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ANNEX

IIT 2018-2023 Technical Annex

CONTENTS

Robotics

Description of 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 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 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 (see Fig. 1). Some of these Priorities have a thematic character (Social Cognition and Human Robot Interaction, Intelligent Companion Robots), while others have 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, biomedical applications).
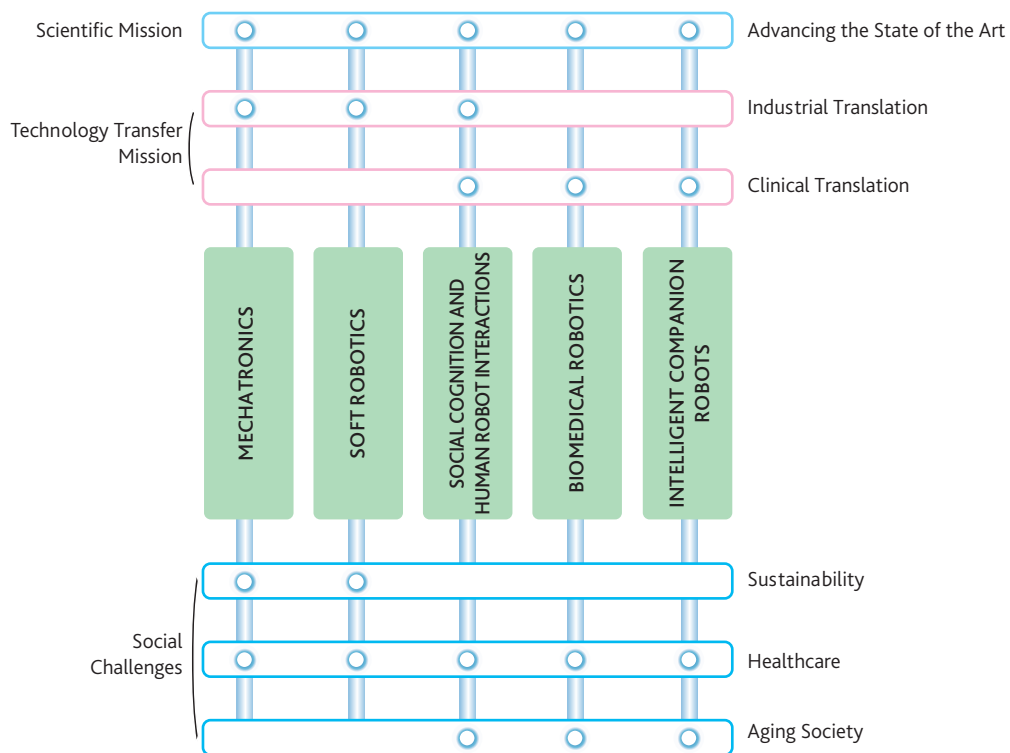

Fig. 1. Priorities of the Robotics Research Domain, contribution to IIT's mission, and impact on the challenges.

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, thus creating new products and innovative industrial processes. To achieve clinical translation, we will create a national Clinical Hub with top clinical research institutions to transfer medical robotics research to the clinic (in close connection with the LifeTech RD). Robotics will thus positively impact the XXI century's challenges of sustainability, healthcare, and aging.

How to fulfill the Scientific Mission: advancing the state of the art

To fulfill IIT's Main Scientific Mission, the Robotics RD will continue to pursue and expand the successful research lines established in the Institute's first 10 years. The Robotics RD agenda 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). In particular, our research program will focus on designing novel "bodies" with new materials carefully engineered to improve performance, efficiency, and reliability. The future "mind" of the robots will include many AI techniques to achieve adaptability, friendliness, and ease of use in the most disparate environments. 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 exploit fully 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.

