation principles will be prototyped and explored within new design philosophies that will convert bioinspired insights into practical and effective mechatronics solutions to be explored in a forthcoming generation of legged robots.

Looking to the market, systems such as R1 have been designed for prompt affordable market applications. Here, the engineering goals are to reduce mechanical complexity (fewer

Figure 2: The IIT Robot species.

parts, no exposed wires, robust sensors), boost the payload-to-weight ratio, and improve the manipulation skills (dexterous hands, a wider range of movement in the shoulder and wrist). The reduced complexity will lower the cost of the robots, which is particularly important for companion robots. These systems will undergo extensive field-testing with end users, in line with the Technology Transfer Mission. The Joint Lab with Fondazione Don Gnocchi in Milan will explore the application of R1 for rehabilitation in care centers and homes, while a Joint Lab with IBM in Genoa will develop AI-based application packages (such as nurse, office assistant, and housekeeper). Advanced dynamical control and whole-body loco-manipulation are vital for complex human-like robots, particularly for locomotion and human-robot collaboration (HRC).

In robot locomotion, a flexible control strategy requires step recovery, walking, and running capabilities on possibly uneven terrains. Here, advances will require the close integration of engineering (sensing, actuation, mechanics), gait generation, dynamic modelling, and control. The Mechatronics Program will investigate locomotion, gait generation, and gait control in bipeds and quadrupeds. With several robust platforms available (iCub, WalkMan, COMAN+, Centauro, HyQReal), we will develop dynamic locomotion profiles. These will advance locomotion and loco-manipulation, particularly for operation in rough, hazardous, and poorly conditioned terrains, where wheeled and tracked vehicles cannot operate. The current locomotion capabilities for flat and moderately rough terrain will include challenging environments (e.g. soft and unstable terrains). The locomotion framework will achieve more autonomy, allowing the automatic selection of the most suitable gaits/behaviors for the environment. We will use combinations of ML and optimization methods to plan movements and control the robot.

With complex systems such as humanoids, it is vital to achieve simultaneous manipulation and control, while maintaining operational parameters such as balance, walking, and reaching. This requires a new advanced approach to the challenge of control. Torque regulation and interaction sensing and control (through hardware and software) will be critical to success in this domain. At IIT, robots such as WalkMan, COMAN+, Centauro, and iCub feature fully integrated torque sensing. In the near future, exciting development in controller design will advance the functionality of these robots and fill a crucial gap in humanoid and legged robot technology.

HRC, where robots and humans share the workspace, will require flexible structures (e.g. compliant bodies) coupled to active compliance and torque-control software. Future activities will address the real-time monitoring of human behavior (e.g. whole-body dynamics estimation) so that the robot can learn anticipatory behaviors in order to interact physically with humans.

Robotics researchers at IIT have excellent links to our world-leading materials science groups (see Nanomaterials RD). In line with the 2018-2023 Strategic Plan, they will draw on this pooled expertise to create the next generation of advanced robots. In particular, the Robotics RD and the Nanomaterials RD share a roadmap for developing new nanocomposites, biodegradable plastics, sensors, and harvesters for the next generation of affordable robots. A key element will be the extensive use of additive manufacturing to produce new lightweight mechanical structures, which cannot be achieved using conventional techniques. These new mechatronic structures will increase the performance of all IIT robots, including consumer-focused robots (e.g. R1) and high-performance systems (e.g. Centauro, COMAN+, HyQReal).

Soft robotics (see Priority 2: Soft Robotics Program) will also extensively use novel materials to reduce weight, while maintaining flexibility, stiffness, and strength. Research in this domain will aim to produce soft, lightweight, sensitive structures, such as manipulators and grippers. We will exploit additive manufacturing technologies and customized sewing machines to generate 3D-fiber-reinforced structural composites that feature large deformation capacity, high load capacity, and variable stiffness. This approach may also influence the design of rigid robots by replacing rigid joints with soft compliant joints or soft and elastic actuators.

Priority 2: Soft Robotics Program

Soft robotics is a young but rapidly growing area of robotics. It uses inherent or structural compliance to develop more flexible, safe, and adaptive robots. Soft robots can undergo large deformations to better adapt and interact with their environment. Soft robotics is a highly multidisciplinary field, merging biology, materials science, mathematics, biomechanics, chemistry, physics, and computational science. Soft robots are an integral part of the new generation of intelligent systems, which integrate seamlessly, safely, and proficiently with humans and the environment.

The following systems abilities are of great interest in robotics: growing, morphing, perception-based behavior, climbing, versatile gripping, highly dexterous manipulation, muscle-free movement, anchoring, and adhesion. Soft robotics can exceed the limits of current machines by developing technologies for general-purpose applications in unstructured environments.

Living organisms operate in a dynamic and unstructured environment by exerting effective, adaptable, and efficient sensorimotor control. Natural evolution has considerably optimized the design of animal and plant bodies, matching their intelligence to their body structure (embodied intelligence) and distributing the burden of generating action between the body and the brain (morphological computation). Natural systems are very efficient. The Soft Robotics Program will take inspiration from these systems.

Continuum Soft Robotics

The scientific approach of continuum soft robotics conceives of robots as integrated systems rather than as an assembly of components. Intelligence is integrated in the body and co-develops with it, emerging from the body's interaction with the environment. The robot's body is based on multifunctional materials that interact with the environment and are compatible with the application ecosystem. This requires a multidisciplinary design process that merges the "green" and "blue" worlds of the natural and digital environment.

An important consequence of these guiding principles is the possibility of reverse engineering biological systems. This reverse biorobotics uses bioinspired robots as experimental models of biological systems. Although often simple and containing no living matter, robotic models (RM) can be useful for experimentally investigating behaviors that are otherwise difficult to observe or manipulate.

The target abilities for continuum soft robots are to traverse confined spaces, manipulate objects, and reach difficult-to-access sites. Potential applications include natural environment exploration and monitoring, archaeology, medicine, space, infrastructure inspection, and search-and-rescue missions. These abilities have been mastered by plants and soft-bodied invertebrates (i.e. octopus, snail, earthworm) and vertebrates (i.e. elephant trunk). The pioneering work on the world's first plant-inspired robot (the Plantoid) has paved the way for the development of soft robotics at IIT. Specifically, work on the Plantoid launched the new fields of plant-inspired robotics technologies and growing robots. The main research pathways of continuum soft robotics are:

- Innovative plant-inspired robotics technologies with new robotic abilities, such as indeterminate growth, movements without muscles, structural materials with morphological adaptability and variable stiffness, distributed intelligence and sensory systems, anchoring/attachment strategies, intrasystem and intersystem communication, and energy-saving mechanisms.

- The design and development of green and environmentally friendly soft robots for environmental monitoring, in line with IIT's Sustainability Challenge. These robots are based on biodegradable and/or zero-impact materials and sustainable forms of energy.

- Plant-inspired networks and embodied AI, inspired by collective behaviors that allow plants to solve complex problems and exceed their capabilities as individuals. We will model plant networks to explore a new paradigm for robot networks and distributed embodied AI.

- Soft-bodied animal-like robots and soft robotics technologies in order to develop soft robots that can adapt their morphology to conduct exploration tasks in extreme and complex environments. We will focus on the sense of touch. We will investigate natural physical interactions in order to develop new soft and embodied sensing processes.

  The goal is to achieve new robotic solutions that perceive their environment through touch and interact intelligently. We will develop a new generation of universal grippers (able to sense, grasp, manipulate, and release liquid or solid objects with a wide range of payloads, dimensions, and shapes). Active touch will be explored in order to achieve tactile-driven manipulation.

Articulated Soft Robotics

Articulated soft robotics combines state-of-the-art intelligent mechatronic design with insights from complex natural systems, such as vertebrates' musculoskeletal ensembles and their control by the brain. The paradigms and technologies of articulated soft robotics include morphological computation, principled simplification, and co-design of the physics and control of soft limbs, sensors, and actuators.

These paradigms and technologies are applied to produce articulated soft robots that can move naturally, intuitively, safely, efficiently, and with high performance when interacting with the environment and other agents (robots or humans). It is also physically and cognitively simple to interface with these robots.

The main research pathways of articulated soft robotics are:

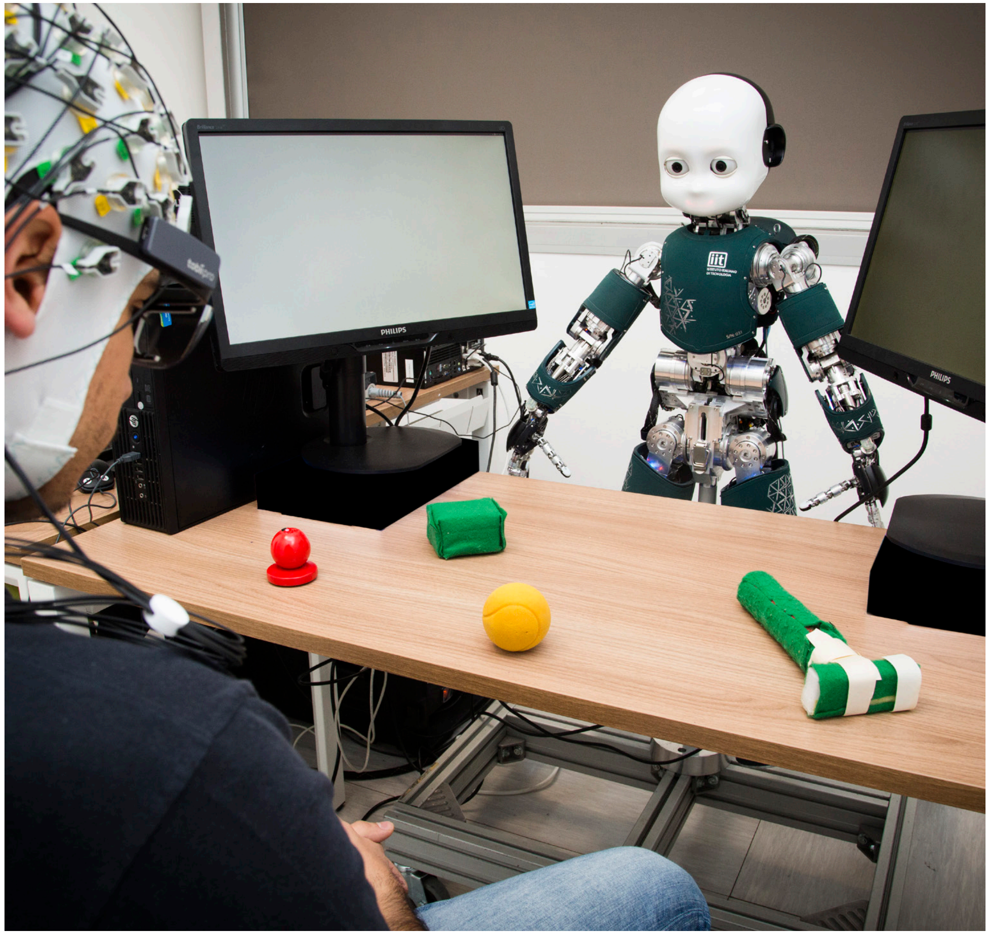
- A new generation of robotic bodies with muscles, joints, legs, arms, hands, and feet that embody the behaviors and abilities of the human neuromusculoskeletal systems. These robotic bodies will have an unprecedented ability to adapt to different environments and scenarios. This will lead to novel autonomous and semiautonomous manipulation and locomotion systems. We expect robots with increased efficacy and efficiency, easier programming and control, and simpler abstraction and integration.

- Efficient, light, and wearable aids to augment, and empower workers and to reduce social differences (e.g. due to age, sex, and physical abilities). The possibilities include exoskeletons, collaborative machines, and intuitive interfaces.

- Next-generation bionic prostheses for the upper and lower limbs that interface naturally with the user and their sensorimotor schema, promoting unprecedented degrees of naturalness, embodiment, and functionality.

- Ergonomic and neuro-aware rehabilitation tools for the assistance and therapeutic support of physical and neural diseases, from hemiparetic patients to stroke survivors.

- Symbiotic teleoperation systems that transcend the limitations of humans and robots to enable a new smart paradigm of remote work, socialization, and caring, not limited by the presence, extent, or possibilities of the human body. This will find application in dirty, hazardous, or remote operation scenarios, such as industrial plants (recycling, nuclear, chemical), infrastructures (roads, ICT, power lines), and natural resources (forests, landfills, mines).



Priority 3: Social Cognition and Human-Robot Interaction Program

Future robots will soon be included in the everyday environment of humans, living and acting in spaces designed for and populated by humans. This physical and/or social contact means that robots must act proactively to avoid impacts or unpredictable behaviors. For humanoids, prostheses, exoskeletons, and surgical systems, success often depends on controlling how much force the robot generates at each instant. However, for robots to behave predictably (according to human standards), they must also display appropriate social signals. Thus, a predictable social robot must address the following issues:

1. How to control its own actions to achieve a goal (i.e. anticipate the effects of its own actions) in a way that humans can understand.

2. How to understand human actions (i.e. how to anticipate the intentions of humans). It is crucial to find the right match between the robot's intent and the human's anticipated responses. To be useful, this must be contingent on the situation and on the human's intentions and skills.

3. How to create anticipatory robotic actions that contribute to improving human factors in collaborative tasks or in environments where humans and robots co-exist, but do not physically interact.

Apart from being predictable, robots generally need to interact in a human-like social manner, appearing friendly, attractive, and intuitive to use. To design such socially capable robots, we must better understand what is necessary for smooth and effective interaction within the human-robot dyad. Addressing this issue requires a rigorous, long-term, and systematic experimental approach to studying the mechanisms that humans use during social interaction. This research will use the methods of cognitive and social neuroscience in well-controlled experimental protocols, in which:

1. Robots will exhibit behaviors typically observed in human social interactions, e.g. gaze-following, human-like movement kinematics, social gestures.

2. Human responses will be measured using behavioral parameters including eye tracking, motion capture, performance measures, and neurophysiological measures (e.g. EEG). These will be compared to responses in natural social human-human interactions.

3. Subtle parameters of robot behaviors will be iteratively manipulated to obtain optimal responses (neurophysiological and behavioral) from the human user.

The expected outcome is a set of robot behaviors that elicit social attunement in the human-robot dyad, and thus a set of guidelines for designing robots tailored to the specific needs and expectations of human partners.

Speech is a special type of interaction that, according to recent neuroscience research, has a shared acoustic-motoric representation in the brain. Despite advances in automatic speech recognition (ASR), robots still have problems recognizing speech during human-robot interactions. This task typically requires high-fidelity recognition of a small number of words in noisy environments. Future robot-centered speech research at IIT will pursue speaker independence (for different speaker typologies, accents, unusual pronunciation, unseen acoustic environments). Importantly, the robot's attentional orienting and the use of multimodal signals (e.g. acoustic and visual) will help to tackle the so-called cocktail party problem. Here, intracranial EEG signals will be used for the multimodal training of ASR algorithms.

In addition, HRC focuses on the physical nature of the cooperation between human(s) and their robotic (single or multiple) coworkers/partners. The goal is to take IIT's advanced technologies in mechatronics and sensory perception systems, and seamlessly integrate them into real-world service and care applications involving direct interactions between humans and robots.

Within this program, our research prioritizes three targets:

- Modelling and analysis of human behavior during physical interactions.

- Intermediate interfaces to improve how the interaction is perceived by the human and the robot (bidirectional).

- Human-in-the-loop robot planning and control.

The first target investigates reliable and intuitive human-robot interfaces that rely on or are inspired by human motor functionalities. The second and third targets aim to enhance the performance of the physical human-robot-environment interaction.

In terms of industrial capacity, HRC will have a strong socioeconomic impact by improving productivity (and safety) while maintaining the involvement of human workers in production processes. In HRC, IIT will synergistically integrate the improved perception of human behavior (e.g. visual perception of posture and movement), human perception of robots (e.g. haptic interface design, speech), and robot decision-making autonomy (e.g. learning and control).

Priority 4: Biomedical Robotics Program

The Biomedical Robotics program covers surgical, rehabilitation, and assistive technologies. It collaborates closely with the Mechatronics, Social Cognition and Human Robot Interaction, and Intelligent Companion Robots programs. It enjoys strong and rapidly developing links with the principal Italian hospitals (IRCCS San Martino-IST, IRCCS G. Gaslini Children's Hospital, the Italian Ministry of Health's National Networks of Clinical Research Institutes). It also collaborates with INAIL[1] through the IIT-INAIL Joint Lab established in 2013 and its latest extension (started in 2020). Under the 2015-2017 Strategic Plan, the Program developed medical systems, starting from a single research prototype and ending with the creation of a start-up company (e.g. from the ARBOT project to Movendo Technology). For the period 2018-2023, we have and will continue to develop this core expertise.

Within the surgical domain, IIT has particular expertise in the micromanipulation and microsurgery of small delicate structures, such as the vocal cords. We will extend this tissue micromanipulation research to generic surgery, while focusing on new opportunities in pediatric surgery and intervention, where the patient's size and anatomical structure are well-suited to robotic assistance for the surgeon, physician, or nurse. We will expand our recent model-based design of flexible tools for minimally invasive surgery. In cooperation with IRCCS San Martino-IST, IIT's roboticists are developing several pioneering approaches to phono-microsurgery. In the coming years, we will conduct clinical trials of these systems in both Robot-Assisted Laser Microsurgery (RALP) and Micro-Robot-Assisted Laser Microsurgery (mRALP). Another focus will be the real-time detection of tissue type (Smart Narrow Band Imaging) and tissue probes. With the IRCCS G. Gaslini Children's Hospital, we will also develop tools for pediatric interventions.

Work on assistive medical technologies will continue to focus on prosthetics, medical exoskeletons, and active rehabilitation systems for different body parts. Important aspects of this work will take place within the IIT-INAIL Joint Lab on Rehabilitation Technologies, which aims to transfer IIT's assistive technologies into high-tech medical products. The strong TT

[1] www.inail.it

aspects of this activity will be complemented by traditional research activities, often supported by EU projects (e.g. SoftHands, SoftPRO, XoSoft, SoMa, Wearhap, ABBI, BlindPad, Glassense). Activities in the domain of assistive and rehabilitation robotics will develop a number of devices, such as:

- A complete prosthetic upper-limb system, comprising a polyarticulated hand, active wrist and elbow, and sophisticated multielectrode myoelectric control system.
- A complete lower-limb system for transfemoral amputees comprising passive, semi-active, and active ankle and knee.
- Orthotics: a lower-limb exoskeleton for personal and clinical use by patients with spinal cord injuries or neurological impairments.
- Rehabilitation devices: a lightweight, portable robotic device to rehabilitate the shoulder.

This work will explore mid-to-long-term neural rehabilitation with robot-assisted therapy, integrating novel sensing strategies to understand how motor rehabilitation affects brain plasticity. This work will lead to the development of neuromodulation strategies for personalized neurorehabilitation technologies. Starting from studies on sensorimotor development in infants, toddlers, children, adolescents, and adults, we will develop new technical solutions to improve sensorimotor skills in visually impaired children and adults. In cases of cognitive disabilities (e.g. dyslexia), vestibular dysfunctions, and locomotion dysfunctions, we will develop technical solutions to help children learn and support sport accessibility for disabled people.

Similarly, we will use sensory augmentation methods (e.g. super resolution of touch, hearing, olfaction) to develop technology for new home-based rehabilitation and in support of independent living for the elderly or disabled. Finally, we will develop real usability tests to determine the extent to which neurorehabilitation technologies can be integrated into the intentional planning and control of everyday activities. We are finalizing an agreement with the Ministry of Health for selected Clinical Research Institutes to conduct these tests as part of a national clinical testing program. We already enjoy strong collaborations with IRCCS Stella Maris, IRCCS Bosisio Parini, and IRCCS Mondino, to name a few, and a Joint Lab with the Chiossone Institute in Genoa (there are currently about 30 established agreements with hospitals, institutes, and the IRCCS). In the long term, we plan to go beyond research to create new consumer/medical products that will enhance rehabilitation procedures and increase social inclusion.

Priority 5: Intelligent Companion Robots Program

The Intelligent Companion Robots program develops bodyware and mindware for interactive robots. It integrates research from several IIT research lines, including mechatronics, materials, ML, vision, and human-robot interaction (see Figure 3). In addition, this program conducts research in robot design (mechanics, electronics, aesthetics) and several core technologies (vision, control, touch). It also uses transversal technologies (ML and AI). The direct investment in research is complemented by formal collaborations with several key market players. Through a Joint Lab with IBM, we use natural language processing (NLP) technologies via Bluemix and Watson. With NVIDIA, we are adding embedded GPUs to our robots to enable deep learning in situ. We are moving towards adoption of wireless connectivity using 5G technology in collaboration with Vodafone (in the context of the 5G trials in Milan) and Ericsson (this activity is funded by the H2020 project 5GTOURS).

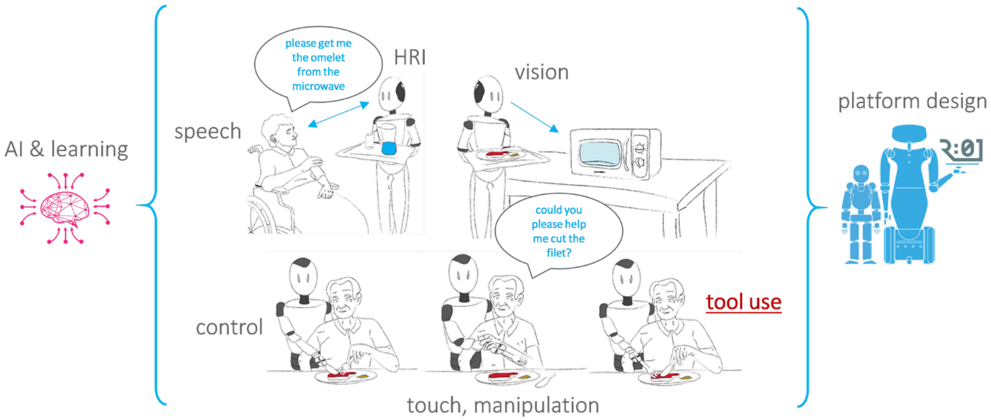


Figure 3: A cartoon representation of the companion research areas.

End users are also already on board. With the IIT-Fondazione Don Gnocchi Joint Lab, the R1 robot will work in several operational scenarios in a fully equipped apartment for patients undergoing rehabilitation in Milan. Another Joint Lab, with Gruppo Camozzi SpA, focuses on developing smart grippers for safe HRC. We are using iCub's control and vision software to control special robotic hardware for a leading international company in the entertainment sector. In the Joint Lab with Honda Research, we are porting iCub's physical HRI controllers to the E2DR and Asimo robots. We are using iCub in intervention protocols for neurodevelopmental disorders (NDVDs) at the Fondazione Don Orione in Genoa and at IRCCS G. Gaslini Children's Hospital. We will use iCub or R1 in a human-robot social interaction approach to engage the elderly in cognitively stimulating games that integrate neuropsychological tests of memory, attention, and executive function. We will work with INAIL to evolve iCub to study collaborative human-robot tasks in industry 4.0 and healthcare applications (project ergoCub).

These many different projects are supported by the ability to seamlessly integrate components via high-quality middleware (YARP), a long-term software engineering endeavor comprising more than 5M lines of code. YARP is compatible (natively) with ROS, allowing integration with a plethora of existing components from the public domain. To facilitate development of complex behaviors, we have developed software tools to model robot behaviors using finite state machines and behavior trees. We have also developed techniques to ensure correctness at design and execution time (funded by the H2020 project RobMoSys).

The iCub humanoid is an example of a successful companion robot development. It has been built in more than 40 copies and is used by researchers in Japan, Korea, Singapore, and the US. New components are being developed continuously. The next major revision, scheduled to begin in 2021, will deliver improved physical performance for the control of whole-body movement (e.g. walking while reaching or grasping), together with battery and Wi-Fi for full autonomy.

Simultaneously, to bridge the gap between research and the market, we have developed R1, the first prototype of a low-cost humanoid. The goal is to demonstrate the feasibility of an affordable humanoid robot with good manipulation capabilities (grasping, moving, and manipulating objects, including switches and doors). R1 allows easy and natural interaction, looks elegant and glossy, and safely navigates its environment. R1 has 28 degrees of freedom and makes extensive use of polymeric materials (with four patents filed). The purpose of R1 is to generate enough venture capital interest to spin off a commercial activity. We will evolve R1 by adding self-balancing capabilities, thus increasing its ability to negotiate small obstacles and rougher terrains (within the limits set by the wheels – see Figure 4).

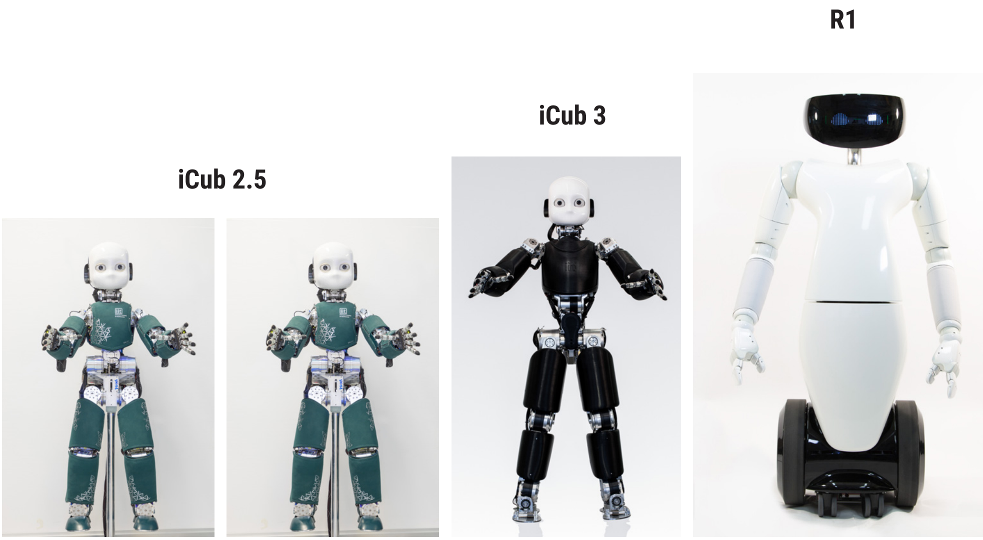


Figure 4: The humanoid programs (companion robots).

The key research directions of the Intelligent Companion Robots program include improving the skin system (international patent) of the iCub (presently 4000 sensing points) and of R1; developing new materials that combine biodegradable polymers with 2D fillers (e.g. graphene); and, with the help of ML and AI, simplifying robot programming to support commercial and clinical use.

For the skin system, we work with the Nanomaterials teams to develop and manufacture solutions that use graphene on stretchable substrates or conductive silicones. Because of their simplicity (to build and decode), we have designed capacitive sensors on new material substrates that exhibit the desired mechanical properties. This provides high sensitivity and resolution where needed and, generically, low hysteresis. In the future, we will prioritize solutions that allow automatic production (e.g. inkjet printing). Improving the skin system will improve the sensing, grasping, and tool use. In combination with ML, this will allow the development of rich representations of objects to support in-hand manipulation and to discover object affordances. For example, recent results for the iCub show stable in-hand manipulation, which in turn allows data collection for multimodal object recognition. The latter achieves 100% recognition rates on a dataset of 30 objects, discriminating between objects of the same shape but different weights (e.g. empty vs. full bottle). In turn, sophisticated manipulation enables object-tool exploration. This will improve the robot's ability to reason the physical interactions between tools and objects, and to acquire tool-use models through learning. A key advance in humanoid robotics is the ability to use tools designed for humans.

We will work with biodegradable plastics of vegetal origin, enriched by nanofillers to tune their mechanical properties. We will adapt these plastics for the additive manufacture of robot components. The robot will thus biodegrade at the end of its life cycle. We will explore the use of conductive and semiconductive inks to print circuit boards directly onto the robot's scaffold, reducing wiring and simplifying manufacturing. We also aim to evolve the companion robots by using new materials to improve their dependability, robustness, and allow graceful failures (e.g. surviving unplanned impacts). Specifically, research will aim to i) reduce the mechanical

complexity (fewer parts, no exposed wires, robust sensors); ii) improve the payload-to-weight ratio (i.e. lightweight robots); and iii) improve the manipulation skills (i.e. dexterous hands and flexible shoulders and wrists). Further innovations include shock-absorbing design, lightweight parallel mechanisms, and the co-design of mechanics with in-the-loop dynamical simulations.

We will expand the research on our software tools (YARP) to reflect the growing scope and complexity of the application scenarios for humanoid robots. In particular, we will focus on nonexpert users. Our goal is to provide methods that allow complex software applications to be built by combining and configuring existing components (graphical programming). For the same reason, we will develop specific AI methods for robotics. Learning in a robot needs to happen in real time (i.e. at sufficiently fast frame rates) without exceeding the limits of computation and memory. This requires incremental methods that scale well with the amount of training data (e.g. O(1)). We aim to achieve sustainable AI by systematically reducing the amount of data required for training (labeling problem) and the amount of computation required to process the data (scalability problem). For example, we have begun to investigate how the structure of deep neural networks influences performance with respect to these two problems. In addition, to simplify the training of robots, we will design architectures made of reusable internal representations, short-term and long-term memory, hierarchical abstractions, attention, and, in general, architectures that can figure out the solution entirely from data, including how to deploy functional resources to the task at hand. These promising technologies are variants of reinforcement learning methods augmented by deep neural networks. We will explore reinforcement learning in the context of cognitive architectures for robotics. To reduce the amount of data, we will further develop efficient signal coding, transmission, and processing. We will rely on unconventional sensory signal compression at the acquisition level, based on event-driven asynchronous encoding, embedded preprocessing, and embedded compression (on FPGA or GPUs).

Initiative: Robotics for a Better Life

IIT's strategic vision and investment in Robotics have made it a top international player. IIT has achieved a critical mass of researchers, demonstrating high productivity and quality in project development and scientific publications. From concept to commercialization, IIT has developed excellent hardware and software platforms at or beyond the state of the art. The plurality of research interests, an interdisciplinary approach, and attention to fundamental science and TT have turned IIT's Robotics into an international brand. The goal of the Robotics for a Better Life (RBL) Initiative is to move forward IIT's excellent performance in robotics in the coming decade. Our aim is to understand and contribute to the changes that the disciplines (plural intended) of robotics will necessarily undergo to match a changing society and its challenges.

Scientific Challenges

RBL is a horizontal Initiative across the five Priorities of the Robotics RD. This Initiative aims to deliver robots and technologies to improve quality of life. The Initiative takes a multidisciplinary approach to advancing research in robotics in order to take the Robotics RD objective of making robots self-aware[2] , adaptable, and interactive, and translating that objective into substantial component technologies. Uniquely, this Scientific Initiative aims to create easily scalable, sharable, and redeployable results, thus helping to minimize redundant development and to maximize efficiency in resource use at IIT. We also take on the task of attracting and involving the largest possible variety of scientific interests and competences from other RDs.

Application Challenges

Despite expectations that robots will soon enter our daily life in big numbers, it is challenging to use robotics outside the industrial setting. RBL will explore opportunities in the most promising and impactful application areas. In full alignment with the developments envisioned within the Robotics Priorities, this Initiative's target applications include robotics for healthcare, assisted living, workers' assistance, sustainable food production for a green planet, and robots for remote and challenging environments. One objective is therefore to understand the challenges of creating real-world, robust applications for sophisticated and interactive robots.

Foundations

Realizing the RBL vision will require concurrent development in several fundamental components to develop robots that can truly serve in real-world applications. RBL aims to develop robots with long-term cognitive and social autonomy, longer operating times, lower body masses, smaller power sources, and more ecofriendly footprints. Such robots should be sustainable in terms of fabrication, operation, maintenance, and eventual decommission at the end of their life. We believe robots should help anyone democratically, without limitations due to cost, education, gender, physical ability, or digital prowess. Therefore, ease of use is also fundamental to fulfilling the RBL Initiative's vision.

Our tenet is that an interdisciplinary approach is required to conduct basic science and acquire new knowledge, which can be used to develop novel solutions that address the limitations on robotics effectiveness in the above-mentioned application domains. AI and analytical methods are not the only technologies that will support these advances. Bioinspiration is also an important approach to designing the next generation of robots. To build robot bodies that come closer to their biological counterparts, one requires foundational knowledge of how the body contributes to intelligence through its physics and morphology. Similarly, designing bioinspired robots requires better understanding of the fundamentals of embodied intelligence. For example, how should a body, its actuation, sensing, and control be codesigned to solve the problems associated with a given range of applications? Can an effective use of morphological computation minimize robotic complexity (e.g. computation, structure)? Can morphological

[2] Here, "self-aware" has no philosophical connotation, but rather denotes "aware" in the sensorimotor sense of a robot operating in a given environment.

computation lead to efficient and resilient robots? Similarly, we must model human cognition, which goes beyond and complements bioinspiration for the physical structures and sensing processes. This modeling is fundamental to creating mechanisms that will enable the new generation of robots to understand and be understood by us. Such robots will adapt to human actions and behaviors and to changes in their surroundings. Finding answers and effectively designing such robot components may be the key to designing intelligent robots with long-term learning autonomy.