How to fulfill the Technology Transfer Mission: industrial and clinical translation

In recent years, IIT's robotics has experienced tremendous growth in the number of Technology Transfer activities. IIT used a broad spectrum of contractual instruments, ranging from traditional sponsored research, start-up, and licensing arrangements through to joint laboratories. IIT already collaborates with Avio Aero, Alsaldo Energia, and Tetrapak under focused research-driven agreements. Joint Labs are particularly relevant. The Moog@IIT Joint Lab will result in the next generation of hydraulic actuators. A Joint Lab with Gruppo Camozzi SpA will study collaborative robots for Industry 4.0. With Danieli Automation, IIT will develop applications for the steel production industry. IBM is helping develop AI packages for the R1 robot in a number of important contexts, such as healthcare. There have also been several start-up activities, the most notable being Movendo Technology in the field of rehabilitation robotics. At the other end of this technology transfer spectrum, we signed a license agreement for our exoskeleton technology with MRK-Systeme GmbH. 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, HalfMan, HyQ), either in their current form or following further development. These projects will be expanded to clinical applications in the domain of robotic surgery (IRCCS S. Martino-IST and IRCCS G. Gaslini Children's Hospital) and in the so-called theranostic robotics program (IRCCS G. Gaslini Children's Hospital). In the latter program, IIT will develop sensorimotor intervention protocols for children with autism spectrum disorder (ASD), using simplified versions of our humanoid robots. With INAIL (IIT-INAIL Joint Lab), we will continue and broaden our development of prostheses (hand, leg), exoskeletons (lower limb), and rehabilitation devices (shoulder).

Contribution to the 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. 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 multi-armed 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.

Contribution to the Aging Society Challenge: intelligent robots

A demographic megatrend will soon affect many developed countries with 40% of the population over 65 by 2050. According to estimates, the 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 greater and more diverse 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. 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 and assistance will ensure that the costs of care for the elderly can be contained, while maintaining or even improving the quality of this care. This

will require robots that are partially autonomous, with advanced AI technologies that provide intuitive interfaces. These robots will need to understand the cognitive and social mechanisms involved in human interaction and natural communication. The goal is to create robots that can monitor a patient's condition, survey a hospital ward, and provide companionship. Importantly, these robots must be affordable enough for the social security systems to subsidize them.

Contribution to the Healthcare Challenge: affordable rehabilitation, surgery, and prosthetics

The forerunner of robotic applications to healthcare is certainly rehabilitation. 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 hand 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 (cf. agreements with IRCCS S. Martino-IST and IRCCS G. Gaslini Children's Hospital). Robots can also contribute to improving the quality of life for people with ALS and Alzheimer's disease, and provide therapy for children with autism spectrum disorders (ASD). In addition, assistive technologies, such as R1, will result in robots that routinely provide care, companionship, and general assistance in home settings.

Description of the priorities of the Robotics Research Domain

From 2018, the Robotics RD laboratories will move to IIT's new Center for Robotics (San Quirico building). The Center for Robotics will house a new enlarged mechanical workshop with full CAD support, the IIT-INAIL Joint Lab on robotic rehabilitation, and the industrial Joint Labs with MOOG, Danieli Automation, and Gruppo Camozzi SpA. Additional activities at the Center will be developed jointly with the Center for MicroBioRobotics (CMBR) at Pontedera (in collaboration with Scuola Superiore S. Anna), the new machine and deep learning teams of the Computational Sciences RD, and the teams of the LifeTech RD, in the Center for Human Technologies in the Erzelli building. In the next years we expect Robotics RD to increase its staff of about 10% (staff to date: more than 300 - including 15 PIs and about 80 technicians) with the inclusion of new PIs in the fields of locomotion and machine learning.

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, HalfMan) (see Fig. 2). IIT's family of cutting-edge robots is not limited to legged systems. With the "Plantoid" robot series, inspired by solutions found in plants, the Mechatronics program has explored completely new designs and operational paradigms, including materials, compliance, soft bodies, and distributed intelligence.

Fig. 2. The IIT Robot Species.