To study, devise, and design the foundations of the robotics of the coming decade, the RBL Initiative will not only establish a dialogue with related disciplines (e.g. materials, biomechanics, neuroscience), but it will also aim to secure the active participation of the scientific community in developing these foundations.

New theories and principles derived from basic science will steer the development of technological components. New materials and fabrication methods for realizing physical intelligence principles will lead to intelligent robot mechatronics with integrated intrinsically smart actuation and advanced multimodal sensing principles. They will be powered by new energy sources and harvesting mechanisms that can supply robots for prolonged operations and use environmentally friendly recyclable materials. A better understanding and modeling of biological cognition principles will lead to advances in long-term learning and perception. This will enable robots to exhibit effective reasoning, long-term adaptation, and the ability to develop and demonstrate common sense intelligence. A key technological enabler will be the development of human-machine interfaces (wearable sensors and transducers) and more adaptable sociophysical human-machine interaction tools. Finally, for responsible robotics innovation, it will be crucial to develop data sharing and cybersecurity tools as well as roadmaps for standardization and sustainability.

The use of robotics in new application domains will introduce ethical, legal, social, and economic (ELSE) implications that are crucial to its acceptance. It is important to study the societal and psychosocial reception and identify opportunities and risks. It also important to understand if and how the existing legislation and standards apply and whether their provisions are a barrier to the use of robots. Therefore, it will be necessary to identify and understand the ELSE implications and derive ethical and legal guidelines. The eventual operation of fully autonomous systems will require engagement with insurance regulations.

Matching Application Challenges and Fundamentals

Table 1 illustrates how fundamental (basic) research topics interconnect and are relevant to the RBL Application Challenges.

Implementation Instruments

The RBL Initiative will contribute to a durable structuring of IIT's Robotics RD. The first implementation phase should run for four years[3] (end of 2024), with an intermediate revision at year 2 (end of 2022). After four years, the results will be assessed to reach a decision on continuation, discontinuation, adoption of corrective measures, and so on.

The implementation of the RBL Initiative will leverage several instruments.

First, it will take full advantage of IIT's cross-disciplinary nature and expertise, which encompasses multiple research lines, programs, and Priorities. We will foster and implement core internal research synergies. These will be driven by the research objectives of the scientific and technological fundamentals and by external collaborations, including with industry, digital innovation hubs, and policymakers. We will build on the legacy of many European and national projects to collaborate with hundreds of research institutions.

[3] The Initiative will be evaluated on a yearly basis by the STC.

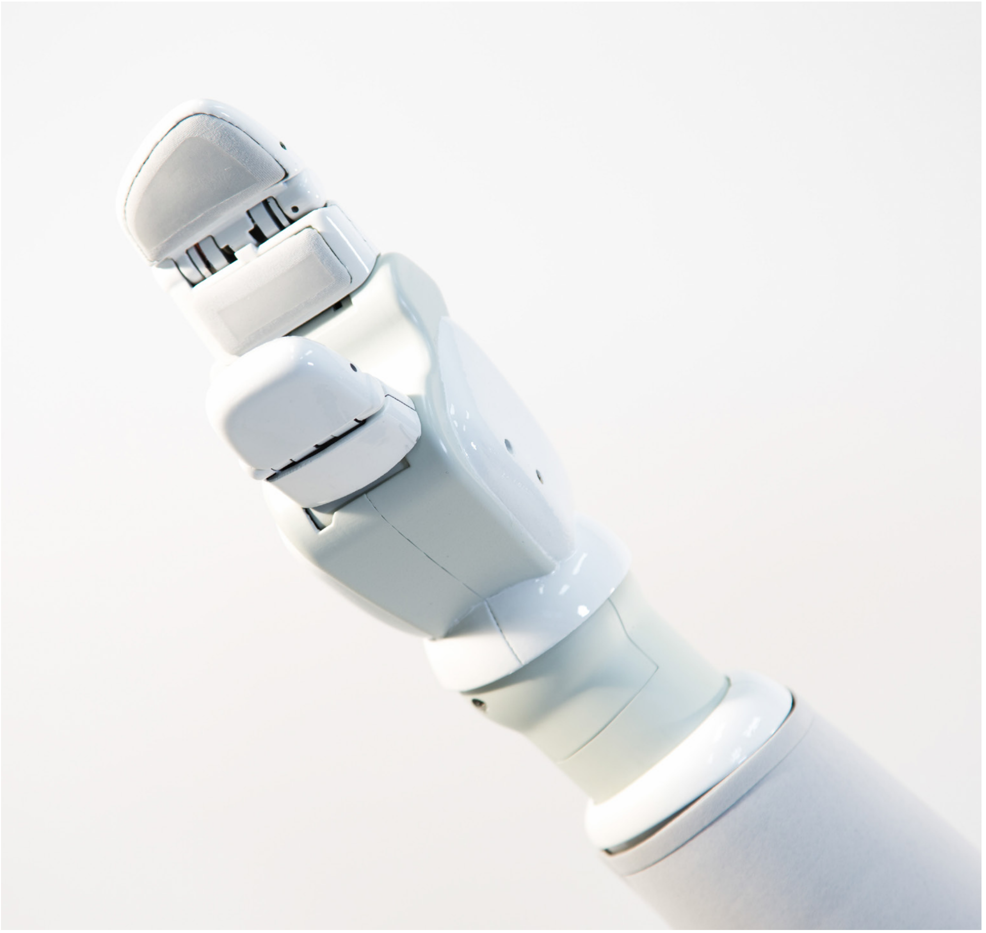
A dedicated webpage on IIT’s main website will share the Initiative’s significant results and success stories, and will link to scientific publications, patents, events, software repositories, and so on. The Initiative’s homepage will provide a unified entry point to robotics research at IIT, highlighting our best results and activities in greater detail (e.g. technical) than the typical institutional pages.

We will set up a shared testing facility that will be available to all IIT Robotics groups to support the validation and benchmarking of this Initiative’s technological outcome. Drawing upon our experience in projects like EUROBENCH, we will set up a dedicated laboratory area with application mockups. By quantifying the performance of IIT’s forthcoming robotic technologies, the facility will allow the research lines to better collaborate and coordinate their efforts to make technologies meet real-world needs.

Rapid technological advances require innovation and standardization. We will collaborate with standardization bodies (e.g. DIN, UNI, ISO, some of which already collaborate with IIT) to revise existing standards and develop new ones, thus helping to reduce wasteful and redundant technological developments.

A key objective of this Initiative is to establish effective mechanisms for communication and interaction to enhance collaborations between and within research lines. We will establish technical forums where ideas can be sketched out in discussion and may give rise to new research directions and collaborations. We will create a tool to support these discussions across research lines.

Biannual conferences and workshops will focus on relevant scientific topics and challenges involving all interested PIs, researchers, technical personnel, and students at IIT. One of the two annual events will be a technically oriented workshop. This workshop will be open to researchers from other institutions. The workshop will include selected speakers invited to contribute their vision in keynote addresses.



Robotics for a better life						
Fundamental Research Topics	Applications Challenges					
	Healthcare	Assisted Living	Assisted Working	Sustainable Nutrition	Challenging Environments	Green Planet
Materials and fabrication	●	●	●	●	●	●
Design principles and physical intelligence	●	●	●	●	●	●
Intelligent human-machine interfaces	●	●	●		●	
Long term learning and perception	●	●	●	●	●	●
Socio-physical human-machine interaction	●	●	●			
Energetic sources and economy				●	●	●
Data sharing and cybersecurity	●	●	●	●	●	
Sustainability and standardization	●	●	●	●	●	●
Acceptability and usability	●	●	●	●	●	●
Ethics and legislation	●	●	●			
Societal and psychosocial aspects	●	●	●			

Table 1: Matching Application Challenges and Fundamentals.

One focus of the second annual event will be TT and dissemination to the general public and media. We will thus elicit feedback from several user groups. The annual event will include ad hoc seminars and webinars on new challenges or scientific breakthroughs. We will work with our industrial network to match career offers to the goals of our students and postdocs. The event may include student competitions (RBL Olympics) featuring demonstrations of their final-year work and thus displaying the latest robotics tech from our labs in a common space.

The RBL Initiative will organize PhD schools and courses on relevant scientific and technological topics in order to attract national and international students and strengthen IIT Robotics' international reputation. Importantly, the Initiative's schools and courses are interdisciplinary, exposing our students to ELSE aspects and investigation techniques and so on. We will work with universities to secure accreditation for our courses. In some cases, we will offer online and offline courses to selected students outside IIT.

Expected Impact

The Initiative tackles key technological and scientific problems that impede the deployment of robots in real-world applications. Its ultimate goal is to enhance quality of life. The Robotics RD's Priorities are aligned with this goal. The Initiative's specific contribution is to federate the IIT robotic community's efforts in an open, multidisciplinary, integrated, lightweight, and nonintrusive structure.

We expect this effort to impact our research in multiple ways, which can be summarized in one word: synergy.

We expect to maximize the following key quantifiable performance indices (in bold):

Having a single website and general public entry point for the RBL Initiative will strengthen IIT Robotics' image, allowing us to attract more searches and contact requests, and distribute them more effectively. It will also help our younger members to build and navigate a map of expertise to find cross-research-line help or inspiration for multidisciplinary issues.

A shared testing facility will advance our ability to develop, test, and validate more flexible systems that work outside the laboratory and can be deployed in real-life applications. We expect the large number of tests to foster research, both directly through validation and experience, and indirectly through the acquisition, storage, and sharing of large experimental data for further analysis and possible reuse.

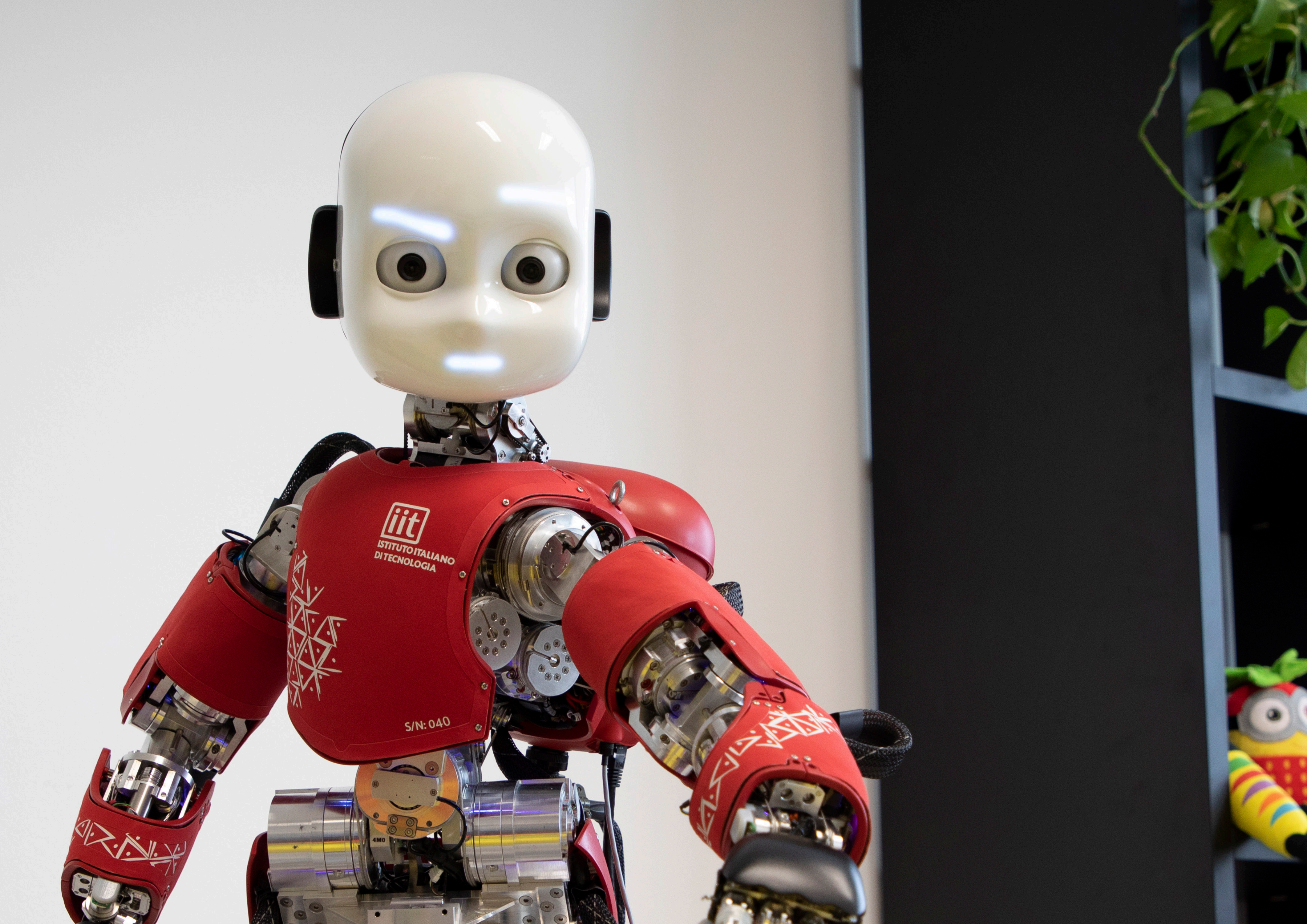
The collaboration with standardization bodies will provide impulses to enter various committees in order to participate in and influence the development of standards. It will also foster an attitude toward standardization that will make it easier to share and reuse components across research lines and to make them more durable and maintainable, thus avoiding redundant efforts and the premature obsolescence of our products.

By organizing RBL events, we will build community across different research lines and thus foster multidisciplinary inspiration (a key goal). Similarly, the events will help integrate societal stakeholders in robotic technologies. The organization of RBL events will enable our younger members and students to increase their exposure to multidisciplinary knowledge, to present their work in talks and/or demos, and to start new scientific cooperations with colleagues of different backgrounds.

The launch of RBL educational initiatives will further enhance our workplace image, attracting more and better qualified applications to our PhD positions. The number and quality of attendants of the online and offline seasonal schools and graduate courses will be a measure of the Initiative's success.

Participants

The Initiative involves 18 senior researchers (11 PIs, various Facility Coordinators, and Researchers from several teams) and 150 staff members overall. The Initiative is inclusive by definition, and we will actively pursue the involvement of all IIT researchers who have an interest in the RBL goals and share its open philosophy.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Initiative: iCog: the iCub Cognitive Architecture

The motor and sensory capabilities of robot body(ware) have improved greatly in the last 30 years. However, robot mindware has not experienced similar progress. Robots' gymnastic abilities far exceed their ability to interact with humans beyond simple scripted gestures and sentences . Although working on robot bodies is still a fundamental aspect of robotics research, it is the relational rather than motoric skills that will drive disruptive innovations in personal robot applications. The main challenge is to integrate real-time control with beyond-real-time prediction and behind-real-time simulations. Beyond-real-time prediction is derived from past experience and recalled by the contingent situation. Behind-real-time internal simulations are driven by motor imagery and exploratory creativity. This means that cognitive robots must understand what a person is doing, anticipate what they are going to do, and act accordingly. This ability to predict the effects of one's own and other's actions is the core of human cognition. The lack of anticipatory skills hampers effective human-robot interaction (and the creation of the personal robot industry). Current AI techniques based on learning from data are an important part of the solution, but cannot provide the full solution. The iCog Initiative's proposal (to be experimentally verified) is that the solution must involve an architecture containing components that act in predictive, context-sensitive, and imaginative/creative ways. These core components/abilities include basic perceptual skills (e.g. discrimination, motion interpretation), attention mechanisms, action selection and control, memory, learning, (causal) reasoning, metareasoning, and prospection. Building these components requires a multidisciplinary scientific endeavor based on robotics, cognitive and neural sciences, and natural intelligence and AI. The study of human cognition is essential.

Goal of the Initiative

The iCog Initiative aims to establish a working group at IIT to discuss theoretical models of cognition in natural and artificial agents and their software implementation. The implementation(s)

Figure 5: The RobotCub project motto: Open Software, Open Hardware, Open Mind (circa 2004).

should become the reference architecture in the field of Robotics and AI and the shared tools of the international iCub community.

This approach extends the three objectives of the FP6 EU project RobotCub (Figure 5), which was the starting point of the iCub humanoid project. The three objectives were: i) a scientific objective to study aspects of human intelligence and cognition; ii) a technological objective to study and implement a cognitive architecture for the iCub humanoid robot and, iii) a social objective to stimulate the creation of a scientific community sharing the iCub as the experimental tool of choice. The rationale is that cognition is such a formidable problem that it can only be addressed by mobilizing a critical mass of interdisciplinary researchers, who share a physical platform as a repository of partial individual solutions that could incrementally converge into a shared cognitive architecture.

Therefore, recalling the RobotCub project's goals, this Initiative's scientific goal is to create a critical mass of research groups (each with its own research methodology and scientific focus) that are interested in the questions of how to implement individual aspects of intelligent behaviors (current state of the art) and how to structure the underlying cognitive architecture.
To design such a cognitive architecture, one must identify its core processing elements and how their functions are dynamically rearranged to implement specific behaviors. By discussing and reasoning about the big picture, engineers, neuroscientist, psychologists can equally contribute to exchanging views and opinions on an abstract level, without being diverted by the details of implementation and experiments. These details can be finessed at the level of individual research groups (there is no need for an engineer to become a neuroscientist or vice versa, but only to understand each other at a fundamental metalevel).

Stemming from this scientific goal, the Initiative's second objective is to implement, share, and test the core components of the cognitive architecture. IIT is in a unique position to achieve this objective, thanks to our technical background (the iCub Tech Facility staff know the iCub's bodyware and mindware better than anyone) and scientific background (IIT's scientific plans are rooted in cognition, perception, learning, and motor control).

The Initiative's third goal is to establish a formal network of international laboratories interested in developing their activities within the iCub Cognitive Architecture framework. We will begin with laboratories that currently use the iCub. Funding for this initiative/infrastructure will be sought through EU programs by building on the iCub project's success story. For example, external funding could be allocated to maintain the iCub platforms worldwide. The fantastic tools developed at IIT to share the iCub's software implementations will be the basis of the cognitive architecture's repository[5].

Generality and Strategic Importance of the Initiative

The iCub will continue to be a common platform where research results can converge, but the Initiative's scientific outcomes are not limited to robot hardware. The results will transcend the specific implementation of a humanoid robot. For any artificial system to interact safely with humans in human-populated areas (e.g. an autonomous car sharing its space with human drivers, cyclists, pedestrians), one requires a cognitive architecture that allows the system to understand everyday contextual information, anticipate the effects of actions (and human intentions), and understand the internal state of individuals. To use an aerospace metaphor, iCub is the wind tunnel that can be used to investigate the architecture that embeds these abilities. This architecture can then be adapted to other embodied systems (similar to understanding the physics of lift).

Finally, the Initiative will have an important effect on the future of education. It is an educational strategy to form a community of PIs with different backgrounds addressing common goals. This is because a community environment is the ideal context in which to train young researchers to work in multidisciplinary teams. In a scientific community, each student has their own focus

[5] Here, we stress the fundamental difference between a software architecture and a cognitive architecture

while acquiring a first-hand experience of the strengths and limitations of other participating scientists. Understanding the limitations of a neuroscientific experiment or a learning algorithm is as important as understanding its successful applications.

Implementation

The Initiative will be characterized by continuous knowledge-exchange activities, starting with open days to bring together all interested PIs. Anyone can contribute to the general idea and/or better understand the Initiative's overall scope.

The group is and will remain open to new contributors. These activities will be structured to stimulate the widest possible participation of PIs, possibly with the contribution of selected external speakers to highlight the Initiative's multidisciplinary scope and to synergize the expertise of all participants. The objective of the start-up phase (0-18 months) will be broad and devoted to discussing and defining a common frame of reference for the cognitive architecture (the shared goals of the Initiative). During this phase, a secondary goal will be to familiarize one another with the activities of the PIs in the areas to which they think they can contribute specifically. This can be stimulated by organizing joint (i.e. cross-PI) journal clubs and more in-depth presentation of students' and researchers' activities.

Among the scientific activities organized by the iCog Initiative, a strong collaboration with the iCub Tech Facility group is particularly important for the implementation and exploitation phase. IIT's iCub Tech Facility maintains, tests, and updates the iCub software architecture. The software architecture hosts a variety of software modules, which will include the cognitive architecture components and the ability to dynamically reconfigure them for a variety of experiments. In addition to being a technological goal of the Initiative, the dynamic reconfiguration of components allows the cognitive architecture to be exploited in a variety of application areas involving human-robot interaction.

The Initiative identifies three main objectives.

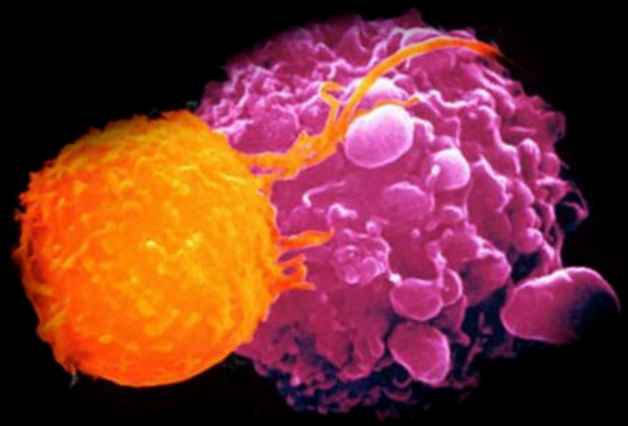
The first significant objective is to define a joint experimental strategy to serve as a convergent testbed of the Initiative's progress. This experimental strategy will not be organized as a demonstrator of specific skills or abilities, but rather with the goal of defining and testing how different skills and abilities could be based on a common architecture, such as the set of representations, learning techniques, and type of memory. Importantly, the Initiative will not aim to integrate different components of the architecture developed by individual groups. Rather, the cognitive architecture will guide the implementation towards a shared view of cognition. The final goal is to implement an architecture supporting the anticipatory behaviors that are the distinctive signature of a cognition-centered artificial system. In this sense, the cognitive architecture will have the same role as the iCub body in guiding/constraining the co-development and sharing of the sensorimotor primitives that guide the iCub movements.

The second objective is to create the basis for an EU-funded, EU-wide initiative to revamp the iCub international community under the cognitive architecture flag, with a leading role for IIT and the participation of all contributing groups at IIT.

The third objective is to create the scientific basis and implementation infrastructure to test applications that require robots with cognitive abilities. In this respect, human-robot interaction is the ideal scenario, imagining a final application where a cognitive robot will support humans in everyday activities at home and in the workplace.

Participants

The Initiative has six core PIs, but, as noted above, the organization is open to more iCub users from IIT and from the international community of iCub users.



The Nanomaterials Research Domain

The Nanomaterials Research Domain (RD) is built on our expertise in materials science and nanotechnology and on IIT's unique interdisciplinary environment.

Research will focus on four Priorities as depicted in Figure 6. The first Priority is to develop materials and nanotechnologies to improve the quality of human life and the environment. To mitigate the increasing environmental impact of human activities in the medium-to-long term, it is pivotal to establish materials and processes that are environmentally friendly in their consumption of energy, resources, waste generation, and potential toxicity.

Among the various strategies pursued by IIT, two particularly important goals in this regard are to use organic waste to generate new biodegradable goods with useful physical properties, and to develop new technologies to remediate water and preserve food.

A second Priority is to develop materials and nanotechnologies for medicine and healthcare. In particular, we will develop solutions for low-cost, high-sensitivity diagnostic kits based on plasmon technologies, and novel multifunctional nanostructures for intelligent drug delivery.

A third Priority will be energy. We will develop materials to harvest, convert (by photovoltaic, thermoelectric, and mechanic conversion), and store energy. We will also explore processes and nanotechnologies to capture carbon dioxide and convert it into valuable chemicals.

The fourth Priority is more fundamental, dealing with curiosity-driven research in the development of new materials such as colloidal nanostructures and 2D materials. 2D materials are mainly investigated in the framework of the Graphene FET Flagship program.

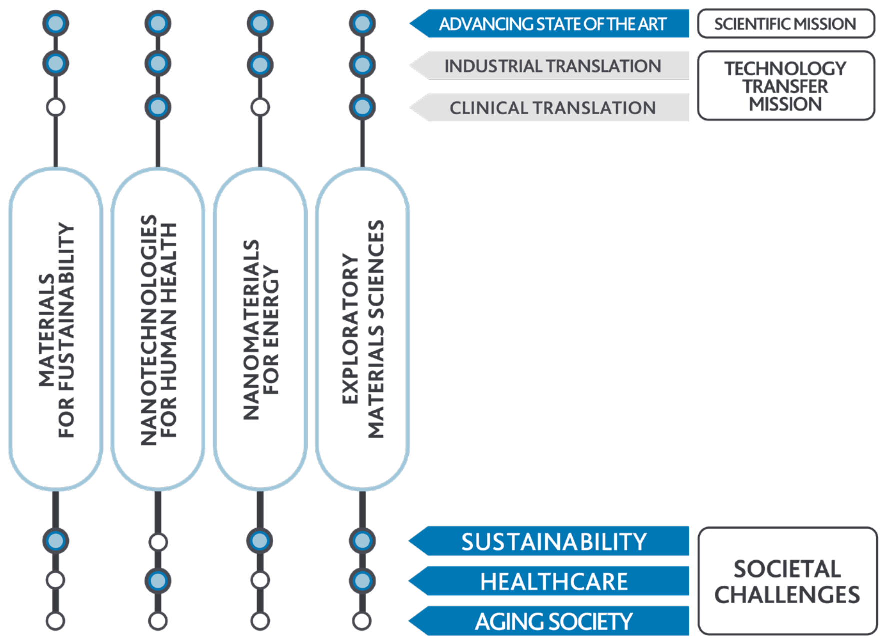


Figure 6: Priorities of the Nanomaterials RD, contribution to IIT's mission, and impact on the challenges.

Scientific Mission

The basic research of the Nanomaterials RD will continue along the same lines as in the previous strategic plan, in areas where IIT has gained a leading international position. These areas include new sustainable/biodegradable materials, nanocomposites and 2D materials, nanofabrication technologies and nanodevices, and new colloidal chemistry approaches.

The materials science know-how will be enhanced by new computational chemistry methods and by establishing new laboratories to investigate matter under extreme conditions (at high temperatures, high pressure, and when exposed to various chemicals and ionizing radiations).

Technology Transfer Mission

Around half of IIT's industrial projects and 45% of its patents originate from research carried out by the Nanomaterials RD, which will continue to be one of the main drivers of IIT's technology transfer (TT). In the coming years, we foresee a strong growth in our translational activity, thanks to the increasing number of collaborations with companies and especially through Joint Lab agreements. The Nikon Center has now been expanded in the new Center for Human Technologies in the Erzelli building, strengthening IIT's position as an international leader in super-resolution microscopy.

In terms of clinical translation, the research developed by the Nanomaterials RD will provide the basic technologies for several clinical collaborations with a network of research hospitals across the country. These collaborations will co-design and test novel diagnostics devices (for genomics, food traceability, etc.) based on plasmonic sensors, and multifunctional drug-nanocarriers (superparamagnetic colloidal particles or polymeric constructs) for multifunctional drug delivery and diagnostics (often referred to as theranostics technologies).

Applications of these technologies will be further discussed in the Technologies for Life Science RD section.

Sustainability Challenge: Sustainable production and a safer environment

The Nanomaterial RD will pursue a two-pronged strategy of new technologies for sustainability: (i) technologies for the circular economy (new multifunctional materials, waste cycle, water remediation, reduction of carbon footprint), and (ii) portable energy sources with improved performance and a lower environmental impact.

Our planet's natural resources are massively exploited by human activities. Earth's ecosystems cannot fully absorb, metabolize, or neutralize the waste that we generate. This has a strong negative impact on the quality of air, water, and food. For human health and for the environment, the most alarming and harmful type of waste is plastics, electronic and electrical waste (e-waste), endocrine-disrupting chemicals (from e-wastes and plastics), and nanomaterials in general.

A strong investment in technology for a circular economy appears to be the only solution to counteract this trend. The circular economy concept is based on an industrial production model that uses sustainable resources and does not generate any waste or pollution. There is growing governmental and institutional support for the circular economy. The United Nations' 2030 Agenda of 17 Sustainable Development Goals as well as the European Green Deal reflect growing acceptance of this paradigm. In line with this concept, and in order to fulfil the Sustainability Social Challenge, the Nanomaterials RD will develop new technologies for water safety and sanitation, new devices for photovoltaic conversion and energy storage, new strategies for CO2 valorization and conversion, and innovative materials made from vegetable waste, food waste, and converted CO2.

These contributions will drive future industrial production, helping to achieve the Sustainable

Development Goals and the targets of the European Green Deal. We target the following main deliverables:

- New biodegradable bioplastic materials and composites that are easy to process and engineer.
- New nanotechnologies for water remediation and purification of drinkable water.
- Carbon-neutral processes, carbon capture, and carbon conversion.
- New affordable technologies for food traceability and smart packaging

Research on new concepts for solar cells, thermoelectric generators, batteries, and supercapacitors will play an important role in energy sustainability. The European Commission's 2011 energy roadmap (Energy Roadmap 2050) has defined four avenues to a more sustainable, competitive, and secure energy system by 2050: energy efficiency, renewable energy, nuclear energy, and carbon capture and storage. In addition to the above-mentioned strategies for CO2 valorization and conversion, IIT will develop:

- New materials for solar cells and printable thermoelectric generators (primarily based on halide perovskites).
- Storage devices based on graphene and other 2D materials.

Healthcare Challenge: Technologies for affordable and personalized therapies and diagnoses

In 2020, the World Health Organization's estimates show that people over 65 outnumber children under 5, with over-65s making up 35% of the world's population. Aging is a major risk factor for cancer, diabetes, cardiovascular, neurodegenerative, and chronic inflammatory disease, as well as other debilitating and life-threatening conditions. Novel technologies are needed to radically transform intervention strategies and as tools to better understand the origin and progression of diseases in a patient-centric fashion. Nanotechnologies applied to medicine (i.e. nanomedicine) offer the opportunity for quantum leaps in the diagnosis, treatment, and management of multiple medical conditions.

Within this context, we will develop novel electro-optical devices to more accurately sequence DNA/proteins and allow an in-depth understanding of intercellular crosstalk in complex tissues, such as the brain and the microenvironment of diseased tissue. These devices will be teamed with a new generation of edible and low-cost sensors for the high-throughput screening of diseases. We will design multifunctional nanoconstructs with built-in patient-specific information. These will be used for drug delivery and biomedical imaging (theranostics) against cancers, cardiovascular diseases, and brain diseases. Finally, we will develop natural and synthetic materials, arranged three-dimensionally over multiple scales. These will be used for novel tissue regeneration applications and organs-on-a-chip for efficient drug screening. Our main research lines will be:

- Nanotechnologies for low-cost, high-sensitivity sequencing and sensing (primarily based on plasmonics).
- Drug delivery systems and theranostic nanoconstructs for human health (primarily based on nanoparticles and polymers).
- Tissue engineering.

Priorities of the Nanomaterials Research Domain

Most of the research and technology activities of the Nanomaterials RD will be carried out at IIT's Center for Converging Technologies (CCT, Morego building), exploiting the four facilities (clean room and nanofabrication, electron microscopy (EM), physical and chemical characterization, and pharma chemistry) and four industrial Joint Lab (Nikon, Camozzi, Novacart, Bracco) established there.

The Nanomaterials RD is strongly supported by the network of IIT Centers at CNI-Pisa, CMBR-Pisa (CMI-Pisa from January 2021), CNST-Milan, CSFT-Turin, CLNS-Rome, CABHC-Naples, and CBN-Lecce, and by the European Graphene Flagship (one of Europe's largest research projects with one billion euros in funding and a duration of 10 years, from 2013 to 2023, of which IIT is one of the leading institutions).

In the coming three years, the Nanomaterials RD should grow by about 10% (currently more than 360 staff members, including 24 PIs and about 30 technicians) by including new PIs in the fields of advanced EM, computational chemistry, and materials science.

Priority 1: Nanomaterials for Sustainability Program

The core of this program is a series of materials solutions and technologies to safeguard and monitor the environment.

The approach will be fourfold: i) we will develop materials that use sustainable natural sources as a starting point in order to minimize the environmental impact; ii) we will identify new technological solutions for water remediation; iii) we will set up efficient and low-cost solutions to monitor pollutants in water; and iv) we will develop sustainable, multifunctional, smart, and interacting food packaging technologies. These four main research lines are detailed below.

Sustainable polymeric materials to reduce plastic waste

Starting from natural monomers, we will synthesize and chemically functionalize natural polymers, composites, and blends. We will prepare and engineer natural self-growing materials based on the mycelium fungus and with a wide range of properties. Using nontoxic solvent processing methods, we will also transform vegetable and other organic waste (primarily from the food industry – see Figure 7) into natural polymeric composites.

We will also transform animal products (wool, chicken feathers, silkworm cocoons) into protein-based polymeric materials. These materials can be used for durable coatings, constructions, textiles, and in all sectors that currently use conventional plastics.

Nanotechnologies for Water Remediation

In this activity, we aim to remediate water from traditional hazardous pollutants (heavy metal ions, organic dyes, pesticides) and from the newer generation of pollutants, such as nanoplastics, drugs (e.g. antibiotics), rare metals, and biopersistent organics. A major goal will be the efficient and simultaneous removal of diverse pollutants at very low concentrations.

We will design porous supports and appropriate surface treatments with polymer films, particles, or combinations of both. We will also develop porous composites made from synthetic or natural polymers combined with natural fillers (e.g. agrowaste particles or their derivatives, including DNA). We will engineer nonpolluting composite materials into porous structures with specific hydrophobic and oleophilic properties. These can be used for the remediation of oil spills and to separate oils from industrial oil-in-water emulsions. We will also functionalize the porous structures with suitable moieties. The chemistry of natural materials and their affinity for oily substances will be exploited to promote the use of sustainable materials. Both absorption and filtering techniques will be explored.

Figure 7: Biopolymer composites from vegetable wastes.

Colorimetric sensors and indicators of water pollutants and acidification

There is a strong interest in low-cost, colorimetric (naked-eye based) nanosensors to detect toxic heavy metal ions (Pb, Hg, Cd) in aqueous solutions. These tests are mostly intended for home users to test tap water or for nonspecialized personnel to frequently test river water, seawater, and industrial drains on site. Therefore, the tests must be rapid and easy to use. We will combine hybrid AuNP antennae with magnetic microbeads, aptamers, DNAzymes, or hybrid nanozymes with strong catalytic activity. The goal is a naked-eye colorimetric readout, while guaranteeing high specificity in real samples and a sensitivity that complies with the exposure limits set by international regulatory bodies. The porous materials developed for water remediation will incorporate sensitive molecules/nanoparticles, which will change color or emission wavelength upon interaction and adsorption of specific organic or inorganic pollutants, or upon a change in pH in their water environment. These composite materials will be used to both identify and remediate water pollution.

Sustainable, multifunctional, smart, interacting food packaging

Packaging is one of the most important technologies for food preservation and transportation. IIT will pursue two research directions to create innovative food packaging that is: i) more sustainable and cheaper; and ii) more active in preserving food and monitoring its quality. For the first research line, we will develop new packaging technologies, using fully sustainable and biodegradable materials to produce highly safe and protective food packaging.

We will use fiber-reinforced biopolymer composites and multilayer packaging strategies to develop packaging that can prevent any interaction between the food and the external environment (i.e. oxygen and humidity transmission), while providing antioxidant or antibacterial protection through the controlled release of active principles to the packaged food. This release may be continuous or activated by a chemical stimulus from the food. The typical technologies used to produce plastic food packaging include extrusion and injection molding. To produce novel sustainable food packaging, we will adapt these technologies to sustainable materials such as biopolyesters, starch, cellulose, PVA, and silk.

For the second research line, we will insert spoilage sensors and indicators directly into the packaging material, significantly advancing the technology of active packaging (Figure 8). For incorporation into food packaging, we will focus on molecules, particles, or polymers that change color, emission wavelength, or electric conductivity (e.g. photochromic, acidochromic molecules, conductive polymers) upon interaction with spoiled food. Food spoilage produces amines, CO2, organic acids, and other bacterial metabolites. These will be monitored or simply indicated by pH-sensitive molecules like spiropyrans and natural anthocyanines, conductive or thermochromic polymeric composite films that will be integrated into the food packaging structure.

Finally, we will explore self-powered labels, written directly onto the food packaging, that embed self-powered electronic components. This technology will mainly be based on organic electronic devices printed on mechanically conformable substrates. These will be directly integrated into food packaging on the production line. “Devices” are here defined as functional units with sensing, processing, and communication capabilities. Depending on the requirements, they can be simple and fully passive (like antennae integrating a sensor), or more complex, comprising a power source, logic circuitry, sensors, and a transmitting module.

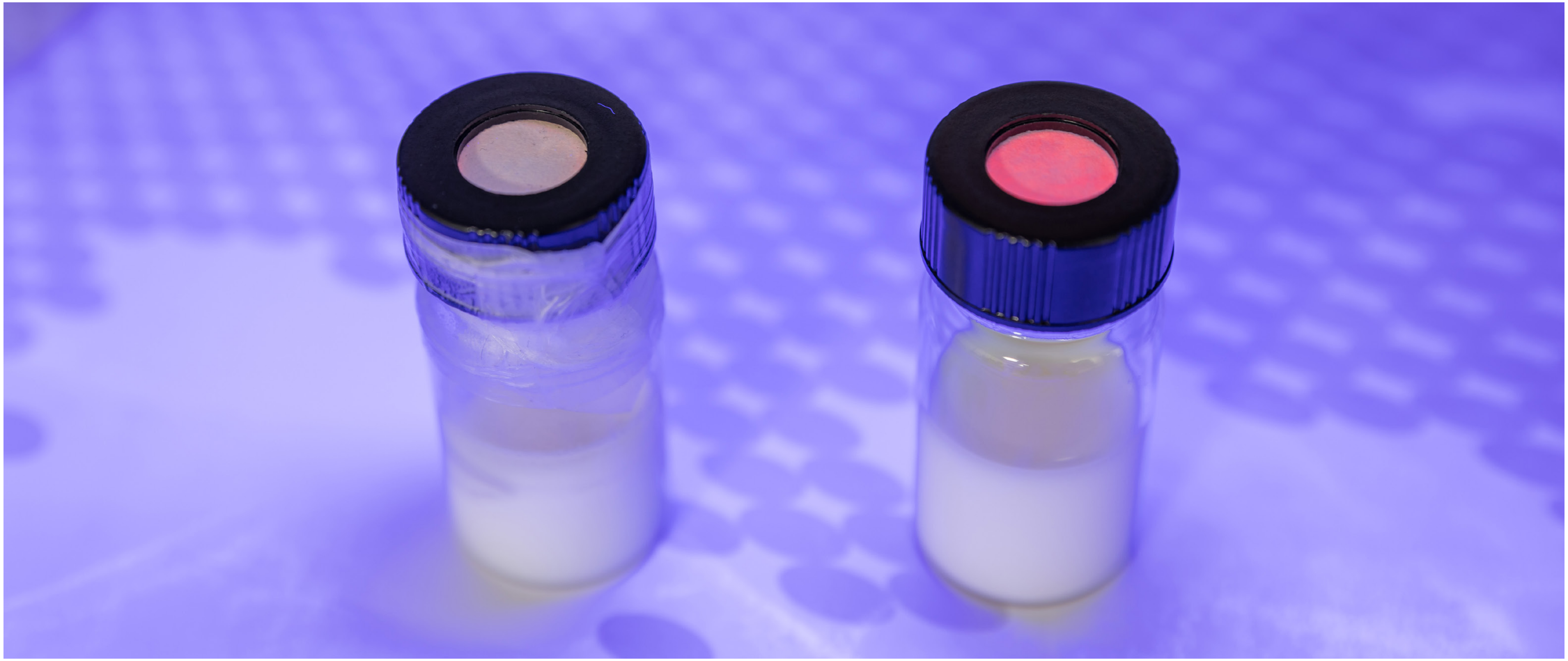


Figure 8: Milk spoilage indicator.

Priority 2: Nanotechnologies for Human Health Program

This Priority deals with the study of new concepts and technologies for human health. It includes three main research efforts: i) the development of low-cost assays based on plasmonic sensors for various biomedical applications; ii) the development of engineered nanoparticles for detection and therapy (or a combination thereof), and iii) the development of technologies for food traceability with innovative low-cost high-sensitivity devices. The direct applications of these technologies to real clinical situations will also be addressed in the Technologies for Life Science (LifeTech) RD section.

Plasmonic ultra-high sensitivity biosensors

An effective way to achieve low-cost high-sensitivity assays is to use plasmonic biosensors based on metallic nanostructures and/or nanoparticles that interact with target and biorecognition molecules. These assays have many applications, including point-of-care tests, quality controls, and personalized medicine.

Two strategies will be pursued:

- Develop colorimetric nanosensors and nanodiagnostics assays, based on naked-eye readout detection. These will use biorecognition molecules functionalized with metallic nanoparticles, which generate strong nonlinearities upon hybridization/biorecognition of the target molecule, changing the solution's refractive index/color. Combining these assays with microfluidics and automated image analysis will allow the results to be recorded quickly and easily. These colorimetric assays will facilitate pharmacogenomic analyses and personalized medicine by discriminating panels of single nucleotide polymorphisms. In the laboratory, these same assays will be used for quality control to detect mycoplasma and nuclease contaminations, and to authenticate cell lines.
- DNA sequencing based on nanopore technologies. Approaches will be developed to produce nanopores with a controlled shape, size (below 5 nm), surface chemistry, and made of materials with plasmonic properties, such as noble metals, for the localized enhancement of the optical field. This will improve biosensing, DNA sequencing, and will possibly expand into protein sequencing, which is an underexplored field. We will integrate microfluidics and advanced nanofabrication techniques in order to deliver a new generation of on-chip bioassays.

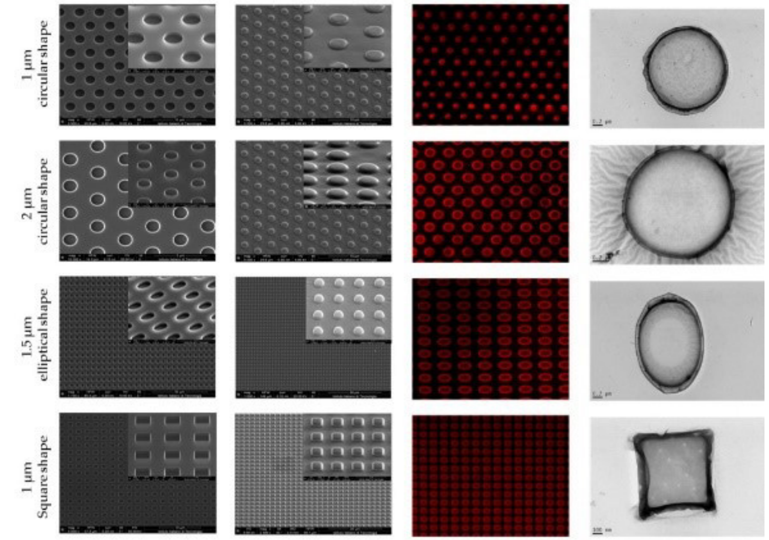


Figure 9: Tailoring the size, shape, surface, and stiffness (the 4S parameters) of nanoconstructs via a flexible top-down strategy.

Combinatorial nanoconstructs for imaging and drug delivery

This program will tackle three main issues to boost the clinical integration of nanomedicines:

- The development of hierarchically structured nanoconstructs to amplify the accumulation of therapeutic and imaging agents within diseased tissues, while minimizing nonspecific sequestration by the mononuclear phagocyte system.

  Hierarchically structured nanoconstructs will be synthesized using a flexible, top-down strategy that combines lithographic techniques, etching, molding, and polymer chemistry. This will allow us to precisely and independently tailor their size, shape, surface properties, and mechanical stiffness (4S parameters, see Figure 9). We will modulate the 4S parameters to modulate nanoconstruct accumulation within diseased tissues and blood longevity in a patient-specific fashion.

- The improvement of loading capacity and stable encapsulation, while facilitating on-command release. We will boost loading capacity and on-command release for anticancer anti-inflammatory molecules and for RNAs and biological substances.

  This will be achieved by realizing nanoconstructs with different types of materials, including synthetic and natural polymers. These materials will be biodegradable, sensitive to stimuli both internal (pH, enzyme/protein concentrations, oxygen tension, ROS) and external (ultrasound, optical radiation, magnetic field), and biologically active. Thus, from the drug molecule to the actual matrix, each component of the injected nanoconstruct will play a specific therapeutic role.

- The modeling of the transport of systemically injected nanoconstructs over multiple temporal and spatial scales. We will develop Hybrid Lattice-Boltzmann and Immersed Finite Element methods (Figure 10) together with microfluidic-based organs-on-chips to characterize the vascular and extravascular behavior of nanoconstructs over multiple spatial and temporal scales.

  Molecular dynamics simulations will be used to design the surface of circulating nanoconstructs that favor the adsorption of specific blood molecules, thus facilitating systemic circulation and molecular vascular targeting.

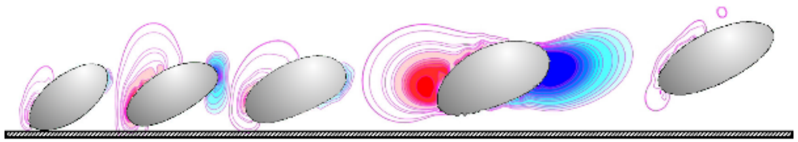


Figure 10: Computational model of the transport and flow field around a soft elliptical nanoconstruct close to a blood vessel wall.

Inorganic Nanoparticles for Hyperthermia and Drug Delivery

We will develop nanoparticles for magnetic hyperthermia and radiotherapy, and combinations thereof. To reduce the injected doses currently used in clinical trials, we will develop magnetic nanoparticles (mostly iron-oxide-based), controlling their size, shape, and composition to optimize their heating performance upon exposure to alternated magnetic fields (Figure 11).

Nanoparticles will be functionalized with smart coatings that have functional responses to external stimuli (heating) or internal stimuli (pH). The resulting particle will merge the features of the inorganic core with those of the functional polymer shell to remotely control the release of therapeutic molecules (synthetic drugs, RNAs) encapsulated by or associated with the coating. This will allow tumor hyperthermia, by local or macroscopic heat effects, to be combined with controlled chemotherapy.

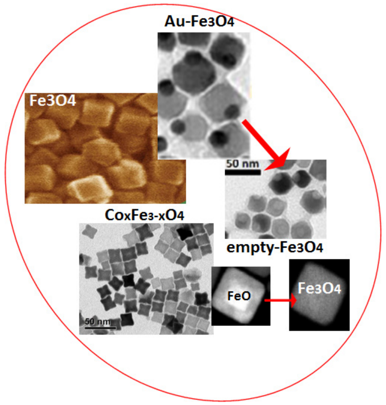


Figure 11: Shape-controlled superparamagnetic nanocarriers.

The in vivo degradation of these carriers will be tailored to find coating compositions that support multiple cycles of magnetic hyperthermia, and to expose the inorganic core to the acidic cellular/tumor environment for final clearance. Efforts will also focus on realizing controlled assemblies of magnetic nanoparticles to provide better magnetic performances than single nanoparticles.

The accumulation of different magnetic-based nanoparticles in the diseased tissue will be modulated via various magnetic field gradients. These thermoresponsive nanoparticles will also be tested in new application fields, such as in Prader-Willi syndromes where body temperature and metabolism could be regulated by the triggered release of antipyretic drugs.

Smart scaffolds and patches for tissue regeneration and controlled delivery of molecules

We will design and develop novel soft polymeric matrices, based on natural polymers and incorporating natural active principles and synthetic drugs (Figure 12). We will develop scaffolds with specific geometries, encoded with morphophysical features mimicking the extracellular matrix of the original tissue. This will allow us to accelerate the regenerative process and to foster the selective differentiation of multipotent stem cells. In particular, materials will be encoded with programmed biological and biophysical signal presentation to instruct specific cell processes (i.e. differentiation, biosynthesis, morphogenesis).

For in vivo applications, cell scaffolds will be realized with biodegradable, nontoxic, biologically active, renewable, and sustainable natural polymers. These scaffolds will appear as multilayered films, porous membranes, and micro/nanocapsules. The degradation of scaffolds and patches will be finely tuned depending on the application. In tissue-regenerative scaffolds, biodegradation will be controlled by the type of injury (e.g. spinal cord injury) and will be slower than in patches for infectious skin diseases.
Patches will be used to heal skin infections and chronic wounds with superior antibacterial, anti-

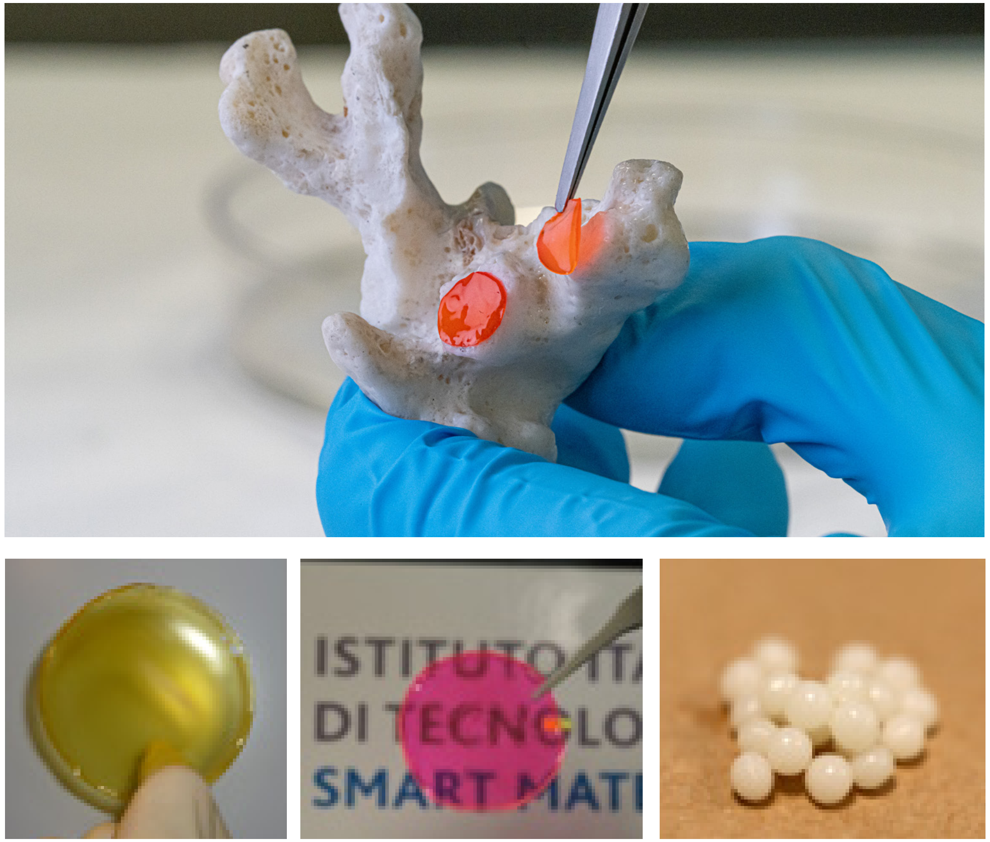


Figure 12: Biomedical devices made of natural polymers loaded with active principles.

inflammatory, and antibiotic performances. Drug release will be controlled by environmental cues such as humidity and pH. Growth factors and electrically conductive inclusions (e.g. graphene) will be incorporated.

Food traceability

We will use our universal and low-cost technology, PCR Developer, to enable the colorimetric ultrasensitive detection of any specific genetic sequence. This technology was recently applied to the genetic traceability of virtually any food item of animal or vegetal origin.

The detection is based on naked-eye inspection of a simplified DNA barcode from a complex food matrix. We will further improve the test portability, reduce the analysis time (through PCR-free isothermal techniques), and optimize the rapid low-cost protocols for extracting DNA from complex food matrices. We will apply our technique to the analysis of complex food fraud involving, for example, thermally processed products or fine ingredients that are diluted/mixed with many different species.

We will develop colorimetric ultrasensitive strategies (based on PCR) and alternative isothermal fast techniques with naked-eye readout for large-scale screenings and POC applications. We aim to optimize known techniques with strong potential but low practical applicability that is likely due to complex aspecificity issues (e.g. LAMP and NEAR). We will also seek to develop novel reactions by combining the particular physical/chemical properties of hybrid nanoparticles/nanozymes with molecular biology and biotechnology. In both cases, we aim to develop strategies for the simple colorimetric inspection of the results. We will develop novel home-testing devices to assess food quality, since nutrition and health are closely related. We will explore hybrid nanomaterial strategies to quantitatively evaluate several food parameters that are relevant to health (e.g. antioxidant levels, sugar content).

Priority 3: Nanomaterials for Energy Program

This program will tackle important challenges related to energy conversion, efficient energy use, and energy storage. It comprises several main research lines, which tap core areas of expertise at IIT: i) halide-perovskite-based solar cells; ii) nanomaterials and photonics for lighting, iii) Li-ion batteries and supercapacitors based on 2D materials; and iv) technologies for capturing, purifying, and converting CO2 into fuels and useful chemicals.

Solar cells based on halide perovskites and on combinations of perovskites and 2D materials

Building on IIT's recent world-class results in the field of printed perovskite solar cells (i.e. 19% PCE in stable 1 cm2 PV cells), we will use top-notch spectroscopic tools to investigate degradation processes in this emerging class of materials and in the related devices. The goal is to improve the design of semiconductors and/or of device architectures, which can guarantee a loss of device performance of no more than 0.5% during one year of operation. Simultaneously, we will develop materials processing for large-area deposition.

This must preserve the efficiency already achieved, while targeting environmentally friendly low-cost processes. We will also exploit 2D crystal-based printable hybrid and perovskite solar cells in order to demonstrate high efficiency and stability. The goals are to design and realize printable 2D-crystal-based electrodes and charge transport layers in order to deliver novel device concepts and to convert the proofs of concept into large-area modules and flexible PV devices with enhanced performance.

In a collaboration with an external industrial partner, we are developing a pilot production line to realize both opaque and semitransparent electrodes by exploiting solution-processed 2D materials, which will be used as interfaces and contacts.

Photonic structures and quantum-confined materials for efficient light-emitting devices

We aim to develop new types of nanomaterials, based on nanoparticles and van der Waals structures, with low toxicity and optimized optical and electronic properties for light emission. For their integration in functional architectures, we will seek to understand and master the surface and surface chemistry of these materials in order to obtain functional composite materials with increased optoelectronic performance.

We will develop methods to incorporate these nanomaterials into different optical and chemical matrixes that preserve their optoelectronic properties and simultaneously improve their chemical and ambient stability. The aim is to develop a versatile platform for lighting devices that goes beyond the state of the art. The results from this activity will also have a positive impact on biosensing and bioimaging.

Low-dimensional materials for Li-ion batteries and supercapacitors

This activity targets the development of a variety of nanomaterials for use as conductive additives in anodes for Li-ion batteries (LIBs), in combination with Si- and Sn-based alloy/de-alloy composite materials.

The target is to fabricate anodes that combine 2D materials with different forms of silicon and tin-based nanostructures displaying high capacity and a long cycle life. In parallel, we will develop high-performance cathode materials, such as Li-rich layered oxide materials, synthesized and nanostructured via bottom-up approaches in combination with 2D material flakes. Scale-up of the most promising material technologies for electrodes will be studied with industrial partners in order to produce coin cells for headset applications and pouch cells. Sodium-ion (Na-ion) and Lithium-Sulfur (Li-S) batteries will also be investigated in order to develop hierarchical (2D and 3D) electrodes to improve their performances. Similarly, we will seek to apply 2D materials, alone and in hybrid structures with other carbon-based nanomaterials, to prepare printed hierarchical electrodes for flexible supercapacitors.

New strategies to capture, purify, and convert CO2 into fuels and useful chemicals

This line combines theoretical chemistry with engineering-driven approaches. The main activities will be:

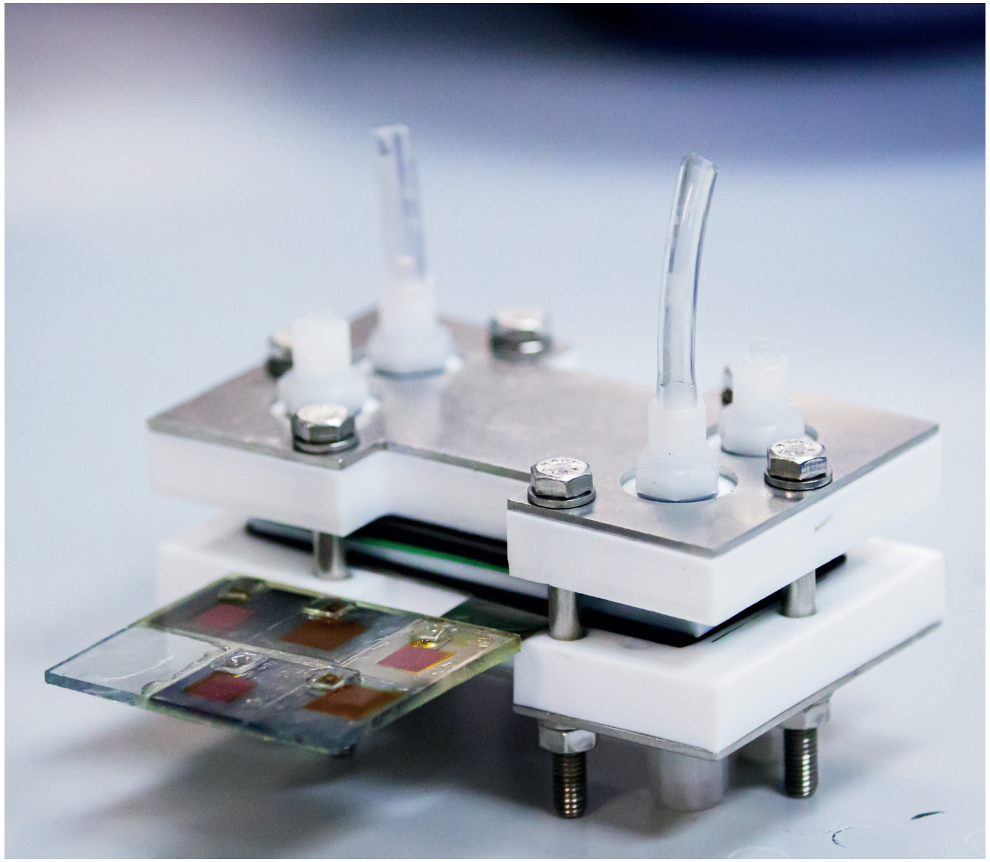
- Development of new materials and methods for CO2 capture. These will include: i) ionic liquids derived from natural sources; ii) use of deep eutectic solvents; iii) polymeric solutions functionalized with CO2-philic groups; and iv) 3D-printed polymeric structures composed of CO2-philic materials acting as sorbent membranes.

- New catalysts for CO2 reduction. We will search for efficient catalysts that can reduce CO2 in the presence of H2 or other reducing agents that use thermal-, photo-, electro- or biologically mediated reactions. We will use different synthesis techniques to finetune the optical, chemical, and physical properties of the catalysts, such as high-temperature combustion synthesis, low-temperature chemical processes, and colloidal synthesis. The design of photocatalysts and electrocatalysts for CO2 conversion will be supported by extensive computational modelling.

- Efficient electrochemical reduction of CO2 into fuels and useful chemicals. Here, we will address two scenarios: 1) a low-cost, high-efficiency, grid-connected reactor, producing reduced forms of CO2 from concentrated streams; 2) a low-cost photo-enhanced device for artificial photosynthesis, capable of exploiting the UV-vis-NIR part of the solar spectrum, suitable for low-concentration mixtures of CO2, or for direct conversion from the atmosphere. We will synthesize new types of nanostructured photocatalysts and electrocatalysts based on metal oxides and carbon materials doped/decorated with metals, nonmetals, or transition metal oxides.

- Microbial biofactories for CO_2 conversion. We will set up microbial programs, where the whole organism and the entire microbial community are the biocatalysts for converting CO_2 into added-value chemicals. We will investigate various types of microbial biofactories, including photosynthetic and nonphotosynthetic microorganisms. Metabolic engineering and synthetic biology approaches will boost efficiency and robustness. Using combustion-based processes, we will valorize biowastes to produce carbonaceous materials and related precursors. In a circular economy, it is crucial to develop processes that transform biowastes into activated carbon-based materials, using CO_2 as an activator. Renewable activated carbons and carbon-based materials can be used as catalyst supports and as electrode components in electrochemical energy devices (e.g. microbial fuel cells).

- Nanostructured materials for methane and CO_2 conversion. The production of next-generation fuels requires innovative catalytic processes that efficiently use new or more convenient feedstock. Thanks to the growing accessibility of natural gas reserves, methane is an important feedstock. However, to be economically feasible, methane exploitation requires efficient, small-scale direct conversion routes, which are still out of reach. In addition to exploiting new feedstocks, the effective conversion of CO_2 will be crucial to achieving a sustainable carbon-based economy. In this context, we will develop new nanomaterials to convert methane and CO_2 to methanol, exploiting thermo- and electro-catalytic routes. Combining experimental and modeling tools, we will focus on two families of materials: supported bimetallic nanocrystals (NCs) and unsupported nanoporous catalysts. To prepare the catalysts, we will use colloidal synthesis methods to precisely tailor the properties of the active sites.



Priority 4: Exploratory Nanomaterials Science Program

Exploratory Nanomaterials Science encompasses the most fundamental research done by IIT in the field of materials science and nanotechnology. It is based on IIT's considerable expertise in materials synthesis, advanced characterization, and photonic nanostructures. This area traditionally focused on colloidal nanomaterials, but recently expanded with new teams working on novel 2D materials and polymer synthesis, metamaterials, and single-photon emitters. The behavior of nanoscale materials and nanostructures is strongly connected with these themes, as understanding the fundamental physical and chemical processes at the nanoscale is essential to their successful integration in many technologies. This program is strongly tied to several other programs at IIT, as it provides the fundamental building blocks for a wide variety of applications.

Colloidal nanomaterials: advanced synthesis and post-synthesis transformations

This activity will identify new synthesis strategies for colloidal nanomaterials with unique features in terms of optical, electronic, and magnetic quality, and with fine control of geometric and compositional parameters. The wide range of materials to be targeted includes: i) semiconductors, such as metal chalcogenides, III-V semiconductors, and halide perovskites, which will be studied for applications in solar cells, photodetectors, light-emitting diodes, and lasers; ii) metals, including degenerately doped semiconductors with tunable plasmonic response, for applications in plasmon sensing and laser hyperthermia; and iii) magnetic materials, for applications in magnetic hyperthermia and magnetic resonance imaging. In terms of electronics applications, an important goal for many of these colloidal nanoscale materials will be to obtain efficient charge transport by carefully controlling the surface properties.

The post-synthetic chemical transformations of colloidal nanomaterials are a powerful tool for exploring new materials and obtaining materials that are difficult to access via direct synthesis. Here, we will target both anion and cation exchange reactions, and use various chemicals that can directly react with the NCs to change their crystal structure and/or chemical composition. We will particularly focus on halide perovskites, which are characterized by a soft lattice, enabling them to react with a variety of chemical agents and be transformed accordingly.

Colloidal nanomaterials: Study of transformations in nanomaterials under extreme conditions

Researchers are still in the early stages of integrating nanomaterials, especially nanocrystals (NCs), with production tools that use techniques such as irradiation, etching, and annealing (typical processes for making optoelectronic devices). There is a lack of systematic knowledge of the modifications triggered in the NCs under those conditions. A further open question is whether NCs incorporated into materials/devices will remain as they are over time, or whether they will transform into other structures. Furthermore, these reactions in NCs have been poorly studied because they require rapid recording techniques. Within this context, we will investigate post-synthetic transformations in nanomaterials. The main objective is to develop new sets of experimental tools to investigate chemical transformations in nanomaterials.

The currently available approaches to novel (nano)materials will need to be expanded to include conditions where various activation barriers can be overcome. At the same time, the implementation of these approaches must allow the thermodynamic barriers to be lowered. Extreme conditions in this context essentially mean high pressures and high temperatures. High-pressure and high-temperature syntheses allow the production of materials with unconventional properties.

This also enables the investigation of the physics and chemistry of extreme environments, such as planet interiors and meteorite formation/impact. In any synthesis, the key questions are: which crystal phases are present? Have new phases been formed? To address these questions, we aim to develop a new crystallographic approach based on the combined used of atomically resolved electron tomography, powder X-ray diffraction and single-crystal electron diffraction on NCs. The latter will be specific to investigating unknown crystal grains and solving their structure.