In addition to our advanced integrated robot platforms, IIT researchers have developed component-level systems, including novel patented high-performance actuation systems, variable impedance actuators, advanced fingertip as well as 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 Scientific Program (and beyond), the Mechatronics program will continue to develop new bodies for our integrated robotic systems, particularly for humanoid and legged robots. 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 and sustainable 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 and decentralized diagnostics inspired by the new concept of "smart, high-performance mechatronics".

Looking to the market, systems such as R1 have been designed for prompt, affordable market applications. Here, the engineering goals require that we reduce mechanical complexity (fewer 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 the so-called 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 R1 applications 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.

In robot locomotion, where a flexible control strategy demands step recovery, walking, and running on possibly uneven terrains, advances will require the close integration of engineering (sensing, actuation, and mechanics), gait generation, dynamic modelling, and control. The Mechatronics program will investigate locomotion, gait generation, and gait control in both bipeds and quadrupeds. With several robust platforms available (iCub, WalkMan, COMAN+, HalfMan, HyQ), 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 on flat and moderately rough terrain will include very challenging environments (e.g., soft and unstable terrains). The locomotion framework will reach higher levels of autonomy, allowing automatic selection of the most suitable gaits/behaviors for the environment. We will use combinations of machine learning 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 control. Torque regulation (through hardware and software) will be critical to success in this domain. At IIT, robots such as WalkMan, COMAN+, HalfMan, and iCub feature fully integrated torque sensing and controllers. In the near future, exciting developments in controller design will advance the functionality of these robots, and fill a crucial gap in humanoid technology.

Human-robot collaboration, where robots and humans share the workspace, will require flexible engineering structures (e.g., compliant bodies) coupled to active compliance and torque-control software. Future activities will address real-time monitoring of human behavior (whole-body dynamics estimation) in order for the robot to learn anticipatory behaviors 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 road map to develop new nanocomposites, biodegradable plastics, sensors, and high-performance batteries/capacitors 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., HalfMan, COMAN+, HyQ).

Soft robotics will also make extensive use of 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 (e.g., McKibben muscles).

Priority 2: Soft Robotics Program

Soft robotics is a new area of robotics that uses compliant and deformable materials to develop flexible, safe, and adaptive bioinspired robots. Soft robotics requires special sensing (soft sensitive skins, deformable sensors) and actuation (compliant artificial muscles, variable stiffness structures, responsive polymers). Its primary impact is on interaction (soft contact, delicate manipulation) and emotions (facial expression, social and cognitive skills, body posture). Although robots that use compliant structures (e.g., series elastic and variable impedance actuators) are often considered "soft", IIT's soft robotics program specifically focuses on 'robots made from soft materials'.

For the 2018-2023 Scientific Plan, the Soft Robotics program will focus on developing continuum robots (i.e. with similarities to the elephant trunk and cephalopod arms) that can grow, evolve, self-heal, and biodegrade. The goal is for these continuum robots to traverse confined spaces, manipulate objects, and reach difficult-to-access sites. Potential applications will be in medicine, space, inspection, and search-and-rescue missions. The Soft Robotics program will require an unprecedented multidisciplinary effort combining biology (e.g., study of plants), materials science (e.g., responsive polymer synthesis), engineering, and biomechanics.

One important element of the Soft Robotics program will explore the "moving by growing" paradigm (GrowBot). Plants grow and continuously adapt their form to the external environment. We aim to design plant robots that deposit and process raw materials to grow and bend in space. In this case, a 3D layer-by-layer manufacturing process inside the robot's body will be combined with the ability to deposit new raw material upon external stimulation without a predefined design. This will require the development of new materials and bioinspired perception and behaviors, such as circumnutations and tropisms. The end goal is to develop 4D-printer-based growing robots with sensing and grasping capabilities. The scientific/technological activities will include: (i) studying growth mechanisms in plants for their relevance to, for example, the design of climbing plant-inspired robots, (ii) developing multifunctional materials for the growth process, and (iii) developing the perception and behavior of the growing robots.