Colloidal nanomaterials: Application in quantum technologies

Single-photon emitters are at the core of many emerging quantum technologies for communication networks and computers. Colloidal semiconductor NCs are intrinsic single-photon emitters that promise to complement current nonclassical light generation systems, leading to versatile and small-footprint devices.

vThe aim is to exploit these materials to fabricate novel electrically driven single-photon sources that can be embedded directly into quantum systems. IIT will develop and identify the best colloidal semiconductor NCs that show reliable and fast single-photon emission combined with functional stability.

A large library of colloidal semiconductor NCs is available and IIT already plays a leading role in synthesizing and studying this class of nanomaterials, which will strongly benefit this investigation. The final aim also requires the development of device fabrication methods to control the deposition of colloidal nanomaterials. In addition, fine positioning of the NC within the device will allow the deterministic fabrication of single-photon sources.

Optoelectronic device preparation at IIT is based on the micro/nanofabrication tools and know-how in various research facilities. Overall, this research framework strongly benefits from the multidisciplinary research carried out at IIT, including materials science, physics, chemistry, and engineering. As an example, new single-NC spectroscopy approaches will be developed to fully characterize in operando the optical properties of the newly synthesized NCs.

Figure 13: A selection of 2D-crystal-based inks developed by IIT.

2D Materials

IIT is one of the leading partners in the European FET Flagship Graphene. In this context, the IIT Graphene Labs will target the production, investigation, and device application of a wide portfolio of 2D crystals (Figure 13). Two main lines will be pursued: (i) synthesis of novel 2D materials and 2D topological insulators; and (ii) processing of 2D materials and their heterostructures.

In the first line, we will synthesize novel 2D materials, with a particular focus on 2D topological insulators and lateral graphene superlattices via atomic intercalation. We will study the electronic properties and search for ordered atoms at the interface that have enough weakly bound states to generate 2D bands on their own, building electronically active 2D stacks. Cutting-edge correlated electronic and structural studies will be possible thanks to a novel combined angle resolved photoemission spectroscopy–scanning tunneling microscopy system (installation 2021 at CNI@NEST). In the second line, we aim to develop 2D functional materials, understand their (opto)electronic and electrochemical properties, and develop energy-saving high-performance photonic technologies, novel biomedical applications, and energy storage and conversion devices. A collaboration between IIT and the recently launched start-up BeDimensional will further deepen knowledge and capabilities on 2D crystals produced by liquid phase exfoliation (LPE) of bulk layered crystals. Applications of these materials will include printable circuits and electrodes for batteries and storage, composite materials with tunable mechanical, thermal, and chemical properties for application in high-performance tires, high-end sporting goods, reinforced materials for protection and construction, and wearable devices.

Novel Materials and Architectures for Photonics, Plasmonics, and Metamaterials

Light provides unmatched versatility for technologies in modern society, including telecommunication, healthcare, and consumer electronics. Controlling light’s properties with components significantly smaller than its wavelength is a great challenge in photonics. Metamaterials have proven to be a powerful solution. We aim to design multifunctional composite materials that combine semiconductor, metallic, dielectric, and magnetic properties. One target is to incorporate optical gain materials (that is, direct band gap semiconductors) in plasmonic structures and metamaterials to compensate for the metallic losses. This loss compensation will open the door to novel concepts for plasmonic resonators for lasing, and towards metamaterial for imaging at well below the diffraction limit. Furthermore, we will explore low-dimensional material architectures based on metal halide perovskites for novel physical and chemical phenomena such as spin textures, ferroelectric phases, and light-matter coupling.

Initiative: Sustainability

This Initiative aims to promote Sustainability to the level of strategic priority at IIT. In the Strategic Plan, Sustainability is one of the Societal Challenges, but it is currently a research Priority in the Nanomaterials RD only. This Initiative will reinforce this Challenge, making it more prominent in the Nanomaterials RD and expanding it to the Robotics, LifeTech, and Computational Sciences RDs, creating strong links, collaborations, and common targets. The Sustainability Initiative is a true cross-domain Initiative, transversal to IIT's four RDs. Many IIT research lines already work on sustainable solutions for societal and environmental problems. The individual scientific results are valuable.

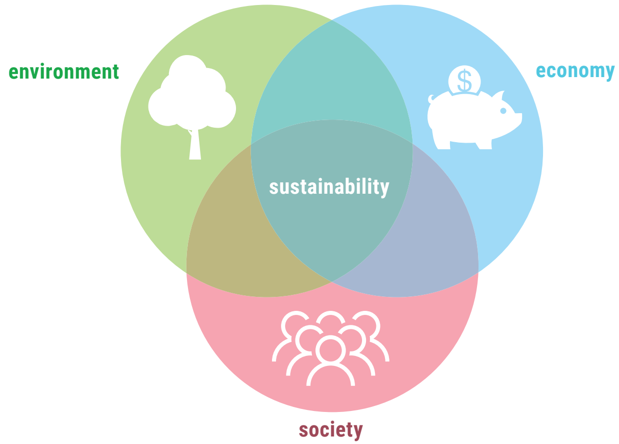


Figure 14: Sustainability as a balance between society, environment, and economy

European projects, including ERCs, are already running and there are already collaborations with industrial partners and Joint Labs. Topics include waste valorization for the development of biomaterials, green electronics, solutions to water scarcity and contamination, the prevention and treatment of diseases with green chemistry solutions, and energy storage from renewable resources. Nevertheless, these efforts are currently scattered, lacking coordination and common objectives, and often not focused on guaranteeing sustainability with respect to the materials and methods. This IIT Initiative will cluster and coordinate the various research activities under new and common technological deliverables, which will tackle specific sustainability goals of global economic, societal, and environmental importance.

Implementation

Sustainable development refers to three interconnected aspects: society, environment, and economy. To be effective, these aspects must be achieved in perfect balance (Figure 14). The key performance indicators of sustainability are varied. For this reason, the United Nations has defined 17 Sustainable Development Goals (SDG), which make up the roadmap to a better and more sustainable future. To align with these global targets, this Initiative will use the SDGs to determine the activities and to monitor and evaluate the outcomes. Specifically, eight of the 17 goals (marked below) will be addressed. In short, the key performance indicators design by the UN will be used as references to measure our common technological deliverables performance. Dedicated groups of PIs, researchers, technologists, and their teams will work on the different SDGs in order to develop technological solutions (demonstrators), documents, and protocols to address specific problems related to each SDG.

The research activities of materials scientists, robotics engineers, life scientists, and computer scientists will be connected and combined to develop the above-mentioned technological solutions. The participating research lines will contribute to the development of materials/nanomaterials, green components, or sustainable integrated systems. They will do this by targeting technological solutions in the form of demonstrators/prototypes for sustainable development in the following SDG areas (see Scheme in Figure 15). In parallel, documents and protocols will be produced regarding the evaluation of the research outcomes, resource management instructions, and sustainability guides to designing complex systems and energy-efficient manufacturing.

Figure 15: The SDGs addressed by the Sustainability Initiative (highlighted by a red rounded box).

In particular, the research activities will focus on:

1. Food protection and monitoring; increasing agricultural productivity with robotic monitoring, data analysis, and intervention systems (SDG2: Zero Hunger).
2. Advanced therapies for epidemic chronic neurodegenerative diseases and malignant tumors; evaluation of how hazardous chemicals and pollution affect human health using various validated models, including 3D organ models; assistive robotics for wellbeing (SDG3: Good Health and Wellbeing).
3. Fast portable diagnostics for water quality; economical and effective water remediation and sanitation technologies to remove persistent and mobile pollutants; water harvesting from nonconventional sources, such as desalination, recovery of potable water from wastewater, and atmospheric moisture (SDG6: Clean Water and Sanitation).
4. Energy microharvesters; CO2 and biomass conversion; energy generation and storage from other renewable sources; new-generation perovskite solar cells (SDG7: Affordable and Clean Energy).
5. Electronics, robotics, and AI in infrastructure deterioration monitoring; alternative materials and systems for robust and energy-efficient infrastructures (SDG9: Industry, Innovation & Infrastructure).
6. Novel materials and monitoring systems to protect the world's cultural heritage; extreme condition robots for natural catastrophes; systems to efficiently convert municipal and agricultural waste (SDG11: Sustainable Cities & Communities).
7. Extraction, processing, and reuse of organic and inorganic waste to produce biomaterials and devices, including electronics and robots. Bioengineering for plastic degradation and valorization of waste gas (SDG12: Responsible Production & Consumption
8. Fish waste valorization, coral healing methodologies, sea pollution portable measurements, prevention of acidification. 3D organ models to measure the toxicity of seawater pollutants including nano/microplastics (SDG14: Life Below Water).

The leading team will comprise the PIs who will lead the eight SDG-related activities. The leading team will organize workshops and seminars every couple of months. In the kickoff meetings, we will determine the final demonstrators of all the SDGs in order to have well-defined working platforms. In the following meetings/workshops, all the contributors to the respective SDGs will participate and present the advances in their research. Contributors to other SDGs will be encouraged to participate in order to create additional cross-SDG synergies. After the Initiative's first year, a reorganization may occur with new research lines arising and inactive research lines leaving the Initiative. At that stage, calls will be opened for shared PhDs and postdocs to work on common goals across the research lines.

By clustering and coordinating multidisciplinary research activities and developing unique technological solutions that promote sustainable development, IIT will become a strong player and influencer in the field, making it highly visible to external research partners and companies, and more attractive to young talented researchers seeking a career in sustainability in a pioneering research institute. Our networking and attractiveness for external funds and investments will increase. The Initiative will also promote relationships, interactions, and collaborations with national and international institutions and policy and decision makers (i.e. ASVIS, European Commission, UNEP) with a view to future decisions on sustainable development. The Initiative's launch is timely, since the European Commission has just announced the European Green Deal calls. Many of the projects within the Initiative can be partially funded by H2020 projects.

Demonstrators

The Initiative will design and develop technological demonstrators for use in IIT's buildings, i.e. energy-harvesting systems, self-powered devices, water recovery and sanitation, and green robotic infrastructure inspections. In this way, IIT's buildings will become the testing ground for our technologies and an incubator to validate sustainable solutions. These demonstrators can be the seed ideas of new IIT start-ups.

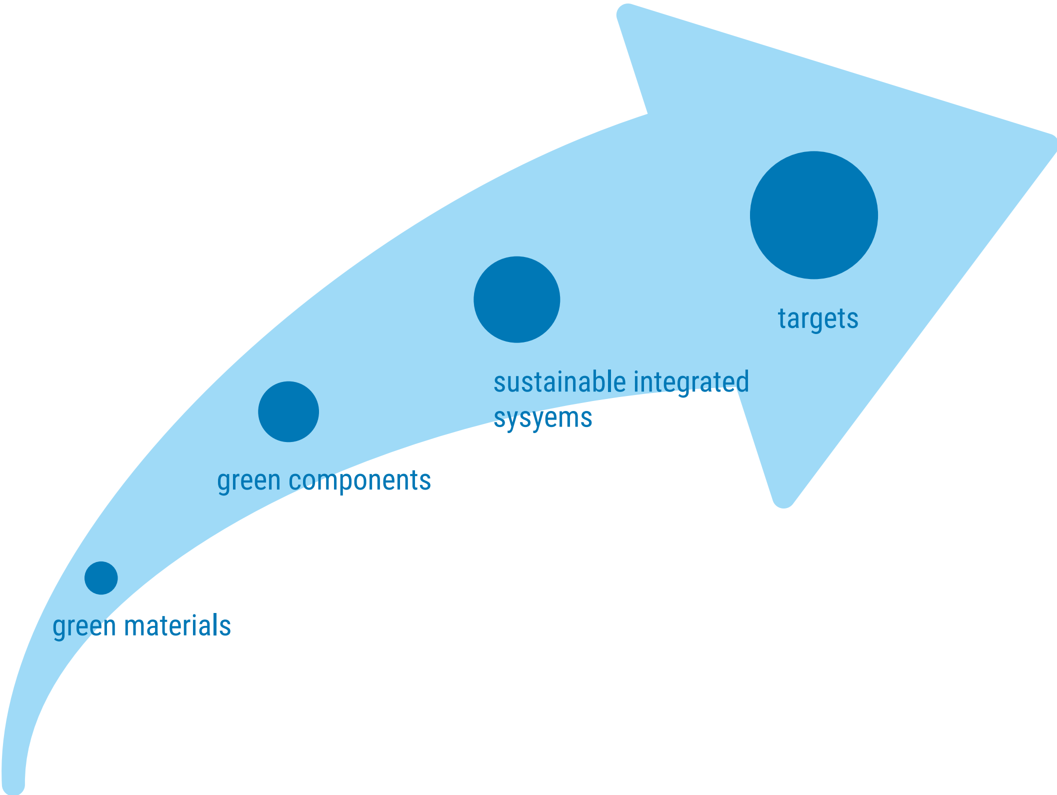


Figure 16: The hypothetical development path of technologies for sustainability from materials to complete integrated systems to address the target goals of the UN's SDGs.

Targets

SDG-2 Food protection and monitoring. Increase agricultural productivity

SDG-3 Advanced therapies for epidemic chronic neurodegenerative diseases and malignant tumors. Evaluation of hazardous chemicals and pollution on human health

SDG-6 Fast portable diagnostics for water quality. Economical and effective water technologies to remove persistent and mobile pollutants from water. Water sanitation. Water harvesting from unconventional resources

SDG-7 Energy microharvesters. CO2 and biomass conversion. Energy generation and storage from other renewable sources, new-generation perovskite solar cells

SDG-9 Electronics, robotics, and AI in infrastructure control. Alternative materials and systems for robust and energy-efficient infrastructures

SDG-11 Novel materials and monitoring systems to protect the world's cultural heritage. Extreme-condition robots for natural catastrophes. Systems to efficiently convert municipal waste

SDG-12 Extraction, processing, and reuse of organic and inorganic waste to produce biomaterials and devices, including electronics and robots. Bioengineering for plastic degradation and valorization of waste gas

SDG-14 Fish waste valorization. Coral healing methodologies. Sea pollution portable measurements. Prevention of acidification. Biological systems for measuring the toxicity of seawater pollutants including nano/microplastics

Support studies

The parallel support studies will be life-cycle assessments, total carbon footprint calculations, resource management, and sustainability guides to designing complex systems and energy-efficient manufacturing (e.g. with IIT's Machine Shop production facility).

Related satellite IIT activities

The research activities will develop in parallel with additional support activities and, especially, with the actions to maintain and expand the ISO 14000 for ENVIRONMENTAL MANAGEMENT, the Plastic Free campaign, and the IIT GOING GREEN campaign of the Technical Services and Facilities Directorate. The Technical Services and Facilities Directorate will be constantly informed of the outcomes of the Initiative's research activities in order to evaluate together how our results can directly impact the IIT GOING GREEN program.

In the framework of more activities in training-by-research, higher education, and continuous professional development, IIT will create a sustainability-specific program open to IIT staff and selected external students. This activity's cornerstones are i) a formal training program based on advanced seminar series and short courses on soft and transversal skills, and ii) sponsored (Master-level) research projects on SDGs, which will be carried out by final-year or newly graduated university students in the laboratories of the participants, or in partnership with selected external partners. With this activity, IIT will contribute to SDG4: Quality Education.

The SDG5 Gender Equality is another UN goal, not strictly related to our research activities, that is nonetheless promoted by IIT, since the Foundation supports Gender Equality with different actions. These actions will be identified by the Research Organization and Human Capital Directorates and incorporated into the Sustainability Initiative's general outreach and communication.

Outreach

IIT's Communication Directorate will ensure that researchers and their wider audience have the relevant information about and awareness of the Sustainability Initiative. This will be carried out in close collaboration with Initiative participants (involving young students and early-stage researchers). A dedicated webpage will be created to publicize research updates and events. Twice a year, workshops will be held for potential research partners/collaborators and related industries in order to make our results known, get feedback on the next steps, create external partnerships, and attract industrial collaborations. We will frequently and dynamically participate in national and international conferences, festivals, and exhibitions.

IIT believes that we need to move towards common sustainable objectives. Taking into account the current sustainability-related activities within the Initiative, we calculate that one quarter of IIT's research budget is already allocated under the Sustainability Initiative's umbrella. After the first year of organization, operation, and evaluation, an open internal IIT competition can assess which new research lines would fit this Initiative. At that stage, new budget and resources may need to be allocated to reinforce the Initiative. The final aim is to arrive at the new Strategic Plan (after 2023) with strong results and visibility, and to propose Sustainability as a central joint Priority of IIT with a consistent percentage of the budget allocation.

Participants

The Sustainability Initiative involves 33 PIs and several Facilities from the Central Research Laboratory in Genoa and from various Centers of the IIT network. The core group is centered on Nanomaterials but there are clear extensions to all RDs.

Initiative: Artificial Intelligence and Automation for Materials Science

This Scientific Initiative brings together PIs to create new strategic synergies between the Robotics, Computational Sciences, and Nanomaterials RDs.

In our vision, machine intelligence will drive a series of automated processes in order to manage experimentally produced big data and result in a "moment of creation". For example, artificial intelligence (AI) and, more specifically, machine learning (ML) will be used to enable fast, automated, optical, and structural screening of the products of several hundred molecular syntheses per month. With >10,000 syntheses per year and a tight selection of samples, our discovery rate will be easily increased to 10 new materials per year for use in new devices.

ML algorithms will be trained to find optimal metasurface designs in order to realize new optical devices with unprecedented functionalities and ultimate performances. ML will be used for the real-time interpretation of single-photon datasets. Algorithms will decode molecular maps (number of molecules per sample position) from biosamples, offering a valuable alternative to the inversion of complex models based on coincide photons statistics. This application will impact the LifeTech RD by providing new optical microscopy tools for bioimaging. The Initiative will increase cross-contamination among RDs.

The Initiative's framework in line with the aims of the European Network ELLIS (see section: Machine Learning and Artificial Intelligence): AI that participates in basic science rather than being a mere technological advance.

Our program is ambitious, combining the design of optical devices with ML; visual recognition with hyperspectral imaging; robot control algorithms with scanning probe microscopy; and AI with materials synthesis. However, the diverse and well-assorted competences of the proponents put us in a unique position to pursue this broad vision. ML will increase the quality, rate, and automation of cutting-edge techniques in materials science.

Topics

Simulation and optimization methods in metasurface design

By definition, metasurfaces are nanostructured surfaces, artificially designed and fabricated with nanofabrication tools. The approach used so far is mostly deterministic in the sense that the nanoelements are simulated with numeric methods to create a library of elements that are subsequently used to design a metasurface with a given functionality.

This approach is time-consuming and, more importantly, does not guarantee the optimal design. Many approximations must be made when moving from design to practical realization. New emerging approaches to metasurface design therefore use inverse design and ML. We aim to develop a new platform where computational methods can autonomously derive new designs for metasurfaces from specific inputs from the user. The challenge is to maintain a large number of free parameters in order to span the largest landscape of possible solutions and thus guarantee that the optimal solution is part of this landscape.

Metasurface design is of great interest to consumer electronics companies. The big manufacturers are investing considerably in next-generation optical devices for electronics. The quest is on for miniaturization, low-footprint, and lightweight design.

With this Initiative, IIT will begin this quest by creating a synergic platform between IIT experts in metasurfaces and in the computational methods typical of ML.

New-generation controllers for scanning probe microscopy

Atomic force microscopy (AFM) and scanning tunneling microscopy (STM) revolutionized material surface imaging. The inventors were awarded the Nobel Prize after their introduction. All scanning probe microscopy (SPM) techniques, which also include scanning near-field optical microscopy (SNOM), are based on a specific probe that scans the sample close to the sample surface (a few nanometers' distance). The common idea is to overcome the diffraction limit of optical microscopy by localizing the probe-sample interaction. The stabilization of the probe-sample distance is then crucial for the operation of these microscopes. However, since the first proof of concept, there has been little evolution in the design approach to the electronic controllers that run SPMs. We will explore the possibility of a new paradigm in designing electronic controllers for SPM. The technology developed by IIT for controllers for humanoid robots (e.g. the iCub dynamic balancing controllers) will be used to design new SPM controllers with improved SPM performance in terms of automation, reliability, and parameter prediction. Automation of imaging steps is not the only output. ML algorithms will replace scientists in running an SPM by autonomously determining the best scanning parameters for ultimate image quality.

Artificial intelligence for designing new materials

NCs of various materials can be prepared by chemical approaches, and have their surface coated with a monolayer of organic ligands to ensure colloidal stability. These materials have the potential to shape technologies as diverse as electroluminescent and liquid crystal displays, solid-state lighting, lasers, scintillators, infrared imaging, and solar concentrators.

The general goal is to discover and synthesize a portfolio of novel perovskite NCs to be implemented in optoelectronic devices. The key challenge is to find the ideal composition of the material with specific optoelectronic characteristics along with the best passivating ligands to ensure long-term colloidal and optical stability. In engineering NCs and surfaces, computational tools are used to generate candidate structures and optimal ligand molecules to passivate the surface of the corresponding NCs. The structural search returns potentially stable structures and properties that satisfy specific structural rules that are communicated to the synthesis activities. In contrast, the ligand search identifies ligand molecules to optimize the syntheses of NCs and to improve nanocrystal stability and optical properties, thus satisfying device needs. Combining these aspects of crystal creation is an arduous problem that requires developments in synthesis automation, computational materials science, and advanced materials characterization. Our medium-term aim is to develop a robotic-based high-throughput platform to synthesize new NCs and to accelerate material discovery and optimization, with support from computational and data analysis tools to improve the experimental parameters.

Augmented single-photon microscopy

Microscope images or microscope datasets are potentially information-rich, but most information is lost or hidden during the image formation and recording. Lately, AI has demonstrated its ability to recover and make some of this information available to the user.

Two typical examples are 1) the ability to recover (diffraction or subdiffraction) structural information from noisy images and 2) the classification of subcellular organelles/structures from label-free images, which was one of the unique abilities of fluorescence microscopy. Many technological advances have transformed the illumination and detection systems of modern microscopes. These advances can boost AI's potential to augment the information content of microscopy images. In a laser-scanning microscope (LSM), the illumination laser beam can be easily modulated in intensity, phase, wavelength, and polarization. Photodetection can be engineered to be sensitive to polarization, wavelength, and phase. In a nutshell, a modern LSM is a multiparameter system, where the typical light intensity image is only one of the possible image formation options. Furthermore, these concepts can be applied at the ultimate level of light granularity (i.e. photon by photon from single-photon microscopy), at high temporal resolution (hundreds of picoseconds) and with high throughput (Giga sample per second). Our vision is to overcome the limits of classical image representation, where a particular property (e.g. the light intensity) is directly mapped on a grid. The new microscope dataset output will be a list of photons, where each photon is tagged with a series of properties of the illumination and detection configuration. In this context, ML will help effectively decode the information requested by the user from the single-photon microscope dataset. This augmented reality will be presented to the user, guiding the next steps in the investigation of a given sample.

Data handling and correlative imaging

Creating new nanomaterials requires a broad set of advanced analyses, including TEM, X-ray diffraction, optical spectroscopies, nuclear magnetic resonance (NMR) spectroscopies, and 3D electron diffraction. New materials can subsequently be used to fabricate new devices like solar cells, light-emitting diodes (LEDs), including down-converting (DC) LEDs and electroluminescent (EL) LEDs.

Further characterizations are then required to evaluate the device's performance. These activities, either advanced or routinized, generate a large amount of data, both experimental (from real devices) and computational (from simulations), which need to be properly collected, organized, and analyzed. Different investigative techniques retrieve different properties. For instance, high-resolution optical microscopy can provide the position of markers inside a cell with ultimate resolution, whereas AFM measures the elastic properties of the cell membrane. Images and datasets collected by different techniques can be correlated to increase performance.

However, data are usually generated in different formats by scientists with different backgrounds. We will use ML tools to handle the generation of interoperable datasets from different characterization techniques and to identify common patterns that can enhance the characterization and optimization of the synthesis and fabrication of new materials and devices. This task will result in a virtual multitools laboratory where AI aligns and merges/correlates the measurements obtained from many sources (available at IIT).

Participants

The Sustainability Initiative involves six PIs, one facility (Nikon Center), and three researchers. The proposal involves the Nanomaterials, Computational Sciences, and Robotics RDs.

Initiative: Visualization of Functional Nanointerfaces In Operando: From Fundamental Processes to Device Design

Currently, there is a strong need to understand, predict, and control complex materials systems, which deliver functionalities that are more than the simple combination of the functionality of their building blocks. Devices often realize their function at material interfaces, but it is difficult to control the structure-property relationships. This is because the interface responds nonlinearly due to the presence of various chemical interactions that are sensitive to the operating conditions. But predicting device operation is crucial to engineering reliable devices. The nanotechnology community has long pursued the target of controlling these interfaces, but the results have been unclear.

The Visualization of Functional Nanointerfaces In Operando: From Fundamental Processes to Device Design (VISPI) Initiative has the ambitious goal of visualizing and describing the photochemical processes of nanointerfaces in operando, mainly (but not only) under optical and electrical stimuli, and with temporal and spatial resolution beyond the state of the art. Importantly, nanointerfaces are ubiquitous, so this activity will cover various Priorities within the Nanomaterials RD, ranging from nanomaterials for energy to healthcare and sustainability.

Approach

The VISPI approach is epitomized by a strategic case study, i.e. a nanointerface where multiple charge-transfer processes occur after light absorption. This is an important step towards the combined solution for solar energy conversion and storage. This case study therefore has a full-blown application domain in the exploitation of solar energy as a primary resource. The combination of energy collection and storage in a single device is an innovative approach to a more efficient, compact, and cost-effective use of solar energy.

In the light-driven solid-state nanocapacitor geometry suggested by Light-DYNAMO (ERC StG, Dr. Kriegel), the materials involved are based on solution-processed zero-dimensional (0D) nanocrystal capacitors (NCCs), such as doped metal oxides, and 2D materials, such as transition metal dichalcogenides. The former is capable of storing multiple delocalized electrons after light absorption, while the corresponding holes are quasi-permanently transferred to the 2D materials. In optimized 0D NCCs, the storage (and thus transfer) of up to 250 elemental carriers per NC of several nanometers in size was observed.

VISPI aims to solve two different strategic problems: a) the fundamental cooperative properties of hybrid 0D/2D structured interfaces. b) light-driven in situ multielectron on relevant timescales. In this regard, it is important to develop in situ technologies that allow us to noninvasively address the electronic structure at the interface before, during, and after light absorption at relevant timescales for these processes.

Within the scope of his ERC Consolidator Grant, BrightEyes, Dr. Vicidomini is developing a new asynchronous read-out single-photon detector array (i.e. a pixelated camera) and a dedicated data-acquisition (DAQ) card that can support the high-throughput data produced by the detector. Indeed, the sensor is designed to not have a framerate. Photons are transferred to the DAQ one at a time, and the photon flux is limited only by the dead time of the single pixel, i.e. each pixel is blind for a few tens of nanoseconds after receiving a photon. Each collected photon is transferred to the DAQ together with a spatial tag (namely, the pixel that collects the photon) and two temporal tags. The first temporal tag is the delay to a specific trigger (e.g. the begin of the experiment, the change in the experimental conditions), with a few nanoseconds of precision. The second temporal tag is the delay to a sync signal (e.g. the sync from a pulsed laser), with a few tens of picoseconds of precision.

Within the BrightEyes project, the final aim of this single-photon detection system is to decipher biomolecular dynamics in live cells. However, the system's unique spatiotemporal characteristics make it a perfect tool for the time-resolved spectroscopy of single NCs to understand their photophysical properties and for in situ single-molecule Raman scattering intensity fluctuations at submicrosecond temporal resolution to study molecular interfacial processes.

Within the scope of her ERC Consolidator Grant, SOPHY, Dr Petrozza is developing tools and knowledge to probe optoelectronic processes at buried interfaces in devices under operating conditions. She is building an experimental tool which will map in space, with a resolution below 50 nm, electronic structures and their photoexcitations, and how they evolve in time on timescales from fs to microseconds to follow a wide set of cascade phenomena. To this end, two-photon photoemission (2PPE) spectroscopy is coupled to a photoemission electron microscope. The system aims to push the time resolution to the fs scale and the lateral spatial resolution to a few tens of nanometers, which has never been achieved within the same experiment. Moreover, the system aims to cover, for the first time, the evolution of dynamics over a broad time window in order to probe a wide set of cascade optoelectronic phenomena with high lateral resolution. This powerful tool will be exploited within VISPI to map, for the first time, the electronic structure of the interface together with the time dynamics of carrier transfer through the interface.

Within VISPI, we will gather the required quantitative information for the predictive design of hybrid interfaces by selectively monitoring the role of chemical-physical processes in the functionality of the light-driven storage device.

Impact

This research activity is expected to produce innovative outcomes in multiple directions. Firstly, the synergy of multiple research lines activities will allow the development of top-notch experimental methods and novel imaging/spectroscopy technologies to holistically answer several open questions in the field of nanomaterials. Subsequently, the visualization of molecular interactions and electronic processes at the nanointerfaces is crucial for the development of devices for light harvesting, energy production, and opto- and bioelectronics. This will strongly contribute to surpassing the state of the art in terms of basic science, and to deliver new technologies that combine efficiency, sustainability, and full integration into everyday life. All these themes have been identified in the Strategic Plan, especially with respect to the Societal Challenges of Sustainability and Healthcare. This Initiative stems from research activities which are currently supported by three ERC projects at IIT. However, the ultimate goal of VISPI is to go beyond the capability of single groups in order to create a critical mass within IIT to develop new experimental tools to study relevant open issues in materials science.

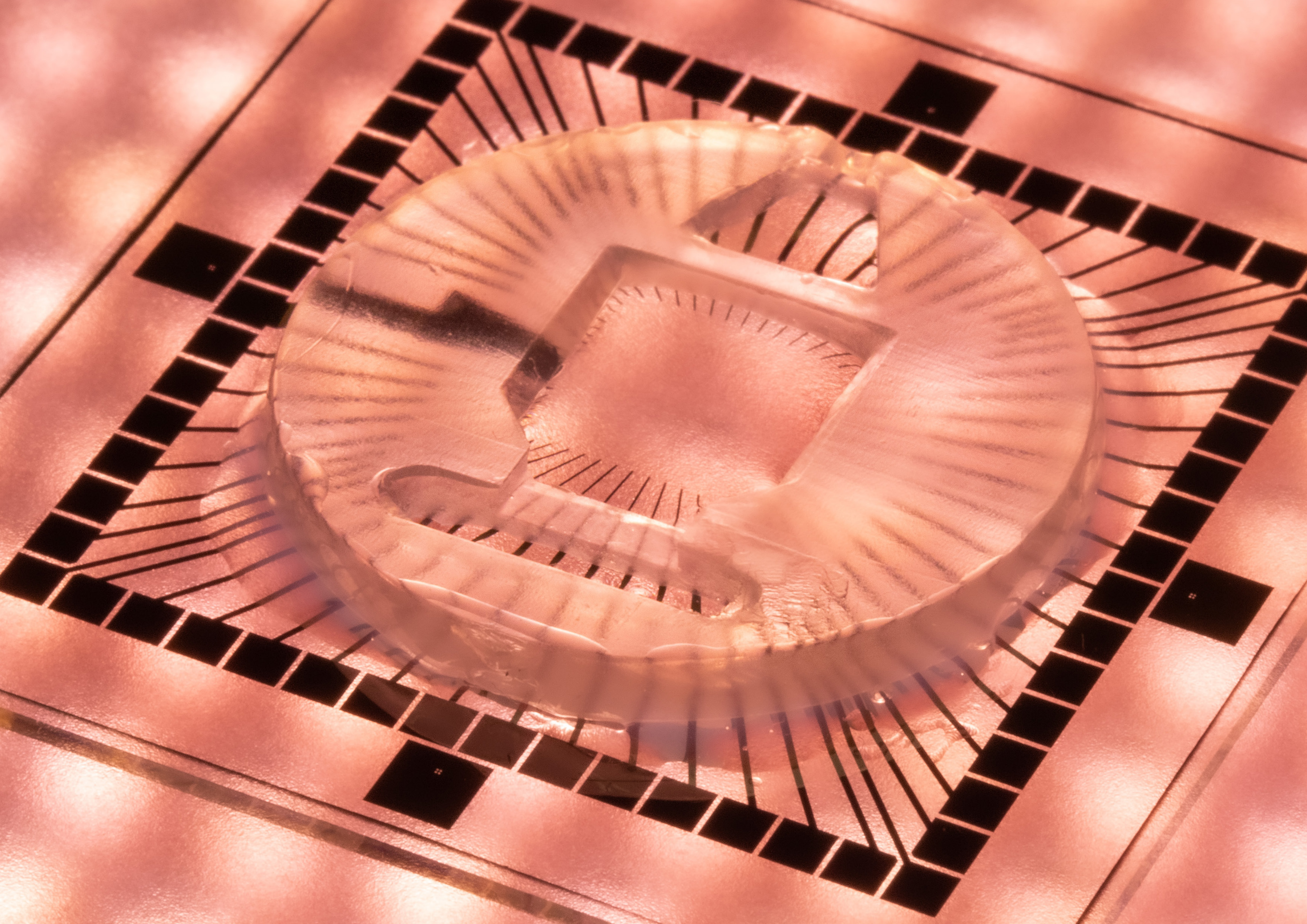
This can happen at two levels:

1. We will pursue the fundamental understanding of the most important underlying processes in buried optoelectronic interfaces related to electronic and structural modifications at relevant scales of time and length. This will be relevant to the studied system/case study, but also to the broader research community involved in implementing hybrid material systems, in which interfaces play a crucial role, e.g. batteries, solar-energy conversion systems, water splitting, CO2 reduction, light-emitting devices.

2. From an experimental point of view, it is problematic to investigate interfaces in operando. Our Initiative will create a critical mass within IIT to develop new experimental tools for studying relevant open issues in materials science. We expect VISPI to become a seed project that will welcome neighboring activities and research lines in the coming years (e.g. microscopy and nanofabrication facilities, some of the new research lines that were recently opened).

Participants

The VISPI Initiative involves three PIs and one Facility (microscopy and nanofabrication).



The Technologies for Life Science Research Domain

The Technologies for Life Science (LifeTech) Research Domain (RD) will focus on three Priorities as shown in Figure 17.

The first Priority (Neuroscience and Brain Technologies) originates from IIT's traditional core activity of neuroscience. The plan is: i) to develop new optical, computational, optogenetic, and molecular tools to efficiently monitor and manipulate brain circuits at multiple organizational and spatiotemporal scales; ii) to study the fundamental processes at the basis of brain activity; and iii) to interface live neural tissue with smart materials. Building on the knowledge accumulated in recent years, a multiscale approach will be implemented to better understand how higher brain functions arise from the integrated activity of populations of neurons and from the structure and function of their molecular constituents. Most of the activities of this Priority are driven by curiosity.

The other two Priorities involve an evolution from a purely basic life science domain to a technological approach to life science which is quintessential of IIT's scientific approach.

RNA Technologies focuses on a postgenomics approach dealing with i) the non-protein-coding portion of the genome and ii) RNA regulatory mechanisms that control gene expression. We will study the role of noncoding RNAs (ncRNAs) and repetitive elements in human physiology and disease. By applying advanced genomic technologies, we will study the aberrant transcriptional mechanisms underlying human diseases, with a particular emphasis on dysfunctions of the human brain and cancer.

We will also investigate how these molecules can be exploited for a new generation of innovative theranostics in personalized medicine. While based on basic science, this Priority has a strong technological component and is likely to have a tangible translational impact on brain and cancer diseases.

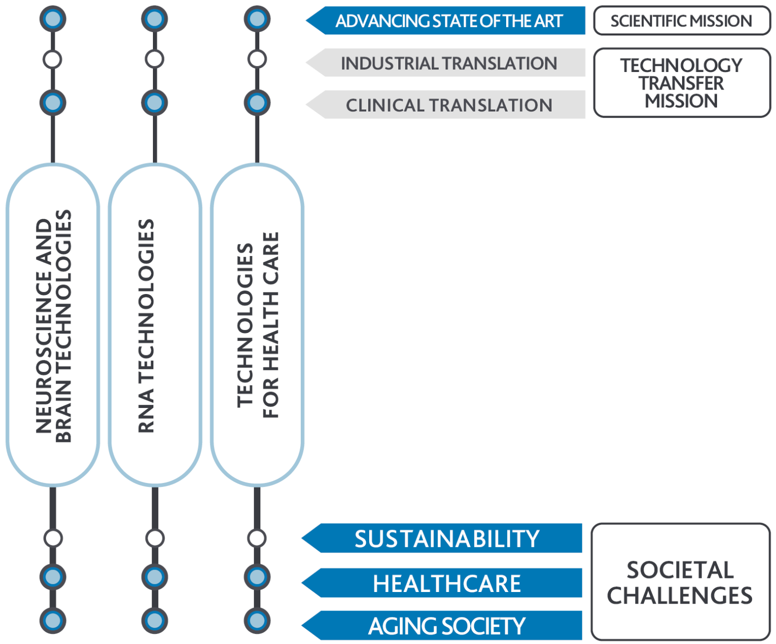


Figure 17: Priorities of the Technologies for Life Science (LifeTech) RD, contribution to IIT's mission, and impact on the challenges.

The Technologies for Healthcare Priority is a unique outcome of IIT's multidisciplinary know-how. It involves a completely new approach based on co-designing, adapting, and testing different IIT technology platforms for healthcare applications. This effort will benefit from a collaboration between life scientists, physicians, and "hard science" technologists. It will be based upon a national agreement with the Ministry of Health and with the Regione Liguria to establish different Joint Labs with research hospitals and clinical research institutions where IIT technologies can be optimized and tested around the patients. The vast list of potential translational technologies exceeds the restricted domain of biomolecular technologies: platforms include genomics and high-performance computing for precision medicine, smart nanomaterials for controlled drug release, prostheses (e.g. mechatronic hands and artificial retina), robots for physical and neurological rehabilitation, and sensing technologies for blind people.

The Priorities of LifeTech synergistically connect neuroscience with cognitive science research in Priorities 3 and 4 of the Robotics RD (Social Cognition and Human Robotics Interaction and Biomedical Robotics), Priority 2 of the Nanomaterials RD (Nanotechnologies for Human Health), and all the programs in the Computational Sciences RD. Special effort will be devoted to promoting and implementing interdisciplinary projects and serendipitous technological innovation.

The success of this integrated vision depends on balancing top-down and bottom-up approaches. To achieve this, we will foster new opportunities for multidisciplinary collaborations among hard and life scientists supporting the creativity of IIT researchers in pursuing high-risk, high-gain interdisciplinary projects.

Scientific Mission

Worldwide, there is a growing understanding of healthy and diseased brain function. This progress stems from the development of advanced genetic, molecular, electrophysiological, computational, imaging, and perturbation tools for dissecting the microscopic neural processes underlying brain function and behavior in experimental animal models.

However, there is a major hurdle in translating this knowledge to the human brain. Evidence on brain function and dysfunction in humans is primarily collected via noninvasive macroscopic mass measures of neural activity. As a result, we are currently unable to take findings of physiological and aberrant macroscale neural activity and translate them into interpretable neurophysiological events or rather into models that can help us understand how the brain works in health and disease. This limits the development of new diagnostic tools and the identification of new targets to treat neurodevelopmental diseases (NDVDs) and neurodegenerative diseases (NDGDs). This explanatory gap drastically limits the return on investment of the world's various human-brain-mapping initiatives.

The Priority on Neuroscience and Brain Technologies aims to reduce this explanatory gap between the detailed neural circuits studied in animal models and their translation to human brain function and dysfunction. To this end, IIT is developing tools to integrate brain investigations on multiple scales (from microscopic to macroscopic).

This includes: i) tools to record microscopic and macroscopic signals, and to optically, electrically, and molecularly manipulate the activity of neural circuits; ii) built-up neurointerfaces for unidirectional and bidirectional communication with neurons; iii) computational methods to integrate studies of different scales, to study the brain's functional organization, to identify the causes of disease, and to make predictions about potential cures; iv) genetic and molecular technologies to exploit the non-coding portion of the genome, and v) interdisciplinary combinations of these techniques.

Concerning the Priority on RNA Technologies, IIT will study ncRNAs and repetitive elements in brain transcriptomes and genomes. Large genomic projects (e.g. the ENCODE and FANTOM Consortia) have greatly increased our knowledge of the molecular constituents of cells. In contrast to the classical view of how gene expression is regulated, the results of these projects have highlighted the central role of noncoding DNA.

The pervasive transcription of the mammalian genome gives rise to a large repertory of ncRNAs, both long and small, whose expression is closely regulated in space and time. There is an ongoing research effort to understand the "grammar" of the structure-function relationship of long ncRNAs (lncRNAs), and how their activities affect neuronal development, plasticity, and behavior, as well as NDVDs and NDGDs. Importantly, genetic analysis in the coding portion of the genome provides a molecular explanation of diseases in only a small fraction of patients. This has led to the concept of hidden hereditability and to the observation of the existence of undetected, disease-causing de novo mutations. A relevant fraction of these is likely due to rare germinal or somatic genomic structural variants of repetitive elements. These may also provide a previously unnoticed source of regulatory regions, with a still-unknown role in brain physiology and dysfunction. The study of the RNA regulatory mechanisms that control gene expression at the transcriptional, posttranscriptional, or epigenetic level, is also extremely relevant to cancer research. In this sense, our focus on RNA connects with the Horizon Europe's Mission on Cancer.

Technology Transfer Mission

The Priority on Technologies for Healthcare (see Figure 17) is expected to substantially impact the transfer of IIT technologies to healthcare. To this end, IIT has set up a comprehensive infrastructure dedicated to Human Technologies (the Center for Human Technologies – CHT). The goal is to assemble a collaborative network of Joint Labs and research/university hospitals. In the start-up phase, CHT has been the driver of the Liguria Hub for Healthcare. Supported by the Regional Government of Liguria, this regional network involves some of the nation's top research hospitals and clinical research institutions, including the IRCCS San Martino-IST, the IRCCS G. Gaslini Children's Hospital, the Galliera Hospital, the Istituto Chiossone for blind people in Genoa, and the Santa Corona Hospital in Pietra Ligure (see Table 2, pag. 79).

CHT has three goals: (i) create Joint Labs within hospitals to allow close collaborations between IIT scientists, physicians, and other healthcare professionals; (ii) use these collaborations to transfer existing innovative technologies and to co-design future technologies; and (iii) build a network of pediatric neuropsychiatry and neurology hospital departments to harvest biological tissues and record medical data. IIT scientists at CHT will then analyze these tissues and data using genomic sequencing, database construction, and data science.

With the completion of the start-up phase in 2020, the initiative will now be expanded nationally with a framework agreement with the Istituto Superiore di Sanità and the Ministry of Health (IRCSS), involving some of Italy's most important clinical research institutions. Other seed initiatives have been launched to engage strategical partners in the clinical oncology network, such as IEO, ACC, and the 5000-genome project, with the aim of fostering further implementation of large and possibly nationwide genomic infrastructures for molecular diagnostics and therapies.

Healthcare Challenge: Neuroscience

Neuroscience for healthcare will capitalize on IIT's know-how on the fundamental mechanisms of healthy/pathological brain development, brain function and aging, and their impact on healthcare.

IIT seeks to address different categories of diseases including NDVDs and NDGDs, stress-related disorders, personality disorders, compulsive/obsessive behaviors, brain cancer, blindness, sensorimotor impairment, and physical impairment due to aging.

These diseases and impairments carry staggering social and economic costs. For example, within the EU, the incidence of autism spectrum disorders (ASD), a subtype of NDVDs, is expected to increase to over 100 per 10,000 children because of wider monitoring and testing methods, with individual lifetime costs exceeding €3M per patient. Similarly, NDGDs pose a great challenge to tomorrow's healthcare systems. According to the WHO, the number of patients with NDGDs will increase from 35 million to 100 million by 2050, with a total annual cost (direct plus indirect) tripling the present European expenditure of €177Bn.

The lack of effective therapeutics is due to a number of factors including: a coarse understanding of the mechanisms at the basis of brain pathologies, a lack of knowledge about the contribution of somatic mutations of the noncoding portion of the genome, the paucity of reliable animal models with predictive validity in humans, the lack of new chemical compounds, the lack of sustainable gene therapies that can easily and efficiently reach the brain, and insufficient information about stratifying patients for personalized medicine.

In line with IIT's mission, the ambition of our neuroscience program is to achieve a consistent impact on healthcare. In particular, the aim is to provide: i) animal models and behavioral tests with increased translational value for human brain diseases, ii) pharmacological and gene/RNA-therapy treatments, as well as efficient delivery systems for brain diseases. This will also take advantage of the knowledge accumulated on RNA biology and technologies within the RNA Initiative; iii) tools for genetic and epigenetic analyses in patients and new biomarkers to stratify them for personalized medicine; iv) neuroprosthetics for NDGDs based on hybrid organic devices; v) pipelines to advance therapeutic treatments designed at IIT from bench to bedside; vi) robotic technologies to assist the diagnosis and treatment of NDVDs; vii) clinical machine learning (ML) and neurocomputational tools for healthcare; viii) fundamental biological knowledge and new fields of research supporting the specific needs of patients and their families, reducing the stigma of mental health; ix) in the post-Covid pandemic period, knowledge on the short- and long-term consequences of stress and social isolation for brain function, development, and aging.

This program will also benefit from the 5000-genome project in Valle d'Aosta, where cohorts of patients with NDVDs and NDGDs will be studied at the CMP3vda, an IIT genomic center for personalized, predictive, and preventive medicine in Aosta. Clinical and genomic data will be stored in a searchable database of electronic medical records, and a biobank will provide tissues of interest from the same individuals, representing an opportunity to directly translate IIT technologies (i.e. theranostic devices, gene therapy/RNA drugs, assistive robotics) to patients for the precision medicine of brain diseases.

To accomplish these goals, IIT will:

1. Improve communication and collaboration between neuroscientists across the basic-to-cognitive spectrum and researchers in the other RDs.
2. Focus recruitment by targeting emerging areas at the interface between RDs. In particular, coordinated recruitment with the Ellis initiative and in the area of neuroengineering.
3. Strengthen collaborations with medical doctors, clinical researchers, and hospitals in Italy and abroad by leveraging IIT's Clinical Network.
4. Establish formal collaborations with contract research organizations (CROs) to design and realize advanced preclinical and clinical studies.
5. Establish formal collaborations with patient associations.

Importantly, this coordinated effort will also increase the visibility of IIT's brain science research within the scientific community and society in general.

Healthcare Challenge: Transforming diagnosis and therapy with a new generation of theranostics based on RNAs and repetitive elements

By gathering large sets of genomic information, researchers will soon be able to define the enormous heterogeneity of human diseases. Ultimately, a single patient may present with her/his personal molecular version of a given disease. If the financial costs are very high and there is no comprehensive repertory of drugs tailored to specific genomic mutations, the challenges for healthcare delivery will be enormous. In this context, the classical approach to biomarkers and drug discovery may not be successful for precision medicine in the long term. Classical drug discovery interprets the genome as encoding for proteins, which are the building blocks of organisms.

The complexity of the proteome gives rise to cells and tissues with different shapes and functions. Drugs must therefore modify protein activity, inhibiting or activating specific signaling pathways. Despite many successes, this approach has led to massive costs and drugs with poor specificity that do not adequately address major complex diseases. Importantly, this approach has been unable to address many rare diseases, where a small number of patients present highly heterogeneous molecular profiles. Furthermore, many proteins are difficult to target, limiting the availability of therapeutics.

ncRNAs present countless new opportunities to pharmacologically modify gene expression at the right time, in the right place, in vivo. With high specificity, RNA-based drugs expand the druggable genome, so it includes the protein coding and noncoding genes, and the regulatory regions. Using common delivery systems to target specific organs, it may be possible to scale nucleic-acid-based therapy at a fairly low cost and with relatively common pharmacodynamics and pharmacokinetics properties. Importantly, drugs can be tailored to a single patient's genome, offering cost-effective personalized medicine to treat highly heterogeneous diseases. In this context, RNA sensing in vivo may be the future of molecular diagnostics. It will require new highly sensitive and reproducible technologies.

The unexplored portion of the genome, containing repetitive elements, offers an innovative framework for understanding the molecular basis of the hidden hereditability of complex diseases. It can be used to elucidate the phenotypic effects of the structural variants of hereditary or somatic genomes. Here, we aim to establish nucleic acids as a driving force for the precision medicine theranostics of NDVDs and NDGDs.

The 5000-genome project in Valle d'Aosta will also be important for this program, allowing the collection of genomic data specific to NDVDs and NDGDs.

Priorities of the Technologies for Life Science Research Domain

The LifeTech RD seeks to develop new technologies and knowledge to understand how the brain functions and unravel the genomic complexity of brain diseases and cancer. It also seeks to impact the diagnosis, care, and therapy of patients by introducing technological innovations in hospitals and points of care. Transforming life science knowledge into applied clinical technology requires close collaboration and co-design work with medical doctors and patient-facing healthcare professionals. IIT will pursue this objective by partnering with research hospitals and research hospital networks to transfer knowledge and technologies, and to identify crucial problems that require technological solutions.

The scientific strategy will be implemented in three integrated Priorities: Neuroscience and Brain Technologies, RNA Technologies, and Technologies for Healthcare. Most LifeTech research and technology will be developed in the new Center for Human Technology within the Erzelli building. Some neuroscience and neurotechnology activity will continue at the Morego building and the Center for Synaptic Neurosciences, located in the IRCCS San Martino-IST (Genoa). Strong support for the LifeTech RD will come from IIT's network of laboratories, including CNCS-Trento, CTNSC-Ferrara, CGS-Milan, CBN-Lecce, and CLNS-Rome.

In the coming years, the LifeTech RD should grow by about 10% (currently more than 340 staff members, including 30 PIs and 39 technicians), with the inclusion of new PIs in the fields of single-cell transcriptomics, RNA structures, and aptamers for delivery.

Priority 1: Neuroscience and Brain Technologies Program

IIT will develop new techniques and gather crucial data to identify the key genomic, molecular, cellular, and circuital mechanisms that contribute to central nervous system function and dysfunction. The challenge is to develop novel tools to integrate brain investigations at multiple scales, from microscopic to macroscopic, in health and disease. The goal is to bridge the explanatory gap between the detailed mechanistic studies in animal models and their translation to the human brain. IIT seeks to understand how higher functions of the brain (e.g. sensory perception, motor coordination, attention) arise from the coordinated activity of large-scale cellular networks (from hundreds to millions of neurons). To this end, we will study the basic functions of the nervous system, model these functions with computational methods, and develop new technologies to record and manipulate brain activity at different levels of organization. The objectives are:

1. Integrate genomics data to rigorously test hypotheses about the molecular basis of neural networks, and how they are controlled by epigenetic mechanisms and neural genome heterogeneity.
2. Elucidate the structural and functional organization of synapses.
3. Understand how higher brain functions arise from the coordinated activity of large populations of neurons.
4. Provide experimental data, recording techniques, and computational methods for large-scale neuronal recording and manipulation with high spatiotemporal resolution.
5. Complement the Computation and Data Science effort by providing cutting-edge computational methods to advance the discipline of systems neuroscience.
6. Translate knowledge from animal model systems to the human brain.

This priority will be implemented according to three distinct but intertwined actions: Multiscale Neuroscience, Brain Diseases, and Neurotechnologies.

Multiscale Neuroscience

Multiscale neuroscience involves studying several key determinants of brain functions with a variety of state-of-the-art techniques available at IIT (i.e. optical, electrical, chemical). The Multiscale Neuroscience program also involves analyzing nucleic acids and linking gene expression to the development of cells, synapses, neural networks, and their responses to neuromodulators. Figure 18 summarizes the activities of the Multiscale Neuroscience action.

Our starting considerations are: i) that the extracellular space of a given developing brain cell also contains other developing cells (cellular environment), and ii) that these cells influence one another through different extracellular factors. With this in mind, we will study the local cellular environment during neural development. The goal is to find the rules of brain circuit formation and wiring that are common to all brain areas, while trying to understand the peculiarities of the different brain areas.

As part of the collaboration with EMBL-EBI in Cambridge and RIKEN in Japan, we will study, at the single-cell level and in vivo, gene expression, genomic structural variants, and chromatin organization. This activity is developed jointly with the "Plasmonic Ultra-High-Sensitivity Biosensors" (Priority 2, Nanomaterials RD), which aims to build a plasmonic-based readout for a nanopore sequencing platform for tissue transcriptomics.

The extreme variety of neuron types will be studied by analyzing a specific type of repetitive element of the human genome, LINE-1 or L1. Interestingly, L1 is the sole autonomous retrotransposon active in the human genome. We will focus on the expression and mobilization of L1 during early embryonic development in order to evaluate its significance in, for example, NDVDs and NDGDs.

One genetic investigation will look at the regulation of sleep and the circadian clock. We will investigate how sleep impacts the central nervous and metabolic systems through genomic imprinting, a novel epigenetic mechanism. At IIT, we delivered the first evidence that specific imprinted genes are important players in sleep regulation. We will focus on two distinct questions: how epigenetic inheritance impacts brain responses to sleep loss, and how evolutionary changes influenced the interplay between sleep and metabolism in disease.

At another level of analysis, we will study the plasticity of synapses, starting from the observation that "regulated" Brownian diffusion of proteins at the nano- and microscale shapes the signaling properties of individual synapses and allows short-range communication between synapses. It is possible to measure the dynamics of dendritic microdomains in brain circuits. We will also develop the technology to study protein diffusion in brain tissue.
Still at the synaptic level, it is known that brain circuits are modulated by specific neuromodulators carrying information about perceptual cues or the motivational state of the individual. There is currently little knowledge about this mechanism, which is highly relevant to behavior. Therefore, we will investigate the spatiotemporal dynamics of neuromodulatory signals at cellular and system-level resolutions.

IIT's research groups have mastered a variety of recording technologies that allow the simultaneous recording of large-scale single-cell populations and mass signals from different brain areas. We will use ML and information theory tools to extract sensory and decision-related information. Similarly, we will use computational techniques to address the problem of understanding the neural code. Little is known about how the brain encodes information about external stimuli in the spatial and temporal sensory-evoked activities. The objective is to understand the computational principles of brain networks during perceptual decisions. To this end, we will develop and use advanced optical systems for large-scale neuronal recording and manipulation with high spatiotemporal resolution (hundreds to thousands of cells at cellular resolution).

Still at the network level, we will combine brain-wide functional neuroimaging with cell-type-specific neural perturbations in physiologically accessible species. We will thus elucidate the

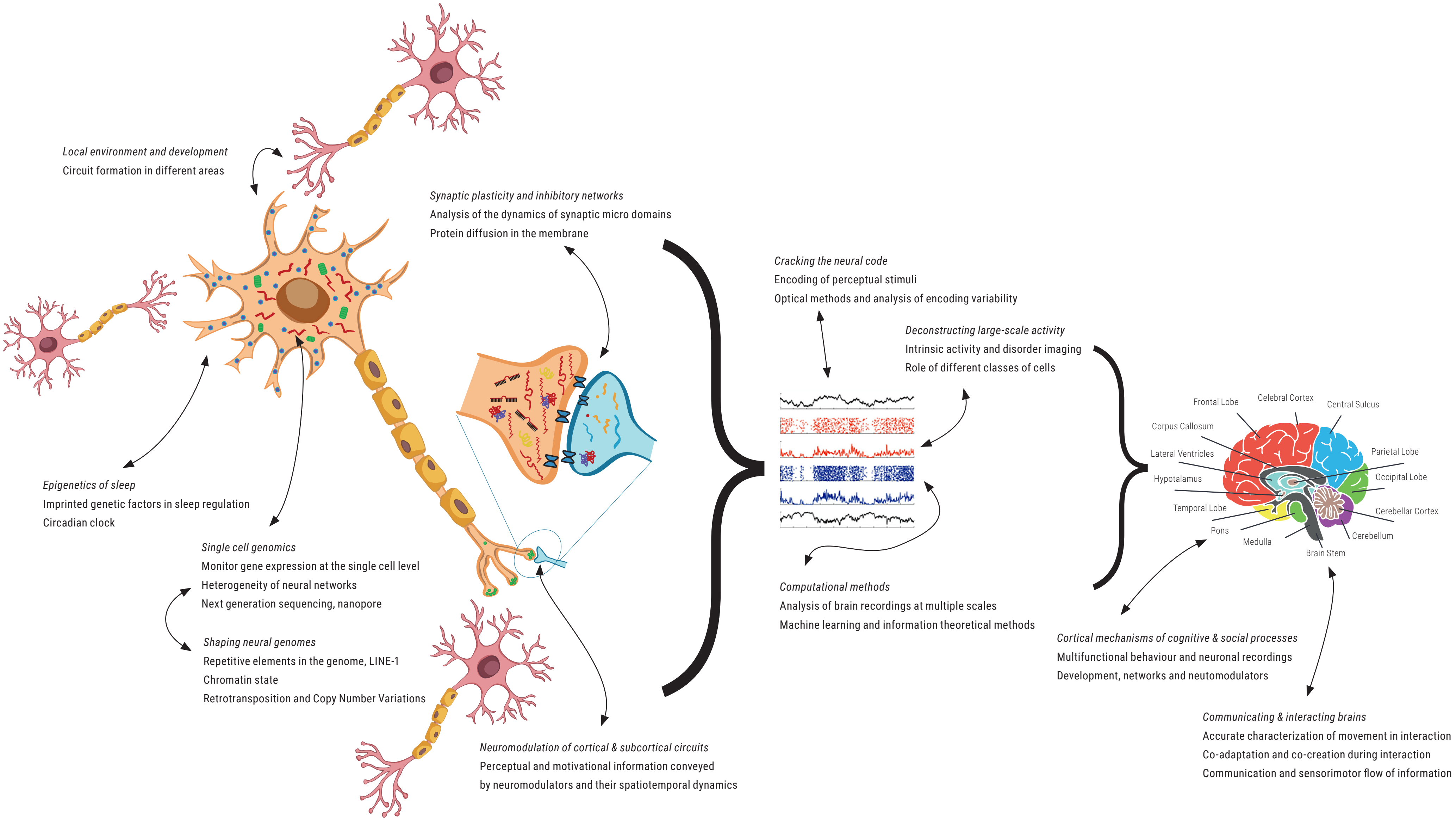


Figure 18: Research directions of the Neuroscience and Brain Technologies Priority.

drivers of macroscale coupling, such as the role of different classes of inhibitory or excitatory cells. These investigations will offer the opportunity to back-translate widely used systems-level measurements of brain function and connectivity into interpretable physiological events.

Perturbations will be coupled to predictive computational models in order to evaluate and test different hypotheses about each individual factor's role in the larger-scale brain signal dynamics. At the behavioral level, we will focus on aspects especially related to the control of behavior in the social context and in social interaction. We aim to investigate the genetics, circuits, and cell-type specific mechanisms underlying corticodependent cognitive and social processes, in particular, by integrating multifunctional behavioral and neuronal outputs (in vivo).

We will look at how these processes are shaped during development in distinct neural circuits and neuromodulators. We will also study social interaction in multiagent coordination scenarios. We will base our research upon the accurate characterization of movements to quantify how motor performance is dynamically co-adapted and co-created between agents. Our focus on behavior will provide the strongest possible baseline for quantifying sensorimotor information flow between agents and to reveal the multibrain signature of successful cooperation.

Brain Diseases

In line with the neuroscience contribution to the Healthcare Societal Challenge, IIT's focus is NDVDs.

We will investigate the abnormal epigenetic modifications during neurodevelopment and their consequences in diseases. The investigation of basic mechanisms of brain development has tremendous conceptual consequences for the treatment of NDVDs. The study of the local cellular environment can identify specific therapeutic windows for addressing aberrant neuronal development with drastically reduced side effects. In particular, early pharmacological interventions by new and more selective chemical compounds, mechanism-based personalized strategies, and RNA interference or CRISPR-Cas9 gene-editing technology coupled to viral-vector-mediated in vivo delivery will be assessed for their efficacy in treating core behaviors in animal models of NDVDs.

Several risk genes associated with ASD and epilepsy have been shown to code for proteins involved in synaptic transmission. We will therefore investigate the impact of aberrant excitatory and inhibitory synaptic function on network activity. By exploiting cutting-edge biomolecular tools, we will attempt to rescue the autistic and epileptic phenotypes in specific mouse models. Since neuromodulators directly affect brain computation at the micro- and macrocircuits, we will investigate dysfunctional synaptic and circuit neuromodulation as causative mechanisms of comorbidities in psychomotor and affective disorders.

Alterations in cognitive control and social abilities are shared features of different NDVDs characterized by a strong genetic component (e.g. schizophrenia and ASD). Using a cross-disciplinary approach, including detailed in vivo studies in genetically modified mice and clinical investigations, we will investigate the mechanisms underlying cognitive and social deficits related to the L1 repetitive elements of the genome. We will disentangle the highly variable responses to pharmacological treatments in order to develop more effective and biologically supported personalized therapeutic approaches focusing on cognitive and social deficits.

We will develop theranostic tools based on the measurement of neurobehavioral specific reactions evoked in psychiatrists, caregivers, and relatives by the interaction with psychiatric patients.

The neurotypical people are therefore considered as diagnostic probes because of their mirroring of the disease. ML approaches will be used to automatically extract the pattern of neurobehavioral convergence/divergence to guide both diagnosis and therapeutic decisions.

Neurotechnologies

We plan to develop new materials and technologies for brain interfaces to obtain an accurate dynamic picture of the brain in action. The following specific technologies will be developed:

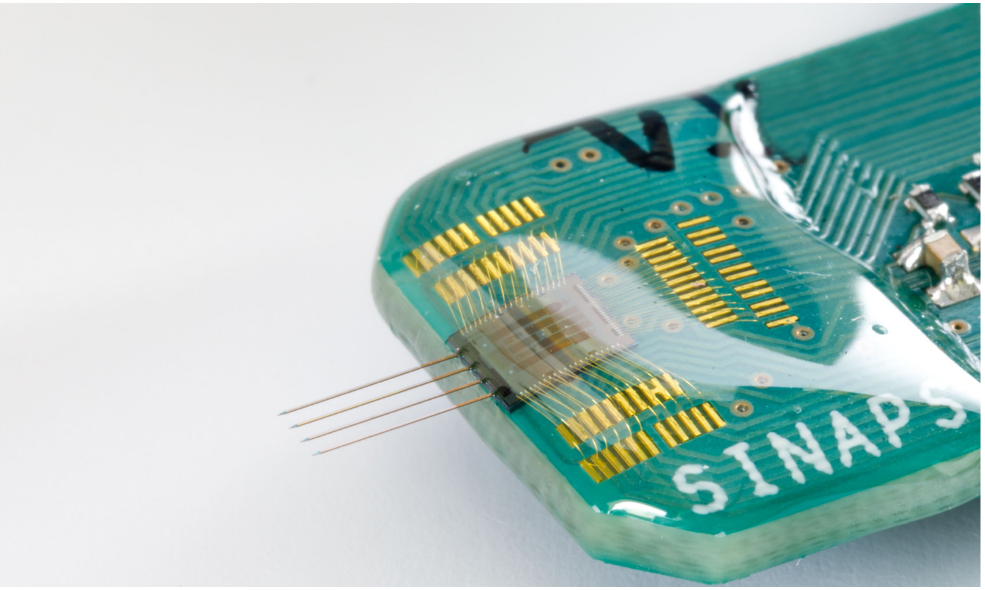
1. Multifunctional neural interfaces. We will develop integrated implantable probes including optical, thermal, and chemical techniques. Probes will be designed to access deep brain regions, including subcortical structures (e.g. thalamus, basal ganglia, hippocampus), which the current technologies cannot directly access at high resolution. We will use tapered and nanostructured optical fibers to correlate electrical and chemical signaling in the brain.

2. Neuroelectronics for multiscale brain interfaces. We will integrate research on micro-/nanostructured bioelectronic interfaces, active dense (CMOS) electrode array neurotechnologies, and neuroengineering of bioartificial hybrid systems. We will study standalone, integrated bidirectional systems with embedded wireless data transmission and power solutions.

3. Blood brain barrier (BBB). The central nervous system poses special challenges for therapeutic intervention. This is because it is isolated from the circulatory system by the BBB. An ideal route for drug delivery is to hijack BBB-crossing mechanisms. Using molecular biology and molecular dynamics simulation techniques, we will engineer peptides that induce transient permeabilization of the paracellular spaces and that may be fused to light-sensitive modules to perform a transient n-demand permeabilization of the BBB.

4. Hybrid synapses and neural interfaces. The similarity between artificial and biological neural networks has inspired the implementation of hybrid neurointerfaces for prosthetics and brain-machine interfaces. We aim to directly couple electronics and living neurons to create hybrid synapses and hybrid neuronal network. Biohybrid synapses will be created by interfacing live neurons with organic neuromorphic and/or memristive devices to mimic neurotransmitter-mediated synaptic plasticity on the artificial postsynaptic side.

5. Nanosparks, photoactive interfaces. We will develop subcellular-sized nanoparticles comprising conjugated polymers that accumulate in contact with the neuronal membrane and promote light-induced capacitive depolarization (see also: Organic retina prosthetics). The goal is to develop injectable photoactive interfaces with the brain. Preliminary tests of these technologies are in progress in animal models of neurodegeneration.



Priority 2: RNA Technologies Program

Manipulating RNA expression in vivo is a new strategy for molecular therapy. It requires a class of therapeutic drugs that promote downregulation of gene expression in dominant diseases, which are caused by the expression of a pathological target gene. Therapeutic molecules have been developed based on small antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and miRNAs. A second, equally challenging class of drugs should be based on RNA molecules that increase gene expression in vivo.

A homeostatic cellular environment may be reestablished by augmented levels and/or the activity of modifiers of pathogenic pathways. Hijacking the neuroprotective function of neurotrophins may be an attractive strategy to preserve cell viability and function in the diseased brain. Most importantly, for patients with haplo-insufficiencies, using RNA drugs to rescue physiological amounts of the target protein would, in principle, be curative.

In this Priority, we will particularly foster interdisciplinary collaborations. Contributions from the "Advanced Multiscale Modeling of Biomolecules" Priority of the Computational Sciences RD will provide the mathematical and computational knowledge to dynamically simulate and predict RNA secondary structures. Contribution from imaging research lines such as "Molecular Microscopy and Spectroscopy" and "Nanoscopy & NIC@IIT" will provide new optical and analytical tools to investigate RNA-based biomolecules in living cells. For RNA delivery and sensing, projects will be carried out together with research lines such as "Combinatorial Nanoconstructs for Imaging and Drug Delivery", "Organic Nanoparticles for Hyperthermia and Drug Delivery", and "Plasmonic Ultra-High-Sensitivity Biosensors", all included in the relevant Priority of the Nanomaterials RD.

RNA Biology

lncRNA structure and function. lncRNA function was initially considered in terms of the ability of their primary sequences to pair in trans with other nucleic acid sequences. However, lncRNAs have also been proposed to work as modular scaffolds that recruit and coordinate different effectors via discrete RNA domains with specific secondary structures.

Researchers are now seeking to identify which crucial RNA structures within lncRNAs and their specific RNA-binding proteins (RBPs) can mediate their activity. This knowledge is important for the design of RNA therapeutics, which combine domains with selective biological activities and antisense sequences for specific mRNA and DNA targets. RNA drug design is currently restricted by our inability to accurately predict secondary RNA structures based on primary sequence.

IIT aims to develop new algorithms to predict RNA secondary structures. One focus will be the role of embedded repetitive elements acting as functional domains in lncRNAs. These results will be considered in the context of their protein partners, according to ENCODE data, and for their specificity in the brain.

This line will strongly benefit from new HPC infrastructure, from collaborations with the Computational Sciences RD and from the proteomics and sequencing facilities at D3 and CHT.

Small and long ncRNAs as regulators of 3D genome architecture. Recent data suggest that ncRNAs play a central role in regulating the epigenome and chromatin. By studying how these RNAs interact with and modulate chromatin, it may be possible to develop a new class of drugs that can modify the epigenetic marks of selective genomic loci. IIT will therefore recruit expertise in long and small nuclear ncRNAs as regulators of the brain epigenome. This approach will be complemented by a computational biology research line to understand the 3D architecture of chromatin organization in vivo.

Long ncRNAs as regulators of translation. Gene therapy of neuropathogenic haplo-insufficiencies is a formidable task and most NDVDs linked to whole-gene hemideletions remain incurable. One strategy may be to develop gene-specific ncRNA activators of transcription and/or translation. A new functional class of antisense lncRNAs (SINEUPs) was recently shown to increase translation of their sense mRNA target. IIT thus plans to optimize synthetic lncRNAs to restore physiological protein levels for each haplo-insufficient gene in NDVD patients. We will use multi-well CMOS programs from human-derived cellular systems for RNA sequence optimization.

ncRNA-dependent control of Neural Stem Cell fate. Neural stem cells (NSCs) generate all neurons and glia of the mammalian brain. The potential roles of NSCs in brain development, lifelong neurogenesis, and cancer emphasizes the need to expand our basic knowledge of their biology and fate regulation. The PIWI-interacting RNAs (PIWI pathway) are essential for proper neurogenesis in the postnatal brain and are associated with age-related disorders such as NDGDs and cancer. We aim to dissect the mechanism and targets of the PIWI-pathway-dependent control of NSC fate. This knowledge will be essential to designing novel RNA therapeutics (e.g. RNA vaccines) or novel diagnostics (liquid biopsies).

ncRNAs in development and pathology. By playing a role in epigenetic and transcriptional dynamics and by acting as branching points with wide-ranging effects, ncRNAs appear to be key targets in adaptation mechanisms and transcriptional reprogramming. Their identification would be a milestone in the understanding of the genomic mechanisms underlying human development and pathologies. To study ncRNAs and their pathways, we are using state-of-the-art genomic technologies (single-cell, single-molecule, spatially resolved omics) to obtain high-resolution analysis of the transcriptome and to highlight different ncRNAs (lncRNAs, miRNAs, eRNAs). We also combine genetic perturbation by CRISPR-technology (CRISPR-KO, CRISPRi/a) with single-cell omic resolution for the high-throughput functional dissection of ncRNA genes, regulatory elements, and RNA motifs, thus identifying the key molecules and their regulatory mechanisms.

RNA Sensing

The complexity of the RNA world has increased massively, which raises questions about the classical approach to studying RNA expression. This classical approach mainly uses gene-specific probes to detect a small number of RNAs in fixed tissues. By freezing them in time and space, it fails to capture the diversity and functional importance of RNA dynamics. Recently, new CRISPR-Cas9-based approaches have targeted native gene expression in vivo. Importantly, new image analysis approaches are increasing the number of RNA species that can be simultaneously detected from a single cell. This potentially creates new ways to study transcriptome-wide gene expression in vivo. Both fields are in their infancy and offer great opportunities to develop groundbreaking techniques for imaging gene expression. With leading molecular biologists and physicist experts in imaging technologies, IIT is ideally placed to exploit these opportunities.

RNA Imaging. IIT plans to develop sensitive probes for the imaging of multiple ncRNAs to follow their dynamics in vivo. IIT will also develop new technologies for the transcriptome-wide image-based analysis of gene expression (see: Clinical Genomics at the Center for Human Technologies). In this context, it is also highly desirable to visualize the chromatin directly in the nuclear space at high spatial resolutions. IIT plans to use new super-resolution methods and a new image analysis framework to quantify the dynamic properties of chromatin-DNA-RNA interactions at the nanoscale (e.g. chromatin compaction). These approaches are core elements of the Liquid Tunable Microscope and they will be carried out in collaboration with the Nanoscopy lab and the Nikon Imaging Center at IIT.

RNA Detection. In the last few years, it has become clear that free and vesicle-contained RNAs are present in the extracellular environment. They may be potential biomarkers and/or effectors of diseases, including those of the nervous system. In general, RNA expression can be used as a biomarker for disease status and/or pharmacological response. It is therefore important to develop new technologies for RNA detection in vivo. It may be possible to exploit molecular interactions at nanoscale levels to produce new classes of highly sensitive RNA nanodetectors.

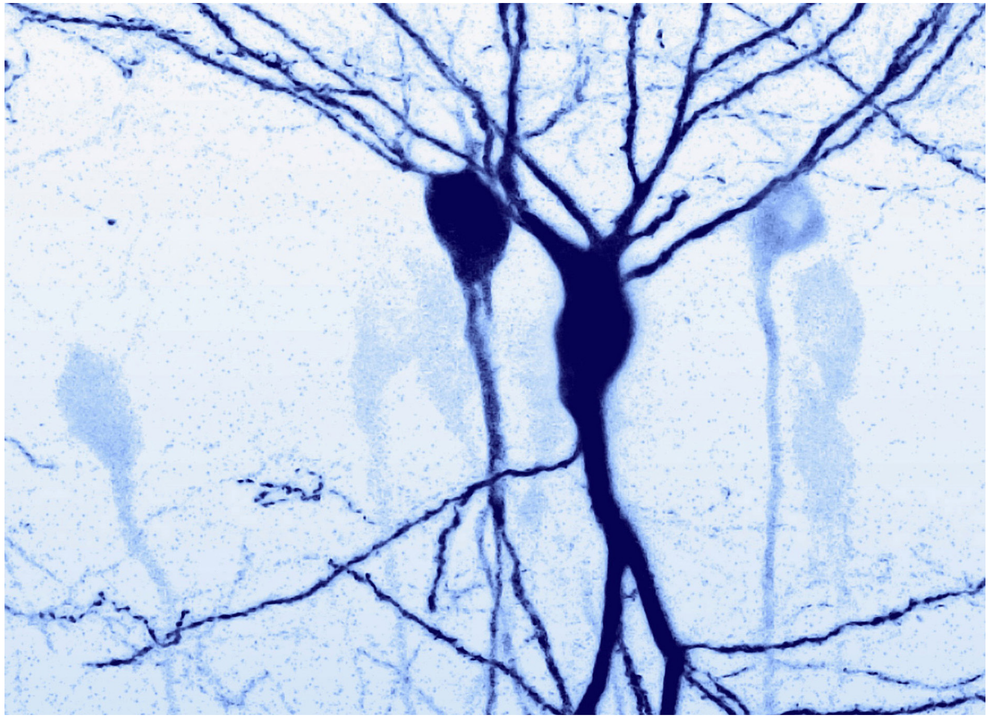
In this context, we will focus on RNA species that are important for the diagnosis and therapy of NDVDs and NDGDs.

RNA Delivery

Delivery is the key factor limiting the broad application of RNA therapeutics. Its importance can be seen in the market value of companies with proprietary technologies for innovative delivery, such as coupling RNAs to GalNac moieties, and chemical modifications of naked RNAs. In the Nanomaterials RD, IIT has world-class nanomedicine expertise in a broad spectrum of nanoparticles with different chemical and structural properties. In the coming years, IIT will use these tools to increase knowledge of the biology of nanoparticle-organism interactions, and to identify new biology-mimicking technologies for delivery to the brain.

Hijacking natural cell-to-cell communication. By hijacking nature's strategies, we may produce new biological insights and technological tools to efficiently deliver nucleic acid molecules to the appropriate target at the correct time. Exosomes are physiological carriers of genetic information around the body, including the brain. By understanding their biochemistry, we can produce exosomes to carry particular molecules, and modify them with membrane peptides to trigger vesicle homing. Furthermore, we can avoid endosome trapping by better understanding the biology of the interaction of nanoparticles and exosomes with the endocytic pathways of neurons and glial cells. Expertise in cell biology of endocytosis could therefore provide important clues about the constraints and intracellular signaling that favor or inhibit the delivery of the nucleic acid to the appropriate subcellular compartment.

Homing. The brain features a staggering complexity of neuronal cell types and connectivity, which currently prevents specific drug delivery to a given cell type and in the correct subcellular or synaptic location. This is critical because unspecific loading may lead to unsustainable side effects. Furthermore, in the absence of cell-specific accumulation, nucleic-acid-based drugs will never reach the concentrations needed to be effective in vivo. Different high-throughput scanning (HTS) strategies are available and under development to select homing molecules, including cell-specific antibodies, RNA aptamers, or peptides from phage display libraries. A new HTS program for one of these approaches may provide new tools and valuable IP to successfully deliver therapeutics for NDVDs and NDGDs to the brain.



Priority 3: Technologies for Healthcare Program

A key lesson in clinical translation is that technologies for healthcare should not only be designed for users, but also with users via a process of co-design and co-development. IIT will confront this challenge by bringing together and enhancing expertise in technologies for life science, robotics, nanomaterials, and computational science. Partnering this expertise with the expertise in clinical and medical research institutions is expected to be transformative in advancing clinical translation. The following section describes translational Initiatives inspired by basic research programs carried out in Neuroscience and Brain Technologies (LifeTech RD), as well as Initiatives arising from other RDs. We also envision the establishment of translational projects based around technological innovation developed by the RNA Technologies Priority. The common factor is that these Initiatives will be patient-centered. IIT does not have on-site facilities for patient-based research. However, it has access to clinical expertise via joint programs and joint labs with clinical and medical institutions. These working relationships foster knowledge sharing, which is crucial in accelerating the translation of innovative technologies into clinical practice.

Clinical Genomics at the Center for Human Technologies

IIT's genomic discovery science program has the potential to drive important improvements in human health. To realize these health benefits, a clinical genomic initiative will be launched at CHT. This initiative aims to identify the genomic basis of the stratification of patients with NDVDs and NDGDs. To recruit patients, collect physiological and behavioral data, and harvest patient tissue, we will partner with the IRCCS G. Gaslini Children's Hospital for NDVD patients and with San Martino-IST for NDGD patients. These collaborations will be extended to other clinical centers via the IRCSS network and the Istituto Superiore di Sanità. All the activities will rely on the sequencing facility at CHT and its close integration with the Computational Sciences RD.

The genome-sequencing effort will focus on identifying haplo-insufficiencies in the protein-coding portion of the genome and in analyzing ncRNA genes and repetitive elements. When available, sequencing will be carried out on post-mortem brain samples. IIT is currently partnering with the IRCCS Ospedale Bambin Gesù in Rome to analyze the noncoding RNA genes and repetitive elements of children with NDVDs, who were negative for mutations in the protein-coding portion of the genome. These represent 60-80% of the patients analyzed.

As part of the Strategic Plan, IIT will establish a new bioinformatics group and IT infrastructure, including a state-of-the-art high-performance computer and massive storage. This will handle and analyze the large dataset of whole genome sequences and transcriptomes.

The connections between gene expression, epigenetics, genomic data, and symptoms are enormously complex. This complexity requires new mathematical and computational approaches to ML and AI. We anticipate a strong synergistic effort with the Computational Sciences RD, in particular with the research activities in the Priorities of Advanced Multiscale Modeling of Biomolecules, HPC Algorithms for Extremely Large-scale Data Analytics, Machine Learning Theory and Algorithms, Deep Learning, Data Science, and Artificial Intelligence, and Computer Vision for Life Science. We will thus obtain information through genomic analysis, ML, and AI algorithms. Along with the activities on in silico models to predict regulatory, therapeutic, or diagnostic molecular strategies, we will pursue efforts to develop robust and reliable in vitro models (tissue on chip, organ on chip). This information will be translated into precision medicine tools and protocols that can be applied to many individuals in collaboration with the above-mentioned network of clinical research institutes and research hospitals.

Working with its clinical network, IIT will harmonize protocols and define standard operating procedures for clinical assessment, imaging, neurophysiology, and the collection and storage of biological samples. In parallel, we will reevaluate existing cohorts and relevant biological material to select samples for advanced genomic studies. IIT will promote the collection of post-mortem brain tissues for molecular analysis, which will be an important aspect of the project.

To achieve these objectives, IIT will develop techniques and bioinformatics pipelines for the complete, accurate, and cost-effective sequencing and whole-genome assembly of human and mouse genomes from post-mortem brains, peripheral blood, and single neurons.

This knowledge will stimulate basic research and help improve existing protocols before they enter the sequencing facility's pipeline. IIT's portfolio of established sequencing techniques will include genome sequencing (whole-genome and whole-exome sequencing), transcriptome sequencing (RNAseq, small-RNA sequencing), chromatin immunoprecipitation sequencing (ChIP-seq), gene-panel sequencing, and more specialized sequencing approaches such as CAGE libraries preparation and techniques to identify genomic structural variants. The program will use state-of-the-art technology, including an Illumina NOVAseq sequencer and a 10x Genomics platform. A particular focus will be somatic genomic variants in the noncoding regions, including repetitive elements and retrotransposons. In this context, we are currently establishing a collaboration with a world-leading company for next-generation sequencing devices.

Nanomaterials for multifunctional drug delivery

As shown in Combinatorial Nanoconstructs for Imaging and Drug Delivery, Organic Nanoparticles for Hyperthermia and Drug Delivery, Smart Scaffolds and Patches for Tissue Regeneration and Controlled Delivery of Molecules Priority of the Nanomaterials RD, a repertory of nanoparticles and soft materials is synthesized for the detection, imaging, and therapy of cancer, cardiovascular, and nervous system diseases.

Nanoconstructs can be hierarchically structured to amplify the accumulation of therapeutic and imaging agents within diseased tissues, and designed with improved loading capacity, stable encapsulation, and on-command release. This includes the use of hyperthermia which, upon exposure to alternating magnetic fields, can synergize with conventional chemotherapeutic molecules in cancer treatment. Collaborative programs with research hospitals aim to facilitate the clinical integration of these nanoconstructs for a more efficient diagnosis and treatment of cancer and cardiovascular diseases. Data and new knowledge generated within RNA Technologies (LifeTech RD) will further support this translational initiative to provide novel molecular tools for patient-specific therapies.

Rehabilitation technologies and prosthetics

IIT is investing considerably in research into high-performance prosthetic limbs and rehabilitation systems. The roadmap of the Joint Lab with INAIL is to expand the reach of these activities and fully realize their potential to alleviate the effects of stroke, paralysis, and physical injury in thousands of patients every year. Activities in the domain of assistive and rehabilitation robotics will develop several devices, such as:
A complete prosthetic upper-limb system, comprising a polyarticulated hand, active wrist, and elbow, and a sophisticated multielectrode myoelectric control system.

- A complete lower-limb system for transfemoral amputees comprising passive, semi-active, and active ankle and knee.
- A lower-limb exoskeleton for personal and clinical use by patients with spinal cord injuries or neurological impairments.
- A lightweight portable robotic device to rehabilitate the shoulder.
- An integrated robotic system for the early diagnosis and rehabilitation of sensory and fine motor dysfunction in neurological or orthopedic disease.

A significant benefit of this program is the strong technology-transfer capacity of the IIT-INAIL Joint Lab on Rehabilitation Technologies, ensuring the rapid transfer of innovative technologies from the laboratory to the patient. One challenge will be to develop real usability tests to determine whether and to what extent prosthetic devices are integrated into the planning and control of everyday activities. This work will also explore mid-to-long-term neural rehabilitation with robot-assisted therapy, integrating novel sensing strategies to understand how motor rehabilitation affects brain plasticity. Ultimately, this is expected to lead to the development of neuromodulation strategies for personalized neurorehabilitation technologies.

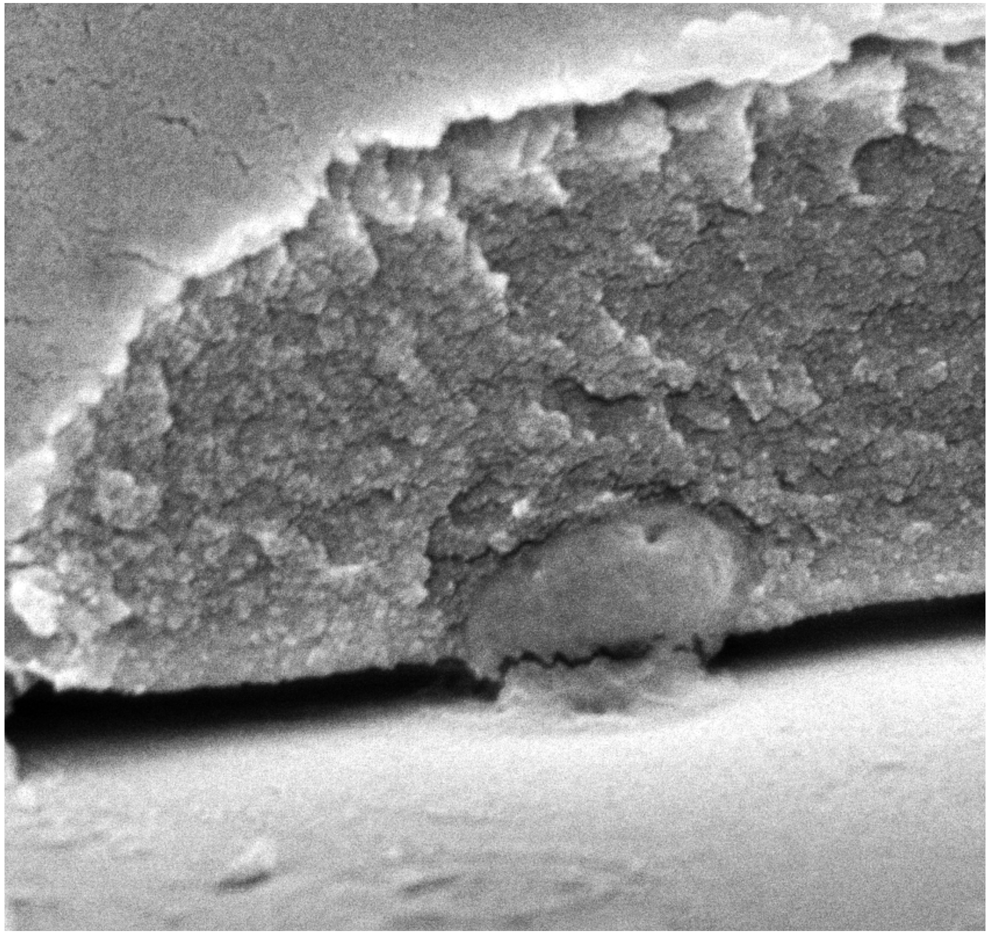
Organic retina prosthetics

In the last five years, IIT's Nanotech teams in Milan and IIT's Neuroscience team at IRCCS San Martino-IST in Genoa have developed a retinal prosthesis made of conjugated polymers that photoactivates neurons and rescues visual sensitivity in a rat model of retinitis pigmentosa.

This technology has quickly evolved from a proof-of-principle stage to a real prosthesis which has been implanted in rats and pigs to optimize the surgery procedures in view of its application to humans. We are currently studying an advanced version of the prosthesis, which exploits the conductive properties of graphene. New "liquid prostheses" made of nanoparticle suspensions or photoactive molecule are in preclinical studies. Currently, IIT is seeking to launch a start-up to conduct clinical trials in humans. The testing and future clinical trial can be extended to include the most recent nanoparticle approaches.

Theranostic robotics

In healthcare, robots have long been used to assist individuals in physically forceful tasks. Thanks to rapid progress in AI and cognitive robotics, there are new possibilities to assist individuals with cognitive and social dysfunctions. This line will develop innovative robotic technologies to assist the diagnosis and treatment of ASD and other NDVDs. The program will bring together cognitive neuroscientists, psychologists, computational scientists, and engineers in interdisciplinary research teams. A dedicated robotic team from IIT's iCub Facility will support the development of robotic-based sensorimotor intervention protocol.



Signature of neurodevelopmental disorders. IIT will use advanced computational methods to identify the motor signature of ASD and other NDVDs. Accumulating evidence indicates that early diagnosis with appropriate intervention is critical to optimizing outcomes for children with ASD. But it is complex and difficult to diagnose ASD in children before the age of five. Recently, motor abnormalities have been identified in young children who are later diagnosed with ASD. This presents a new target for early assessment.

IIT's goal will be to identify and quantify disorder-specific changes in movement patterns. Additionally, we will investigate motor cortex excitability by transcranial magnetic stimulation in children with ASD and controls at CTNSC. This will allow us to characterize the cortical local circuitry within the framework of a study of the role of recurrent and inhibitory circuits in ASD. These studies will be accompanied by clinical genomics studies and by studies investigating the functional connectivity of the autistic brain. The ultimate goal is to provide potential new computational markers for the early diagnosis of ASD and other NDVDs.

To support clinical translation, a related goal will be to develop an accessible tool to analyze body movements. Optical motion-tracking systems are expensive laboratory-based systems requiring specific technical knowledge and skills. In collaboration with the Electronic Development Laboratory, IIT will develop a portable, noninvasive, low-cost, and easy-to-use kinematic detector (KiD) to record young children's free motions outside of controlled lab settings.

Robotics-based intervention protocols. This research line will develop sensorimotor interventions for ASD based on human-robot interaction. Atypical movements in ASD are thought to disrupt perception of others' actions and to compromise interactions.

We will systematically vary the behavior of iCub in an interactive human-robot task to train children with ASD to move with more typical kinematics. Given the link between 'doing' and 'seeing', we expect this sensorimotor training will transfer to social functioning, improving the ability of children with ASD to perceive and predict the actions of others. As part of a well-established collaboration with the IRCCS G. Gaslini Children's Hospital in Genoa, an interdisciplinary team of cognitive neuroscientists, robotic engineers, clinicians, and therapists will define the intervention features (phase I), then test its clinical efficacy in children with ASD (phase II). If successful, testing will be extended to IRCSS's national network (phase III).

Robot-assisted training of social cognition mechanisms. In addition to identifying and addressing atypical movement patterns in NDVDs, the intervention program will also target cognitive mechanisms such as attention, executive functions, and visuospatial skills. We will design novel human-robot interaction protocols, which integrate a humanoid robot with protocols adapted from experimental psychology.

The interaction will be designed to train cognitive skills in human user at various stages of brain development. The mechanisms include, but are not limited to, attention (also joint attention), executive functions, visuospatial skills. With the use of such methods, we will monitor the development and improvement of cognitive and sociocognitive mechanisms, nonverbal communication, and learning in typically and atypically developing individuals.

Sensor technologies

Building on studies of multisensory development, we will identify and develop new technological sensory solutions to improve the ability of children and adults with sensory (e.g. visual deficits) and cognitive disabilities (e.g. dyslexia) to interact with the environment.

Research (behavioral and EEG) and technology design will be integrated to i) improve the motor, spatial, and social skills of visually impaired children and adults; ii) foster learning skills at school (e.g. mathematical and geometrical skills); and iii) improve sport accessibility for disabled people. A related aim will be iv) to design novel technologies that augment the human senses. For example, we could use augmented acoustic reality as a primer for spatial awareness in both able and disabled people. This research will involve an interdisciplinary team of cognitive neuroscientists, engineers, clinicians, and therapists. To develop user-centered technologies, we will collaborate with end users (e.g. the Joint Lab with Istituto Chiossone and IRCCS Mondino) and private companies. Wearable electronics will be developed in order to unobtrusively record and monitor physiological, health, and wellness parameters. Piezoelectric sensors will be integrated with other optical, MEMS, and electronic technologies in order monitor the body's physiological status. Collaborators include the European Space Agency, the Joint Lab with the Fondazione Don Gnocchi, the Policlinico di Bari Hospital, and Harvard Medical School.

Human behavior and brain stimulation

One emerging technology is the use of combined noninvasive brain stimulation and training to potentiate learning and accelerate recovery after brain damage and to sustain cognitive functions in healthy humans. We are developing this technology in collaboration with Villa Rosa Rehabilitation Hospital in Trento.

Our innovative visual, attentional, and motor rehabilitation techniques coupled with noninvasive brain stimulation have strong translational potential in clinical treatments, and have already been tested in stroke patients with excellent results. We will validate, extend, and elaborate the basic noninvasive brain stimulation procedures in healthy humans, in aging and in stroke, in order to test their efficacy on recovery of cognitive function and quality of life. We will also use imaging techniques such as EEG and fMRI to test what physiological features at baseline (using resting state functional connectivity) could be predictors of good responders to treatment (a precision medicine approach based on individual response).

Correlation measures between behavioral improvement and physiological changes will also help identify the optimal protocols to promote recovery in neurological patients and prevent decline in the elderly. Companies producing the brain stimulation devices (Starstim and Neuroconn) will provide engineering and technical support to develop new in-home (remotely controlled) treatments for stroke patients.

Robot-assisted microsurgery

Robots can assist microsurgeons by enhancing their levels of precision and dexterity, making the control of surgical tools easier and more intuitive, and improving access to and visualization of difficult-to-reach parts of the anatomy. In cooperation with IRCCS San Martino-IST, IIT is developing a pioneering approach to robot-assisted phono-microsurgery, with clinical trials already planned in Robot-Assisted Laser Microsurgery (RALP) and Micro-Robot-Assisted Laser MicroSurgery (mRALP).

One challenge will be to extend the model-based design of flexible tools for minimally invasive surgery to other surgical specialties, including endoscopic surgery and pediatric surgery (in collaboration with IRCCS G. Gaslini Children's Hospital). We will also develop simulators and exercises to train surgeons in operating microsurgery robots and performing successful micro-operations. Another focus will be the real-time detection of tissue type (Smart Narrow Band Imaging) and tissue probes.

IIT Platform	IRCCS Gaslini (Genoa)	IRCCS San Martino (Genoa)	IRCCS Bambino Gesù (Rome)	IRCCS San Raffaele (Milan)	RCCS Medea (Lecco)	IRCCS IEO (Milan)	IRCCS Mondino (Pavia)	IRCCS Don Gnocchi (Milan)	Istituto Ortopedico Rizzoli (Bologna)	Galliera (Genova)	Centro Protesi INAIL (Budrio)	Istituto Chiossone (Genoa)	Other Institutes (§)
Clinical Genomics	●	●	●		●	●				●			
Low-cost, disposable, ultra-sensitive diagnostics	●												
Nanomaterials for multifunction drug delivery	●	●		●						●			●
Medical Chemistry	●		●						●	●			●
Nanosparks and artificial retina		●										●	
Brain interfaces													●
Rehabilitation technologies and prosthetics	●	●					●	●		●	●		●
Theranostic robotics	●				●			●			●		●
Sensory technologies	●	●			●		●			●		●	●
Robot-assisted microsurgery	●	●											

Table 2: Overview of the translational initiatives contributing to Priority 3: Technologies for Healthcare (RD LifeTech). (§) Other Institutes including: IRCCS Stella Maris (Pisa), IRCCS SDN (Naples), ASL 2 SAVONESE, Ospedale Santa Corona (Pietra Ligure), Piccolo Cottolengo di Don Orione, Centro Riabilitativo Boggiano Pico (Genoa), Ospedale Valduce Villa Beretta (Costa Masnagna), Ospedale Riabilitativo Villa Rosa, Ospedale di Trento, Ospedale S.M. della Misericordia, Udine.

Initiative: The RNA Initiative

The RNA Initiative is a key action to position IIT at the forefront of the discovery and therapeutic exploitation of the latest advances in RNA biology. The expertise of the participants encompasses fundamental RNA biology, advanced imaging, computational science, neuroscience, drug design, and drug delivery. The Initiative is a sandpit for ideas and collaboration, a conduit to streamline drug development, and a springboard to establish far-reaching clinical and industrial collaborations. Stemming from the program outlined in IIT's 2018-2023 Strategic Plan, this integrated approach accompanies clinically targeted basic research to translation into pharmaceutically actionable technologies. We thus tackle the complexity of RNA fundamental biology, while tapping into a buoyant industrial landscape.

Why an RNA Initiative now and at IIT?

Our understanding of the functional output of the mammalian genome has enormously increased in the last two decades. This has profoundly changed our comprehension of how cell works and how evolution has shaped biological complexity. A growing body of knowledge points to RNAs as a major class of pharmaceutically actionable elements. In particular, our Initiative focuses on noncoding RNA transcripts, for which there has been the most rapid growth in knowledge. These include different classes, such as long noncoding RNAs (lncRNAs), small noncoding RNAs (sncRNAs), circular RNA (circRNAs), and transcripts derived from Transposable Elements (TEs), such as SINE (short interspersed nuclear element) and LINE (long interspersed nuclear element).

Several classes of sncRNAs have been identified, including enhancer RNA (eRNAs), microRNAs (miRNA), PIWI-interacting RNAs (piwiRNAs), and tRNA-derived fragments (tRF). These noncoding RNAs present opportunities to spatiotemporally modify gene expression. RNA-based drugs can thus extend the druggable genome with high specificity to both protein-coding genes and regulatory regions, and so provide an almost unlimited reservoir of new pharmacological agents. Further, they are the quintessential personalized medicine, moving from a one-size-fits-all approach, which at best transforms highly heterogeneous diseases from lethal to chronic, to patient-tailored and deeply acting cures.

The Right Time

The excitement following the discovery of RNA interference in the late 1990s and the consequent large investments crashed against technical difficulties that seemed unsolvable. Three decades later, RNA therapeutics has reached the point of profitability. In the last five years, both private investments and market capitalization of RNA drug companies have tripled to \$3 billion and \$50 billion, respectively.

These investments have been translated into robust pipelines leading to almost 500 RNA drug development programs. Of these drug candidates, 32% are in early-stage clinical trials (phase I or II), 3% are in phase III, and 5 drugs are awaiting regulatory decisions. The most commercially successful drug to date has been Nusinersen, an antisense oligonucleotide able to modify mRNA splicing to treat spinal muscular atrophy. Nusinersen had \$4.7 billion in sales up to the end of 2019. These figures demonstrate the technology transfer potential of the RNA Initiative.

The Right Place

This Initiative is a unique opportunity to create non-incremental knowledge in RNA biology and drug discovery by taking advantage of the achievements and expertise of IIT scientists, all leaders in their field, and by fostering their collaborations in high-risk high-gain projects. There are still relatively few RNA-centered research institutes worldwide, putting IIT at the forefront of innovation in strategic forward-looking planning. These institutes will serve as benchmarks to evaluate the Initiative's medium- and long-term performance. The broad spectrum of expertise is a unique opportunity to confront the roadblocks that limit understanding of RNA biology and its translation to the clinics. These roadblocks cannot be overcome by a single laboratory, but need a combined effort with multidisciplinary expertise. By taking advantage of the right balancing between bottom-up collaborations and the identification of larger common goals, the RNA Initiative aims to generate disruptive knowledge in basic biology, technological platform development, and drug discovery.

Overall Organization and Objectives of the RNA Initiative

Goals are positioned in a two- or five-year timeline to complete the current strategic plan and to envision the next one:

- Discovery of new ncRNAs.
- Increase IIT's patent portfolio in RNA technologies.
- Unveil the role of discovered ncRNAs in organisms' physiology and diseases.
- Identify the fine details of mechanisms of RNA action by linking structures to function.
- Develop new RNA-based technological platforms.
- Establish new start-ups and sponsored research agreements with external companies in the field of RNA therapy.
- Reach the Investigational New Drug stage for at least one RNA molecule.
- Establish IIT as a world leader in the field.

To achieve these goals, we plan to organize our activities according to Work Packages (WPs) with specific objectives and deliverables. This structure facilitates creative, bottom-up, collaborative projects between investigators with different expertise while maintaining the Initiative's general framework. It also provides performance benchmarks. In WP1 "ncRNA discovery", we aim to discover new ncRNAs, determine how they can answer the biological questions of interest, and identify potential RNA drugs and drug targets. To this end, we will study the development, physiology, and disease of the central nervous system and cancer progression. In WP2 "New technological platforms", we will establish and improve technological platforms to study ncRNAs at genomic and structural levels. In WP3 "Towards RNA medicine: computational approaches", we will develop and apply computational methods to predict and describe secondary RNA structures and their protein interaction networks. In WP4 "Towards RNA medicine: imaging", we will develop technologies for RNA imaging in the field of super-resolution microscopy, deep-tissue imaging, and time-resolved spectroscopy. In WP5 "Towards RNA medicine: post-transcriptional modifications and chemical synthesis", we will identify and study RNA post-transcriptional modifications. In WP6 "Towards RNA medicine: from delivery to manufacturing", we will streamline the development of RNA drugs. In WP7 "Management, implementation, technological transfer, and dissemination", we will manage and disseminate the RNA Initiative. In particular, we will coordinate the activities of the participants' laboratories towards a common goal of creating new IPs that exploit economic values and increasing awareness in scientific communities and society of IIT's leading role in RNA biology and medicine.

To address this vision, we will use an integrated set of molecular, cellular, and animal models developed by IIT investigators over the years, and a broad spectrum of technologies that span several disciplines. They include:

- complex biological model systems (genetically engineered mouse models (GEMMs), human IPS directed to neural lineage, neural stem cell cultures, primary cultures, 3D cultures and organoids, patient-derived xenografts)

- patient data/samples (primary cultures and tissue and liquid biopsies, FFPE specimens, consecutive patient cohorts)

- technologies for acute/constitutive manipulation of genes and ncRNAs in vitro/in vivo (Spit-Cre, CRISPR-Cas9)

- technologies for high-resolution and high-throughput biochemical characterization of RNA-based interactions (RNA-DNA, RNA-RNA, RNA- protein)

- technologies for epitranscriptomic characterization (characterization of RNA modifications, i.e. m6A - miCLIP)

- genomic technologies (all second-generation sequencing applications and third-generation sequencing)

- bioimaging technologies (super-resolution microscopy (SML and STED), 2PE and nonlinear microscopy, fluorescence fluctuation spectroscopy, FRAP, fluorescence-lifetime imaging microscopy)

- technologies for single-molecule RNA imaging (FISH)

- a series of ad hoc computational tools developed internally to characterize a) RNA interactions (catRAPID, CROSS, catGRANULE); b) RNA metabolism (INSPEcT); c) RNA modifications and analysis (Nanocompore, IsomiRage).

The Initiative also benefits from a continuously developing clinical network for i) integrating RNA biology with biomedicine; ii) identifying promising drug targets, and iii) hosting clinical trials. This includes a) a Joint Laboratory between IIT and IRCCS G. Gaslini Children's Hospital, with special emphasis on pediatric diseases; b)

The 5000-genome VdA project to integrate genomics in the diagnostic pipelines of Parini Hospital, Aosta, with a focus on NDVDs, NDGDs, and cancer, and the construction of a tissue biobank and a searchable electronic medical record database with clinical and genomic data; and c) the European Institute of Oncology (IEO-hospital, in Milan), which hosts one IIT research center (CGS) and provides access to clinical data and biological samples for cancer studies.

Participants

The RNA Initiative involves an integrated approach and complementary expertise to achieve non-incremental discoveries about the biology of ncRNAs in health and disease and to develop new technologies and platforms for RNA therapeutics. It involves 17 PIs, 2 researchers, 1 technologist, and 1 external collaborator. It spans three RDs (Technologies for Life Sciences, Computational Sciences, Nanomaterials).

Participants are located at the CCT, Morego, Genoa; the CHT, Erzelli, Genoa; the Center for Genomic Sciences, Milan; the Center for Life Nano Science, Rome; and at the Center for Advanced Biomaterials for Healthcare, Naples. The participants' wide spectrum of expertise includes ncRNA biology in health and disease, neuroscience, oncology, synthetic biology, computational biology, imaging, and drug delivery.


E4
COMPUTER
ENGINEERING

The Computational Sciences Research Domain

Massive computation, the achievement of the Exascale, and non-Turing computation technologies and infrastructures have (and will have) a major impact on IIT's Strategic Plan. Two major developments in computational science are: i) massive simulations of physical systems, which are repeated numerous times to generate robust statistics; ii) data mining of vast datasets to identify unexpected patterns (i.e. big data analytics).

The first development is impacting many fields, including drug discovery, material and nanoparticle design, and, more generally, condensed matter physics but also biology (e.g. protein folding, secondary RNA structure). The second development is playing a key role in artificial intelligence (AI) (e.g. for robotics) and genomics. Both areas need infrastructure, including high-performance computing (HPC), big data storage, and cloud computing. HPC will be crucial for computational life science, materials science, and robotics. Big data storage will be crucial for genomics and, more generally, for personalized medicine programs. Cloud computing will be pivotal for efficient data processing in robotics via ultrafast Wi-Fi connections, such as 5G. In this context, one of the main objectives of the 2018-2023 Computational Sciences RD is to establish a dynamic interplay between HPC, big data analytics, and AI. We will achieve this by developing a new portfolio of HPC codes, ranging from new tools for multiscale simulations to machine-learning (ML) algorithms.

The Computational Sciences RD will focus on four Priorities in the fields of life science, materials science, and data science for robotics and health (Figure 19).

The first Priority will be to develop HPC algorithms and software for multiscale simulations, bridging physical, chemical, and biological complexity. The second Priority will be computational modeling to design better nanomaterials, innovative medicines, and next-generation drug delivery systems. ML and deep learning (DL) are the focus of the third Priority. This Priority

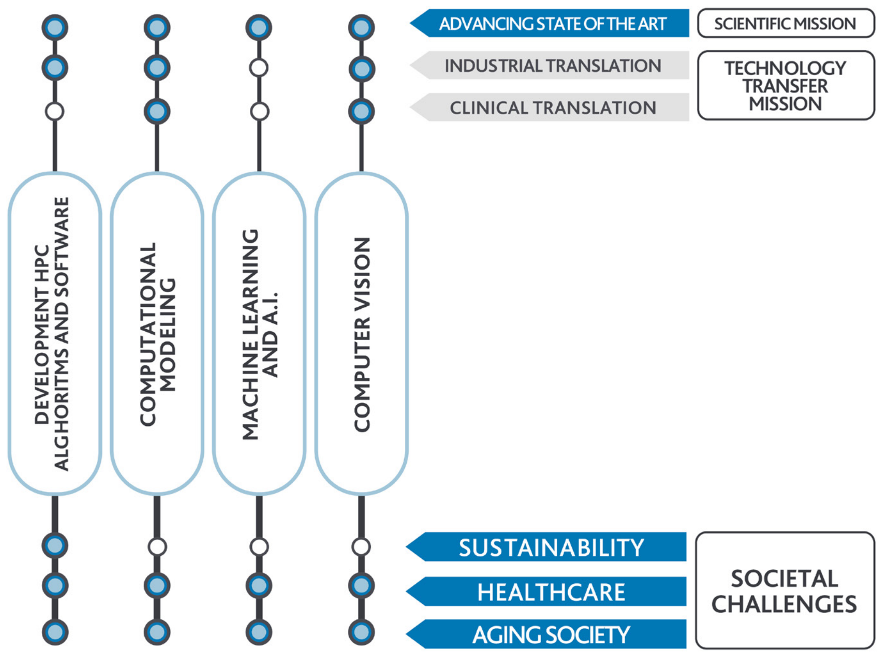


Figure 19: Priorities of the Computational Sciences RD, contribution to IIT's mission, and impact on the challenges.

will be dedicated to new theories and models to develop next-generation algorithms and high-performance code for AI and bioinformatics. Finally, the fourth Priority will concern computer vision for robotics and pattern recognition techniques, with applications from ambient intelligence to healthcare. The Computational Science RD originates from the small Compunet team launched in the previous Strategic Plan. Though small, the Compunet has been successful in generating a high return on IIT research and transversally driving multidisciplinary innovations from robotics to chemistry.

The 2018-2023 Strategic Plan aims to create a world-class Computational Sciences RD at IIT, with the twin goal of boosting the research of all other RDs (from AI to bioinformatics) and autonomously generating new frontier research fields.

Scientific Mission

Computational Sciences will integrate data science and computation to achieve two objectives. First, we will develop new theories, algorithms, and software for life science, materials science, and robotics. Second, we will provide theoretical and computational support to the other RDs. We will design and develop advanced physics-based multiscale approaches (from quantum physics to mesoscale modeling) and data-rich methodologies (e.g. ML, DL). In terms of big data in genomics, high-throughput DNA-sequencing technology (i.e. NGS) provides unprecedented possibilities for personalized medicine. Genetic screening will generate data in the order of petabytes. This, in turn, will require highly parallel bioinformatic algorithms and tools to extract meaningful patterns by integrating and correlating heterogeneous data, which may be incomplete and/or uncertain.

All this will require efficient algorithmic and software design and implementation, capable of fully exploiting the unprecedented computational power of the most modern hardware architectures for pre-Exascale computing. At IIT, we will develop and optimize codes for HPC, providing our researchers with flexible and efficient tools, enabling the full exploitation of state-of-the-art computing architectures. In the period 2018-2023, substantial amounts of data will be generated, especially bioimages, genomics data and clinical records, which need to be stored and analyzed.

A large HPC infrastructure coupled to a big-data storage facility will be a key strategic asset for efficiently processing data and extracting patient-relevant information. This will be achieved initially in collaboration with the Italian supercomputer center CINECA (or any other European HPC facility) and subsequently (from 2020) through IIT's infrastructure too (the Petascale HPC, Franklin, was installed in September 2020).

Technology Transfer Mission

The technology transfer (TT) of the Computational Sciences RD will be boosted by the development of new software and informatics tools (i.e. protocols, databases, (bio)informatics pipelines and workflows). In particular, we will create a pipeline of activities to develop professional software for genomics and materials science.

This will include choosing the most effective models, developing new equations, theories, and formalisms, and developing innovative codes and market-ready professional software for the scientific community. One recent example of TT is the high-tech startup company, BiKi Technologies, which develops drug discovery software based on molecular dynamics. Next, we will focus on the generation of code and software for ML (for genomics and robotics) and computational chemistry (for materials science). Developing professional code is crucial because nonoptimal algorithmic implementation reduces our ability to harness the huge computational power of the latest generation of HPC architectures. Additionally, a sound knowledge of the underlying architecture of modern computer hardware, such as general-purpose graphic-processing units (GP-GPUs), is required to unlock their full potential.

Thus, the 2018-2023 plan for Computational Sciences at IIT must foster fruitful interactions between scientists and software engineers, creating a shared language. In particular, we envision the integration of HPC and big data analytics as a strategic and essential asset for the future of bioinformatics and precision medicine research. Similar developments have already taken place in the field of condensed matter physics, where atomistic and multiscale simulations increasingly benefit from HPC as the research becomes more ambitious. We will modernize and optimize codes for HPC infrastructures in collaboration with CINECA, which has extensive experience in HPC and code refactoring for innovative hardware architectures.

Healthcare Challenge: Designing and developing a data storage facility and novel high-powered computing codes

The two contributions to the Healthcare Challenge will be: (i) designing and developing a data storage facility for genomics and clinical records; and (ii) designing and applying new tools for multiscale simulations in nanochemistry, biology, and genomics. In terms of the first contribution, genomic-wide association studies (GWAS) for humans are changing medicine's central paradigm, by defining pathology and associated treatments at the level of individuals. Personalized medicine promises a quantum leap in our ability to fight complex diseases.

The field is evolving rapidly and will generate hundreds of Petabytes of data worldwide each year. These heterogeneous data (omics, clinical records, imaging) must be managed, stored, and analyzed. Therefore, we will develop specific workflows for the data storage and querying of next-generation Petascale to Exascale databases, together with a new user-friendly web portal for these activities. These novel tools will ultimately help experimentalists and medical doctors to more easily identify biologically and medically relevant patterns. The end user will benefit from a professional, flexible, and modern environment to exploit big data and HPC in personalized medicine. The second contribution will be to design and apply new tools for multiscale simulations in nanochemistry, biology, and genomics. The computational biology, chemistry, and physics communities are paying increased attention to multiscale simulations from the atomistic (quantum chemical calculations) to the mesoscale levels. These novel computational paradigms can help researchers deal with the complexity of large nanoparticles and with the 3D nature of DNA and RNA for the multiscale modeling of chromatin and RNAs.

Aging Society Challenge: Big-data-driven polypharmacology

Neurodegenerative diseases (NDGDs), including Alzheimer's disease (AD) and Parkinson's disease (PD), almost exclusively affect elderly people. No effective cure exists for AD or PD, so new drug discovery approaches are needed. In this context, multitarget-directed ligands (MTDLs) have the potential to exert synergistic therapeutic effects by affecting multiple targets. According to network theory, when targeting a network infrastructure with features resembling those of pathological interactomes and transcriptomes, the best strategy is not to strike a localized blow, but rather to simultaneously shut down multiple nodes.

This may explain why MTDLs are expected to provide better options than conventional single-target drugs when it comes to treating complex neurological disorders. Here, we will take on the challenge of rationally designed MTDLs by using systems biology and bioinformatics activities to exploit the huge amount of NGS data generated and/or collected by the Center for Human Technologies (CHT). In particular, we will develop new computational tools based on ML and/or DL for big data analysis. These tools will be used to prioritize combinations of pharmaceutical targets that traditional knowledge-based methods might not have identified. Indeed, traditional combination strategies rely on a local, often episodic, and aprioristic knowledge of the potential targets. Here, we aim to revert this paradigm, using novel analytical tools, ML, and cluster analysis to mine omics data in order to identify novel targets, which will flag up unprecedented target combinations that could elicit the desired therapeutic effect if modulated concurrently.

Priorities of the Computational Sciences Research Domain

The Computational Sciences Research Domain (RD) will be organized in four programs that cut across other RDs. As shown in Figure 20, the Development of HPC, Algorithms, and Software Program will be crucial to fully exploiting modern computational infrastructures and optimizing code and software for bioinformatics, genomics, and materials science. Combining big data and bioinformatics with HPC will be one of IIT's main strategic objectives and future strengths. The Computational Modeling Program will cut across life science and nanoscience, primarily dealing with statistical mechanics, ab initio models, and multiscale simulations for broad application. ML will be instrumental in a number of areas of science and engineering, including robotics and life science (genomics, clinical data, personalized medicine). Finally, the Computer Vision Program will target rehabilitation, therapy, robotic vision, safety, and cybersecurity. The four programs will be fully integrated to achieve the ambitious goal of integrating next-generation big data technologies with HPC to advance the state of the art in data science and computation (for Exascale computing). The dynamic integration of these two areas, traditionally running on separate tracks, is one of the biggest challenges for Computational Sciences. In 2018-2023, we will tackle this challenge by building appropriate infrastructures for HPC and big data storage, and by developing innovative algorithms and codes to fully exploit these infrastructures.
Most of the Computational Sciences research and technology will be developed in the new CHT in the Erzelli building, supported by CNCS-Trento, CBN-Lecce, CNI-Pisa, and CNST-Milan. In the coming years, the Computational Sciences RD should grow by about 50% (currently more than 150 staff members, including 13 PIs and 12 technicians) thanks to new PIs in the fields of analytical modeling of nanosystems, bioinformatics, quantum chemistry and data science, AI, and ML.

Additionally, in 2017, IIT launched a new PhD School in Data Science & Computation in collaboration with the University of Bologna and Milano Politecnico. This major European PhD school is Italy's largest in the field. Other national and international key actors could be involved in this and other programs to increase synergies in the Computational Sciences RD. This may

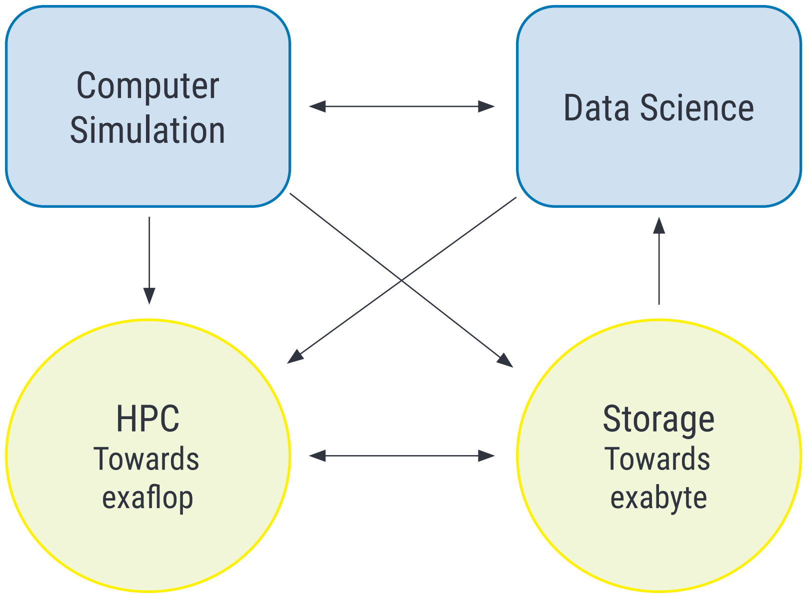


Figure 20: Interplay between Computer Simulation and Data Science. Computer Simulation is expected to generate huge amounts of data, which require next-generation data analytics to extract patterns and relevant information. Data science algorithms will require increased computer power from modern HPC architectures because data will approach Petabyte dimensions.

include the International School for Advanced Studies of Trieste (SISSA for the doctoral program), EPFL (for computational materials science), ETH, and USI (Università della Svizzera Italiana). IIT and USI recently signed a memorandum of understanding, which covers joint computation and data science activities.

In 2020, we created the data storage facility for the CHT at Erzelli. The data storage facility for genomics and clinical records will be structured in three main levels: i) a small amount of storage associated with next-generation sequencing (NGS) machines for the small amount of data coming directly from NGS experiments; ii) a medium-sized amount of local storage (a few Petabytes) to store raw data and aligned sequences in databases (possibly along with clinical records); and iii) a large external infrastructure of more than 100 Petabytes for the long-term storage of raw data, particularly for redundancy and disaster recovery. The small facility is almost up and running. The largest facility will be built in collaboration with CINECA. The medium-sized infrastructure will need to be created to appropriately store genomics data from NGS experiments. For the local medium-sized storage facility, we will follow a stepwise strategy to build the data storage, setting up the DBMS facility (databases, database-management systems) incrementally to aggregate genomics and clinical data. Initially, we will develop a pipeline to manage the genomics data only. Subsequently, we will expand the database to acquire, manage, and analyze clinical records. As for HPC, we will enlarge our internal GPU clusters and strengthen our strategic collaboration with CINECA. Massive data storage and HPC will be key infrastructures for IIT's 2018-2023 strategic plan. The same infrastructure is being replicated for the 5000-genomes project in Valle d'Aosta, which will use a common data and processing framework with the Liguria site, thus establishing an important first seed of a standard Italian network for genomics and bioinformatics.

Priority 1: Development of High-powered Computing Algorithms and Software Program

Advanced multiscale modeling of biomolecules

In recent years, there has been an exponential growth in the number of large biological structures resolved at nearly atomic resolutions. This is due to progress in powerful experimental techniques for structural biology (e.g. cryo-electron microscopy, as reflected by the 2017 Nobel Prize in Chemistry) and advanced reconstruction algorithms that can define larger supramolecular assemblies (e.g. virus capsids). The resulting atomistic models can comprise up to dozens (or even hundreds) of millions of atoms and reach up to 100-500 nm in size. There have been pioneering attempts to dynamically simulate these systems with Petascale supercomputers. However, we still require computational approaches to investigate these structures in order to, for example, identify interaction hotspots or new drug-target regions. The final goal is to develop and use multiscale methods to attain the same accuracy that is currently possible for small protein structures. This will allow further analyses, such as virtual screening and similarity searches for electrostatic patterns, which will exploit this exciting new information for drug discovery and delivery.

Multiscale modeling will also benefit from novel approaches to modeling electrolytic solutions, since traditional methods (e.g. those based on Poisson-Boltzmann theory) fail to correctly describe systems in which ion-ion correlation is important (e.g. systems involving high ionic concentrations or multivalent ions). Additionally, methods for describing molecular interactions (e.g. molecular mechanics or RISM) are not designed to simulate systems where constant electrostatic potential is enforced. On the other hand, computational tools built upon electrostatics theories can describe constant potential regions, but neglect interactions that are not electrostatic in nature. They therefore cannot correctly represent, for example, the finite size effects of the ions, or the effects of substrate morphology on the zero-charge potential and differential capacitance. As such, these approaches poorly predict how the solution affects the behavior of highly charged biomolecules, such as nucleic acids. Innovative approaches will need to consider the effects of the electrode's shape and structure as well as the solvent's physicochemical properties. These approaches will provide an advanced description of ionic solutions and integrate descriptions of constant potential systems with atomistic force fields, at a relatively low computational cost. They also have great potential for the computer-aided design of electrode-cell interfaces, photovoltaics, the interpretation of scanning tunneling microscopy experiments in a wet environment, and so on.

In genomics research, multiple lines of evidence suggest that the 3D organization of chromatin on the kilobase-to-megabase scale plays an important functional role. Indeed, DNA and RNA are intrinsically multiscale molecules. Even with the use of large supercomputers, traditional single-scale approaches cannot account for the prohibitively large number of variables involved in the complex regulation of DNA and RNA life cycles and activity. The spatiotemporal interaction of DNA and RNA with proteins (e.g. nucleic-acid-processing enzymes) is a key aspect of multiscale modeling and genomics research. Innovative multiscale approaches will allow a better understanding of the structure, dynamics, and assembly of the nucleosome and chromatin fibers, and their role in pathological conditions. Additionally, multiscale modeling is crucial to computationally devising nanomedicines and modeling RNA. These two scientific activities will also be conducted by computational scientists at IIT in the 2018-2023 period. Indeed, the discovery of many long and short noncoding RNAs is a great challenge for researchers seeking to describe the structure-function relationships of RNAs. Representative examples of long noncoding RNAs (lncRNAs) seem to be organized according to modules folded into secondary structures, with limited primary sequence homology. However, the nature of these domains and sequences is unclear. There are still no satisfactory computational methods for systematically identifying lncRNA secondary structure motifs. Moreover, there are just a few examples of successful deletion analysis to assign biochemical activities or biological function to specific structures. In this context, we aim to develop novel multiscale approaches to modeling lncRNAs and their interactions with proteins and DNA. The goal is to identify classes of lncRNA domains, which would be a major breakthrough. This knowledge may also lead to the construction of synthetic RNAs, which could be used to manipulate gene expression in vivo, including the treatment of NDGDs and cancer.

Quantum material theory

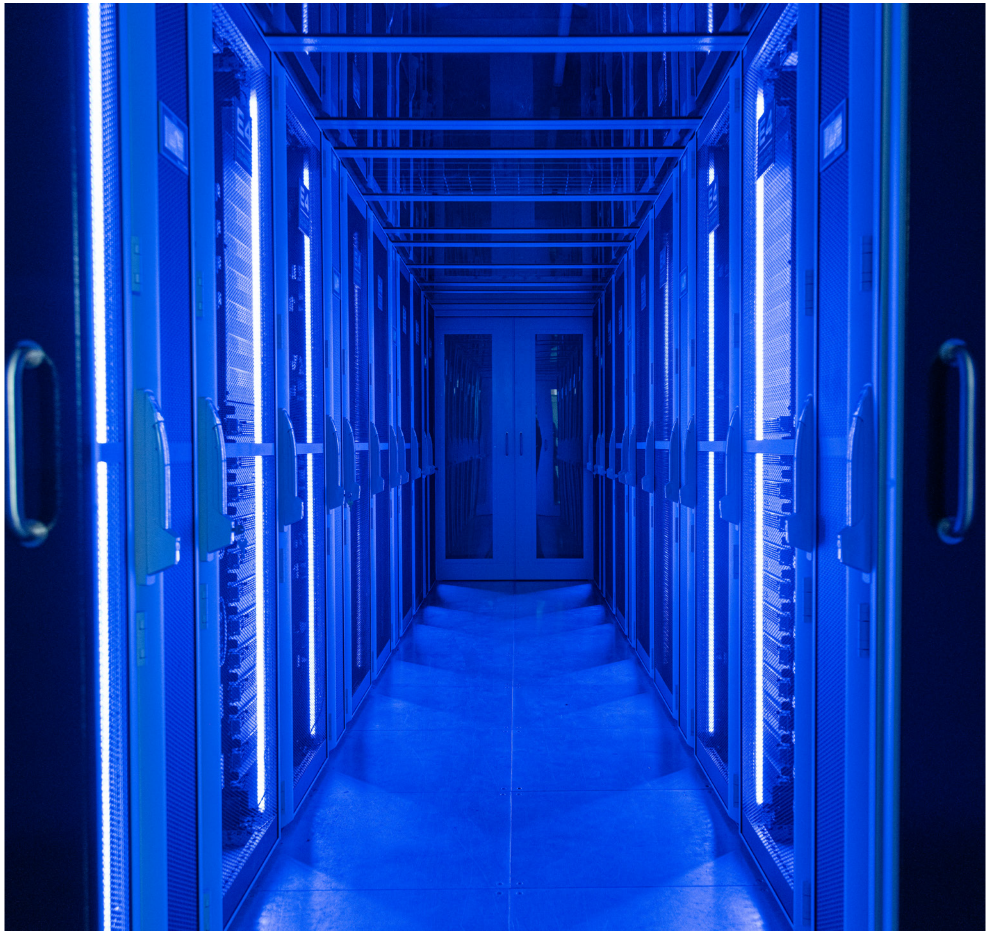
Density functional theory (DFT) is the most popular theoretical framework in quantum chemistry and solid-state physics. Its accuracy depends on approximations for the exchange-correlation (XC) energy functional and, in the case of orbital-free DFT (OF-DFT), approximations for the kinetic energy (KE) functional. Both XC and KE functionals are the subject of intense theoretical investigations, and there is particularly strong interest in metageneralized gradient approximation (meta-GGA), which depends on the kinetic energy density and/or on the Laplacian of the density. We will introduce a new class of meta-GGA functionals (u-meta-GGA), which depends on the screened Hartree potential. It can ensure a realistic description of core regions and of any of the one- or two-electron regions, allowing a better reproduction of the exact electronic density. Developing accurate u-meta-GGA XC and KE functionals will make a strong contribution to the accurate modeling of the electronic and optical properties of large systems, with particular relevance for nanoscience and biology.

Novel quantum approaches are also expected to have a remarkable impact on plasmonics. Indeed, neither classical electromagnetism nor quantum hydrodynamic models take into account the exact core-valence coupling (which plays a key role in noble metals) or the atomic structure of nanoparticles (which is very important at small distances). Time-dependent density functional theory (TDDFT) can include both effects. Despite being limited to systems of less than one thousand atoms, TDDFT is a reference approach in plasmonics. Quantum effects in noble metal nanoparticles have already been studied. However, ab initio methods have not yet been used to investigate new plasmonic materials, such as heavily doped semiconductors. We plan to develop innovative protocols based on TDDFT to model the optical properties of metals and semiconductor clusters of different sizes, doping/charges, and compositions. These studies will help researchers to understand the underlying physics of these materials, to develop multiscale methods, and to design new plasmonics materials.

Eventually, we plan to develop novel first-principle-based methods to model functional materials and embed the results into an efficient second-principles framework, which is suitable for simulating nanoscale phenomena and devices.

HPC algorithms for extremely largescale data analytics

New computational architectures and dedicated software tools can generate vast amounts of simulation data, which cannot be analyzed by conventional methods. In parallel, scientists have developed numerous theories, algorithms, and models to tackle the challenges of computational chemistry and biology. However, their initial implementations are often not engineered to fully exploit the power of the most modern computational architectures. For example, ML approaches are likely the best suited to automatically identifying a simulation's most significant features, freeing up the user to focus on the most informative data and to uncover unexpected patterns. Therefore, theoretical and computational scientists at IIT will develop HPC implementations of advanced computational approaches and use ML methodologies to handle large amounts of data and to unlock the full potential of massive computations in life science and materials science. This will result in a dynamic interaction between data analytics and HPC simulations, as illustrated in Figure 20.



Priority 2: Computational Modeling Program

Computational drug design, discovery, and delivery

Computational methods play a crucial role in designing better medicines. These methods range from statistical approaches (QSAR, QSPR, ML, etc.) to multiscale modeling of large biomolecules. They are currently used for several drug design endeavors.

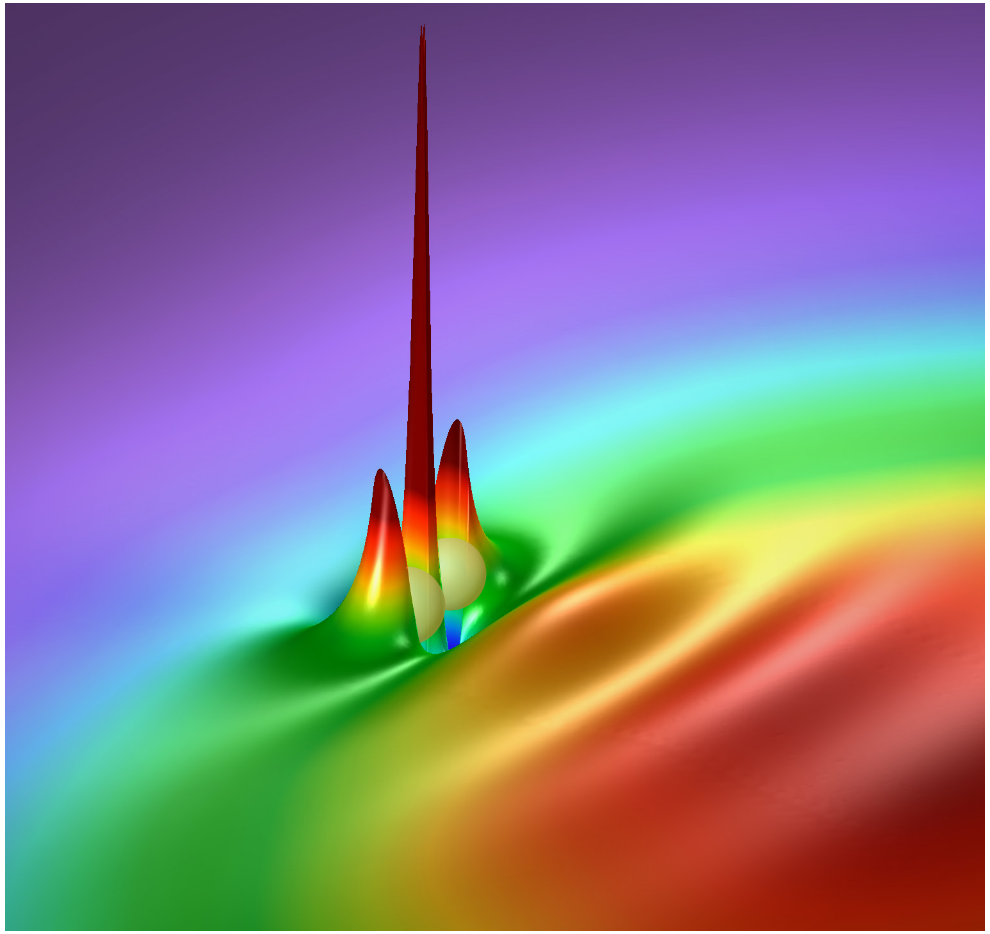
These computational methods are also pivotal to a better understanding of DNA and RNA. This information is extracted, read, and interpreted by specific enzymes that operate on the long linear nucleic acid polymers that form the genome. While it is crucial to study the genetic information embedded in DNA and RNA sequences, it is equally crucial to understand the specific enzymatic machineries that allow DNA and RNA to pass genetic information from one generation of cells to the next. These essential enzymes include polymerases and nucleases. One example, the Cas9 nuclease, is used in the CRISPR/Cas9 gene-editing tool and has potential applications for medical genome research. In this context, we will develop and apply multiscale approaches, from picosecond to millisecond timescales, to help decipher the structural and functional determinants of these key nucleic-acid-processing enzymes, when in complex with nucleic acid polymers. Simulations will reveal the underlying principles of the enzymatic processing and catalysis of genetic material. These investigations will therefore provide a detailed analysis of the chemical reactions needed to merge and split DNA and RNA filaments and of the large-scale structural assemblies that form nucleic-acid/protein complexes. An improved understanding of how enzymes process DNA and RNA will accelerate the development of nucleic-acid-processing biocatalysts (i.e. DNAzymes, RNAzymes). These could be used for important applications in nanoengineering, epigenetic mechanisms, and drug design.

The recent pandemic outbreak compels the scientific community to deepen its knowledge and design capabilities regarding the entire spectrum of therapeutic agents. In this respect, a further research activity will involve conducting advanced computational and statistical studies in order to understand the molecular determinants of protein-protein interactions, with particular attention devoted to the antibody-antigen recognition. These studies will be instrumental to perfecting computational tools and approaches for the design of antibodies binding to predetermined antigens, significantly enriching the available weaponry against present and future diseases.

Additionally, we will focus on in silico drug delivery because it was recently shown that monolayer-protected nanoparticles can be functionalized to obtain nanodevices with unique properties. These have promising applications in fields such as nanomedicine, diagnostics, chemosensing, and even catalysis (nanozymes).

The molecules that form the coating monolayer make the main contribution to the nanoparticle's functionality. Indeed, the outer coating monolayer offers a straightforward path to realizing large multifunctional chemical systems. However, the complex, hybrid, and flexible nature of the coating monolayer has so far made it difficult to investigate its structure, organization, and dynamics. In this context, rational approaches based on computer-aided molecular design could fundamentally transform the current empirical design process for functionalized nanoparticle monolayers. We will develop and conduct multiscale simulations (atomistic, coarse-grained, and mesoscale modeling) to study and characterize these functionalized nanoparticles. This investigation will elucidate, for example, the interaction at the nanoparticle/membrane interface, and the protein corona that controls a nanoparticle's biological behavior.

The computational investigation and design of monolayer-functionalized nanoparticles is still a relatively unexplored field. By developing a computational framework for designing functionalized nanoparticles with programmed abilities, this research line will positively impact nanochemistry, computational chemistry, and functionalized nanoparticle engineering, potentially boosting knowledge in all areas of nanotechnology, with positive socioeconomic implications for areas such as energy and healthcare (intelligent medicine and diagnostics).



Computational materials science

Here, we will develop innovative protocols for simulations of i) nanoplasmonics, ii) environmentally friendly organic reactions, and iii) 2D materials.

Nanoplasmonics. The goal here is to harness quantum effects in deeply confined light modes to develop novel and efficient nonlinear processes, which can be triggered at very low input power. In particular, we will develop a full nonlinear semiclassical theory that can be tailored to a specific optical phenomenon, such as self-modulation. The focus will be on orbital-free techniques, such as quantum hydrodynamic theory (QHT), for which electron energy functionals are expressed in terms of macroscopic quantities, such as electron density, rather than the single electronic orbitals. To this end, we will work on improving the current state-of-the-art energy functionals, with particular emphasis on dynamical aspects, in order to extend their validity to the nonlinear optical regime. By integrating a whole range of mesoscale phenomena under a unified description, we aim to lay the foundations for nonlinear optical interactions at the nanoscale in plasmonic systems. This activity will advance the state of the art, resulting in methods to understand the physics of a variety of multiscale structures. It will provide the tools to engineer and design novel nonlinear integrated plasmonic devices. The practical realization of these devices will be pursued in the context of nanogap plasmonic systems. These structures present a strong multiscale character with elements ranging from hundreds of nanometers to a few microns, while still maintaining features that are just fractions of a nanometer in size. These systems could make it possible to observe novel nonlinear optical surface effects as well as nonlocal and quantum effects on much larger scales.

Environmentally friendly organic reactions. We will run computational modeling of biomimetic solid catalysts with a particular focus on green chemistry. The strategy combines the study of enzymatic reactions and the subsequent design of bioinspired catalysts with improved selectivity and activity towards selected chemical transformations. The reactions of interest include the transformation of greenhouse gases into nonpolluting and possibly value-added chemical species. Examples are provided by methane and carbon dioxide, which are converted by monooxygenases and carbonic anhydrase into methanol and bicarbonate, respectively, under mild conditions. The catalyst design does not just involve a mimetic approach of the enzyme reactive center. It is also aimed at understanding and reproducing the interplay between metal sites and soft matter in the protein's enzymatic cavity. This interplay will be addressed by modeling the functionalization of biomimetic solid catalysts with organic flexible surfactants and by investigating the impact of this functionalization on catalyst performances. We will work closely with experimentalists in the Nanomaterials RD to validate this approach.

2D materials. We will continue the Graphene Flagship activities started during the Core1 phase, focusing on two cutting edge research activities to be developed in Core2 and later in Core3 (until 2023). First, we will develop theoretical schemes to achieve electrical plasmon launching in high-quality encapsulated 2D materials. Second, we will lay down a theory to study the nonequilibrium dynamics of carriers and excitons in 2D semiconductors, including transition metal dichalcogenides (TMDs). Semiclassical Boltzmann transport theory codes will be written up, allowing the calculation of the dynamics following photoexcitation. By using path integrals on the Konstantinov-Perel's time contour, we will look at the formation dynamics of excitons and plasmons. Particular attention will be devoted to studying the coupling between plasmons and excitons in van der Waals stacks. Finally, we will start theoretical work on two entirely new topics. The IIT Graphene Labs will work on "Quantum Batteries". These are systems of coupled quantum units (e.g. electrons in semiconductor quantum dots) controlled by light- or time-dependent local gates, where quantum mechanical resources, such as entanglement, are expected to bring remarkable gains in the performance of charging/discharging processes or, more generally, in energy storage. Additionally, we will try to lay down a theoretical framework based on effective medium theories to understand the mechanical, thermal, and electrical properties of composites based on 2D crystals.

Priority 3: Machine Learning and Artificial Intelligence Program

Machine learning theory and algorithms

The objective of the program is to develop new AI and ML algorithms with application to robotics, computer vision, and data science in general. These methods will allow us to decipher the information hidden in datasets that are increasingly more complex and structured. This information can then be used to produce new interpretable models and, ultimately, scientific theories for natural and life sciences, and to develop novel AI technologies.

ML is becoming the key to AI modeling and is playing an increasingly crucial role in science and engineering. In ML, data are processed by a learning algorithm, which extracts information in the form of regularities and patterns associated with the data, ultimately allowing predictions to be made from new data points. ML provides tools and techniques to investigate and model complex datasets from science and engineering. Within this program, we will develop new ML methods, understand the principles, and implement them in the form of intelligent robots or predictive models in the data science domain.

The key challenges in ML for the Strategic Plan 2018-2023 are to: i) develop learning systems that can learn to perform tasks of growing complexity; ii) study learning frameworks that allow knowledge from previously learned tasks to be transferred to solve new tasks more efficiently; and iii) develop theoretical tools for DL. To tackle these challenges, we will focus on modern ML algorithms, such as those based on representation learning, multitask learning, and lifelong learning, which are still poorly investigated. In particular, 'lifelong learning' refers to ML systems that can improve over time by dynamically and quickly adapting to unexpected tasks/circumstances, for which they have not been specifically trained or programmed. Here, the long-term goal is to develop fundamentally new ML mechanisms. These mechanisms should facilitate continuous learning at runtime and allow previously learned information to be applied to novel situations, much as biological systems (especially humans) do. This evolution of ML will result in more functional and safer systems and increase ML's relevance in the Intelligent Companion Robots program.

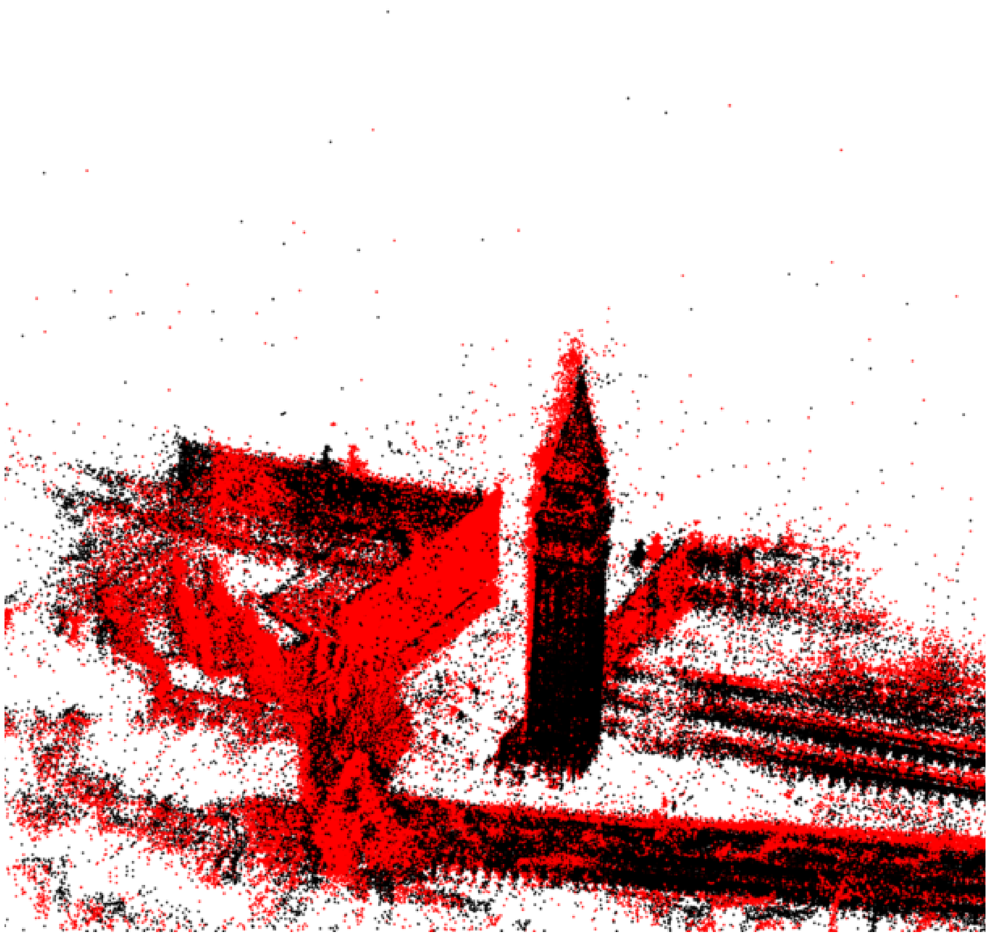
We will further characterize and analyze the statistical performance (generalization capability) of learning algorithms, developing tools for statistical learning and probability theory. A further key tool will use numerical optimization and convex analysis, which is playing an increasingly important role in the development of efficient algorithms for computational statistics and ML. The emphasis is on developing efficient algorithms and software that can handle massive datasets (such as those produced by robot vision) and possibly structured datasets (such as those produced by genomics and clinical records). Eventually, we will also study the conditions that can be used to control and certify the performance of learning algorithms.

Machine learning, data science, and artificial intelligence

The progress in collecting huge amounts of data from all branches of engineering, natural science, and medicine opens exciting frontiers. In fields such as robotics, it offers the opportunity to develop artificial agents that can learn to perform challenging tasks and safely adapt to human environments. In natural science and in medicine (particularly medical genomics), it opens the way to new data-driven approaches to understanding complex diseases. Modern datasets are massive and often come in complex structures (e.g. strings, graphs, histograms, images), which cannot easily be observed and interpreted.

Recent DL approaches have strengthened ML. DL has been extensively used in a wide range of data science applications, and DL networks are now the premier class of ML approaches. They can cope well with static data (images) by using convolutional neural networks and autoencoders, and with data sequences (videos, speech, strings) by using recurrent neural networks and its most famous variant: long-short-term memory networks. All these data types can be efficiently managed by DL architectures, which benefit from the big data regime of today's applications. IIT's multidisciplinary and interdisciplinary environment is perfect for implementing and challenging DL approaches. IIT's Robotics, Technologies for Life Science (LifeTech), and Nanomaterials RDs provide terrific data sources, which must be processed and interpreted automatically. Here, the goal is to inject machines with intelligence capabilities while understanding and explaining the data. Crucial DL topics include multitask learning, domain adaptation, adversarial training strategies, unsupervised learning, and related areas. If addressed, they will lead to automatic and autonomous system abilities, capable of tackling problems that were deemed difficult, if not impossible, to solve just a few years ago. To address the need for large datasets to train DL networks, one strategy will be to use information (e.g. images, movies) that we will mine from the Web with principled algorithms that minimize noise in the images without requiring manual annotation.

Our goal is to automatically create task-specific databases of images from the Web by exploiting ML algorithms and NLP query expansion strategies. We will use these databases to develop DL architectures especially suited to the needs of robot vision. By aligning a given list of queries with semantic ontologies like WordNet, we will create representations of perceptual and semantic knowledge bases, on demand and without the need for manual intervention. DL algorithms will eventually be applied to the omics domain, improving our understanding of several diseases, and facilitating earlier diagnosis and more effective treatments. This will lead to personalized medicine solutions. DL algorithms can be used in a wide variety of areas and should eventually allow the prediction and early treatment of incipient diseases.



Priority 4: Computer Vision Program

Like ML, computer vision cuts across many disciplines, with applications in robotics, genomics, behavior analysis, health, and so on. We will develop practical applications for computer vision by using ML methods, ad hoc models, and prior knowledge of the data.

Computer vision for robotics

In robotics, scene understanding is crucial to allowing high-level functions of autonomous platforms (see the Robotics RD). For example, computer vision systems can classify ongoing conditions and predict events, recognize human activities, and predict human actions at an unprecedented fine-grained resolution. This is particularly effective and important for human-robot interactions, where vision is the most used modality to navigate complex 3D environments, and to socially engage with and assist human users. For the ongoing Industry 4.0 revolution and beyond, machine vision methods are fundamental tools that can help operators to perform repetitive and stressful tasks, such as visual inspection or other specific operations in dangerous environments.

Image and video (and other sensing modalities/signals, such as sound) are the main sources of information, specifically for high-level reasoning and learning. Activities are focused on behavioral analysis and the understanding of 3D scenes, with special attention to nonverbal (human) behavior and social interactions. In addition, we will combine audio and other sensor data with video data for scene understanding. This is because augmenting the data sources should result in more informative representations and improved comprehension abilities. This is particularly true in complex cases, where visual information alone is not sufficiently discriminant to perform a task efficiently. Similarly, given the advent of 3D sensors and joint visual/range sensory devices, video data can be complemented by 3D data to improve scene understanding. In this context, standard 3D point clouds, extracted from different sensors, can provide high-level semantics, i.e. identify the classes to which the 3D cloud belongs, then encode the spatial relations between objects to support other ML tasks, such as scene recognition and visual question and answer. A further key line of research is to develop computational architectures that can recognize objects, regions, and their position and relations in 3D. Higher-level semantics for 3D interpretations will require ML to infer graph representations of the scene, including the relevant spatial relations among objects and regions via physics-based geometrical reasoning. These visual graphs will connect to NLP semantic structures, with each helping to disambiguate the other (e.g. via geometrical reasoning).

Computer vision for life science

In the healthcare domain, the advanced monitoring capabilities of computer-vision-based systems can be used to investigate behavioral and neurological pathologies by modeling clinical data together with the behavior of patients in a controlled environment over time. In the long term, this technology should produce tailored (personalized) solutions.

For example, in support of neuroscience, we investigate behavioral phenotyping (i.e. in mice), with a particular focus on brain connectomics (structural and functional) to identify neural correlates of behavior. This can be investigated from different perspectives, including social behaviors, their brain correlates, and the characterization of cells and neuronal network connectivity to analyze the overt behavioral manifestations of certain mental disorders (e.g. schizophrenia, autism spectrum disorders (ASD)). By analyzing electrophysiology, and structural and functional brain imaging data (and genetics), we can derive hypotheses about brain functions and pathologies, including how to assess and monitor the effectiveness of drug treatments. These investigations require advanced multimodal tools to consider all the available data sources. Ultimately, these studies may provide insights that can be used to design actual treatments. To this end, we will exploit feature representations that are automatically extracted (i.e. learnt) from data using DL. In particular, we will consider both supervised and unsupervised methods since, in many cases, annotated data or other prior knowledge are not fully available. Unsupervised methods can scout the data's intrinsic characteristics to identify natural classes (and patterns) of interest. Our goal is to develop new applications in this domain by applying and exploiting the availability of multimodal data.

In the biomedical domain, computer vision is becoming a crucial tool for investigating behavioral pathologies (e.g. ASD, schizophrenia) and NDGDs (e.g. AD and PD, amyotrophic lateral sclerosis, mild cognitive impairment). Computer vision uses multimodal neuroimaging data (e.g. DTI, fMRI, EEG, PET) more holistically than in the past. Moreover, the analysis can now move beyond neuroimaging data to include genetic and behavioral information. This information is then elaborated in a joint inference model for more predictive informatics tools and early diagnosis.

Additional Strategic Research Directions

The six Scientific Initiatives described previously were the result of a bottom-up selection and construction process, which aggregated PIs spontaneously according to their interests. Notably, five of the six Scientific Initiatives have a computational component, related to simulation or to AI. This trend was observed and captured in the Strategic Plan. The Horizon Europe program, specifically the Partnerships (PPP), foresees a strong alliance on “AI, data and robotics” which will shape the calls of the program’s Pillar 2. IIT’s PIs were successful in the predecessor of Pillar 2 (e.g. ICT) and secured considerable amounts of competitive funds (up to 100% of the budget invested by IIT).

In light of these trends, IIT’s strategy will emphasize certain themes and strengthen several of the Priorities described earlier in the four RDs. This means that resource allocation may start veering towards high computational and AI content across all RDs.

Machine Learning and Artificial Intelligence

Together with the University of Genoa, IIT has established the first ELLIS node to be approved in Italy. The ELLIS Society is a highly prestigious European network for fostering research in ML and AI. This large network (currently more than 30 partners) was created for three reasons: 1) ML is at the heart of a technological and societal AI revolution, 2) Europe is not keeping up, and 3) the distinction between academic research and industrial labs is vanishing. The goal of building a virtual lab is to create enough critical mass to train and maintain talent in this field in Europe and to transfer results from the disciplines of AI to products and services.

This is in line with IIT’s twin missions. In particular [taken from our Ellis webpage]:

“The overarching goal of the ELLIS unit in Genoa is to facilitate synergies between machine learning, robotics, and the study of natural intelligence. The research areas are (1) Machine Learning: from Data to Artificial Intelligence, (2) From Natural to Artificial Intelligence, and (3) Robotics: From Intelligence to Action. The mission of the ELLIS unit in Genoa is to develop foundational research in ML/AI, to strengthen ties with applied research at IIT and University of Genoa (including Robotics, Natural Intelligence, and ML for Health), and to cultivate an intellectually stimulating and engaging environment for faculty (PIs), junior researchers, and PhD students working across these areas. The unit also plans to strengthen and expand AI research in Genoa by hiring in key areas such as human-centered ML, reinforcement learning, online learning, and areas of mathematics that play an important role in ML (e.g. numerical optimization, probability and statistics, optimal transport). The ELLIS unit Genoa commits to promoting research excellence in ML and modern AI in Italy via dissemination and training activities, ultimately making the unit the reference point for ML in Italy and a key node for ML in Europe.”

Seven IIT PIs participate in the Ellis node in Genoa, with research topics including foundational ML, natural intelligence, cognition, robotics, and computer vision. IIT committed to supporting the network's development and grew the Ellis node. Over the next three years, the Brain Magnet Program will invest in hiring PIs in reinforcement learning and DL. These PIs will research the theory of machine intelligence and its applications to studying natural intelligence, robotics, materials science, healthcare, and life technologies. This complements IIT's investment in the field of HPC and will create enough critical mass to attract further funding to the group.

In addition, the TT plans to create a business accelerator are a complement to the AI ecosystem with Industry 4.0 resources (Competence Centers), the EDIH, and a network of VCs, funds, and so on. AI is one fundamental element of the innovation world.

Atomistic and Molecular Simulation

Within the Computational Sciences RD, Atomistic and Molecular Simulation is a strong area with exceptionally accomplished scientists. These scientists aim to develop and apply new methods to calculating, with high levels of accuracy, the thermodynamics and kinetics of molecular systems in life science (e.g. drug discovery) and materials science.

For instance, we have pioneered the field of molecular simulations applied to drug discovery with a focus on kinetics and residence-time prediction. IIT's novel methods have resulted in professional software, which is now part of BiKi Technologies, a high-tech SME and IIT start-up that commercializes software for drug discovery. Other examples of our expertise include multiscale simulations, continuum modeling (e.g. electrostatics), and the study of key biological mechanisms involving, among others, ribosomes and nucleic acids (e.g. metal-ion-mediated reactions).

Recently, Prof. Michele Parrinello joined the Computational Sciences RD. Prof. Parrinello is internationally recognized for his seminal contribution in the field of atomistic and molecular simulations. The Car-Parrinello method for ab initio molecular dynamics simulations has been used extensively worldwide, as demonstrated by the more than 12,000 citations of the paper that first reported this innovative approach. His other key contributions in the field include the development of a statistical mechanics approach, dubbed metadynamics, which is widely used for enhanced sampling simulations and free energy estimations in life science and materials science. IIT thus has international standing in the field of atomistic and molecular simulations, with IIT scientists having expertise in quantum chemistry, statistical mechanics, method development, and their application to biology, medicine, (nano)materials, and biophysics.

The next frontier in this field will be the systematic combination of atomistic and molecular simulations with ML and AI. Indeed, ML and AI is increasingly being used to identify patterns and regularities in the incredible amount of data generated by simulations, and to build models in chemistry, biology, and materials science.

In the near future, we thus aim to achieve three concrete objectives by combining ML with simulations. First, we will analyze extensive MD trajectories with ML-based algorithms to extract relevant information and hidden patterns that can then be used to generate reaction coordinates and physical paths. Second, we will develop and apply new potentials, using ML codes trained with quantum level theory calculations in order to generate reliable forcefields, particularly for the nonstandard functional groups in (in)organic molecules and nuclei acids (DNA, RNA, and chemical modifications thereof). Third, we will develop and apply generative methods for sampling simulative spaces and "inventing" new chemical entities in the fields of drug discovery and nanomaterial. By combining these models with molecular and atomistic frameworks, we may create innovative paradigms to study systems from atoms to mesoscale. The perfect match for these activities is our new HPC infrastructure, Franklin (256-GPU cluster), installed in September 2020, and technological support from the growing number of HPC developers/ software engineers. IIT is hence a fully rounded international reference center in the field of atomistic and molecular simulation, from theory to high-performance codes.

Non-Turing Computation

Sampling the distributions of interest in simulations (e.g. the Boltzmann distribution) requires unlimited computational power. This need has prompted the exploration of new avenues in non-Turing computation. Here, we have explored quantum technology (QT), based on state-of-the-art hardware and software and moving towards next-generation code for QT. The important challenges in quantum computing (QC) include scalability (namely a high number of qubits) and precision. Regarding precision, there are two major sources of errors in QC: i) the qubit latency related to the qubit's interaction with the environment; ii) the intrinsic precision for single elementary operations. To address these issues, two major technologies are emerging: i) adiabatic QC by DWave, for which the qubit connectivity is a major limiting factor; ii) gate-model QC based on superconductors (IBM, Google, Rigetti) or on trapped ions (IonQ, Honeywell, Alpine Quantum Technologies). The latter set of technologies is usually called "Quantum Computers" whereas adiabatic QC is less universal and related to functional form minimization (a fully non-Turing technology). Currently, superconductors are leading the competition, with IBM reaching 65 qubit and Google 53. Both companies are expected to achieve 1000 qubit by 2023 and 1M qubit by 2029. The hardware competition has already begun, with the US and China being the major players. A European strategy is therefore urgently needed (IIT can promote this request at the European level and participate in the current discussion and planned programs).

For the software, three different platforms give accessibility to QC: IBM, Amazon, and Microsoft. SDKs (Software Development Kits) are available to program the complex machines with mainstream computer languages (chiefly Python, C++, or Java). Just a few examples of application code have been reported, leaving many areas unexplored. The current applications include cybersecurity, quantum AI, and a smart way to solve the Schrödinger equation for quantum chemical calculations. Additionally, a promising application from the Canadian company ProteinQure aims to solve protein folding, which is one of the greatest problems in biology. Additionally, QT can impact logistics, financing, and risk analysis in the short-to-medium term.

Within this context and considering the cost of QC hardware, IIT will build a network of Italian academic and industrial players to develop innovative QC applications. This will involve a stepwise strategy. First, an entry-point investment will provide access to hardware resources for initial algorithmic implementation. This will be needed to achieve preliminary proof-of-concepts in quantum chemistry and quantum ML. Second, we will build a national QC network, including government institutions (IIT, INFN (National Institute of Nuclear Physics), the Trieste hub with SISSA, ICTP, universities) and multinational industries (Leonardo, ENI, ENEL, Telecom, UNIPOL). We will thus build national QC expertise, particularly in algorithms and codes. The national network (e.g. by creating a foundation) should also generate a critical mass of investments, visibility, and access to EU funds to allow the real-world deployment of the developed software, with the hardware development and know-how involving a European effort.

Bridging the Gap between Neuroscience, Materials Science, Machine Learning, and Artificial Intelligence

Neuroscience at IIT reflects the complexity and breadth of modern neuroscience. IIT neuroscientists work with diverse tools and at multiple levels of organization (molecular, cellular, circuits, systems, and behavior) to link fundamental neuronal mechanisms to behavior and cognition. Neuroscience plays a crucial role in AI (and vice versa), bioinspired robotics, and nanomaterials for healthcare. Multiscale neuroscience at IIT is thus key to IIT's vision of a "true interdisciplinary synthesis among disciplines". The broad molecular-to-cognitive spectrum of research activities makes IIT Neuroscience uniquely positioned to engage synergistically with other IIT research endeavors, both within the LifeTech RD, and with the Computational Sciences, Robotics, and Nanomaterials RDs. Therefore, a priority goal for the next three years will be to promote the partnership between neuroscience, AI, materials science, and robotics, and thereby contribute to IIT's missions of promoting excellent and translational science, and new human-centered science and technology.

AI and ML are transforming the ability to explore how neural computations work at different hierarchical levels in both health and disease, from molecules and genes to synapses, neurons, circuits, and human behavior and cognition. This effort might lead to major discoveries and disruptive technologies for healthcare, such as machines that can take on more human-like intelligence and directly interact and interface with natural intelligence. Key to these developments is understanding how the nervous system processes and exchanges information at all scales of organization. IIT is well-positioned to contribute to this endeavor, with a portfolio of basic neuroscience from animal models to humans, including neurogenomics, pharmacology, synaptic and circuit physiology, neurodevelopment/plasticity/regeneration, integrative and network neurophysiology, computational neuroscience, and cognitive neuroscience. In addition, IIT has a wide range of neurotechnologies, including single-molecule technology to reveal the dynamic organization of molecular complexes at the nanoscale; neuroelectronic devices and optical methods to stimulate and record large-scale networks with high resolution; non-invasive and minimally invasive recording and stimulation methods for humans; hybrid prostheses to restore impaired function; fine behavioral measures and motion capture; neuroimaging; computational methods for the analysis and modelling of data bridging multiple scales; hybrid interfaces for communication between neurons and devices; assistive and bioinspired robotics, including adaptive brain-robotic interfaces based on emotion-driven controllers; and applications of robotics for healthcare.

To this end, coordinated activities with the Ellis initiative at the interface between artificial and natural intelligence will boost the transfer between neuroscience, sensor engineering, and cognitive robotics. The aim is to derive new brain-inspired algorithms for ML and AI and to use computational methods to better understand the brain.

The promotion of a mutual reinforcement between neuroscience, AI, materials science, and robotics will strategically advance our neuroscientific knowledge and facilitate the flow of basic neuroscience into applications ranging from wearable neuroelectronics and bioartificial hybrid devices to innovative sensory engineering solutions for prosthetics, rehabilitation, assistive robotics, and cognitive robotics. This neurotechnology ecosystem will boost IIT's capacity to develop industrial collaborations and spin-off opportunities to produce neurotechnology devices. This will include the strategic development of processes and partnerships for their certification for use in humans.

Besides the above-mentioned computational approach to neuroscience, which has a long tradition of interaction with AI, we stress the technological aspect. IIT is strong in developing innovative neural interfaces by studying different principles of recording and modulation (e.g. chemical, optical, electrical), biohybrids and neuromorphic technologies, organic materials and fabrication technologies, and the integration of intelligent algorithms. IIT will further develop tools to record and analyze the brain at all scales of organization. This technology can be used for novel biomedical devices for monitoring or intervention in healthcare in the domain of neuroprosthetics and interactive robotic applications.

In terms of critical mass, IIT's neuroscience is extremely qualified, having secured 17 ERC and 7 NIH grants. International visibility is also growing, with regular publications in first-class journals such as *Science, Nature, Nature Neuroscience*, and *Neuron*.

Appendix 6: Acronyms

2D: Bidimensional materials

AD: Alzheimer's Disease

AI: Artificial Intelligence

ASD: Autism Spectrum Disorders

BBB: Blood Brain Barrier

CABHC: Center for Advanced Biomaterials and Healthcare, Naples

CBN: Center for Molecular Biotechnologies, Lecce

CCSL: Center for Computational and Statistical Learning, Cambridge (USA)

CGS: Center for Genomic Sciences, Milan

CHT: Center for Human Technologies

CINECA: Italian Supercomputing Center

CLNS: Center for Life Nanoscience, Rome

CMBR: Center for Microbiorobotics, Pontedera (PI), effective until December 2020

CMI: Center for Materials Interfaces, Pontedera (PI), effective from January 2021

CNB: Center for Nanotech for Brain, Boston (USA)

CNCS: Center for Neuroscience and Cognitive Systems, Trento

CNI: Center for Nanotechnology Innovation, Pisa

CNST: Center for Nanoscience and Technology, Milan

COMPUNET: Computational Sciences

CRL: Central Research Laboratory, Genoa

CSFT: Center for Sustainable Future Technologies, Turin

CTNSC: Center for Translational Neurophysiology of Speech and Communication, Ferrara

DS: Down Syndrome
DTI: Diffusion Tensor Imaging
EEG: Electroencephalogram
EM: Electron Microscopy
ERC: European Research Council
EU: European Union
FET: Future and Emerging Technologies
fMRI: Functional Magnetic Resonance Imaging
HD: Huntington's Disease
HPC: High Performance Computing
HRC: Human-Robot Collaboration
IEO: European Institute of Oncology
IFOM: The FIRC Institute of Molecular Oncology
INAIL: Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro (National Institute for Insurance against Accidents at Work)
IP: Intellectual Property
IRCCS: Istituti di Ricovero e Cura a Carattere Scientifico (Scientific Institutes for Research and Care)
ISS: Istituto Superiore di Sanità (National Institute of Health)
LifeTech: Technologies for Life Science
ML: Machine Learning
Moog@IIT: IIT-Moog Joint Lab
MTDLs: Multitarget-directed Ligands
NANOMATERIALS: Nanotechnology and Materials
NCs: Nanocrystals
NDGDs: Neurodegenerative Diseases
NDVDs: Neurodevelopmental Disorders
NIC@IIT: IIT-Nikon Joint Lab
NLP: Natural Language Processing
NSYN@Unige: Center for Synaptic Neuroscience, Genoa
PD: Parkinson's Disease
PET: Positron Emission Tomography
PI: Principal Investigator
RM: Robotic Models
RD: Research Domain
SPTs: Single-Particle Tracking Techniques
TT: Technology Transfer
WHO: World Health Organization

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