An important consequence of this work is "reverse biorobotics", which uses bioinspired robots as experimental models. Although biologically simple and containing no living matter, robotic models (RM) could be extremely useful for experimentally investigating behaviors that are otherwise difficult to observe. RMs could also be used to simulate entire species that are extinct, loosely defined, or even hypothetical. RMs will test and validate biological hypotheses of plant root development, for example, or how mechanical and environmental stimuli affect root growth.

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:

- How to control its own actions to achieve a goal (i.e. anticipate the effects of its own actions) in a way understandable by a human;
- 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 as well as the human's intentions and skills.

Apart from being predictable, robots need to, in general, interact in a human-like social manner, appearing friendly, attractive, and intuitive in 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 interactions. At IIT, this research will use the methods of cognitive and social neuroscience in well-controlled experimental protocols, in which:

- Robots will exhibit behaviors typically observed in human social interactions, e.g., gaze following, human-like movement kinematics, social gestures;
- Human brain reactions will be measured using behavioral parameters such as eye tracking, motion capture, performance measures, and neurophysiological measures such as EEG; and compared to brain activity in natural social human-human interactions;
- Subtle parameters of robot behaviors will be iteratively manipulated to obtain optimal responses (brain and behavioral) from the human user.

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

One very special type of interaction involves speech, which, according to recent neuroscience research, has a shared acoustic-motoric representation in the brain. Despite advances in automatic speech recognition (ASR), it is still problematic for robots to recognize speech during human-robot interactions. This task typically demands 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 will help to tackle the so-called cocktail party problem, as well as the use of multimodal signals (e.g., acoustic and visual).

Conversely, Human-Robot Collaboration (HRC) focuses on the physical nature of the cooperation between the human(s) and 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 interdisciplinary targets:

i. Modelling and analysis of human behavior during physical interactions;
ii. Intermediate interfaces to improve how the interaction is perceived by the human and the robot (bidirectional);
iii. Human-in-the-loop robot planning and control.

The first research target investigates reliable and intuitive human-robot interfaces that rely on or are inspired by human motor functionalities. The second and third research targets aim to enhance the performance of the human-robot-environment physical 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 an improved perception of people's 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 S. Martino-IST, IRCCS G. Gaslini Children's Hospital, and the Italian Ministry of Health's National Networks of Clinical Research Institutes). It also collaborates with INAIL through the IIT-INAIL Joint Lab established in 2014 and its latest extension (started in 2017). Under the 2015-2017 Strategic Plan, the Program developed medical systems, starting from a single research prototype right through to creating a start-up company (e.g., from the ARBOT project to Movendo Technology). For the period 2018-2023, we will develop this core expertise further.

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 S. Martino-IST, IIT Robotics is 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 Micro Surgery (μRALP). 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 has the goal of transferring IIT's assistive technologies into high-tech medical products. The strong technology transfer 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 a 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 to 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. 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 the Bodyware and Mindware for interactive robots. It integrates research from several IIT Programs, including mechatronics, materials, machine learning, vision, and human-robot interaction (see Fig. 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 (machine learning 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 technologies (NLP) via Bluemix and Watson. With NVIDIA, we are adding embedded GPUs to our robots to enable deep learning in situ. Additionally, we have signed an agreement with Vodafone to test 5G technologies that will keep robots connected to the cloud with low-latency radio links. End users are also already "on board". With the IIT-Fondazione Don Gnocchi Joint Lab, R1 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 the development of "smart grippers" for safe human-robot collaboration. We are porting iCub control and vision software to special robotic hardware for a leading international company in the entertainment sector. Finally, we will use iCub in intervention protocols for neurodevelopmental disorders (NDVDs) at IRCCS Gaslini Children's Hospital as well as human-robot social interaction approach to engage the elderly in cognitively stimulating "games", which integrate neuropsychological tests of memory, attention, and executive function.

The Intelligent Companion Robots program revolves around the ability to integrate components seamlessly owing to 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.
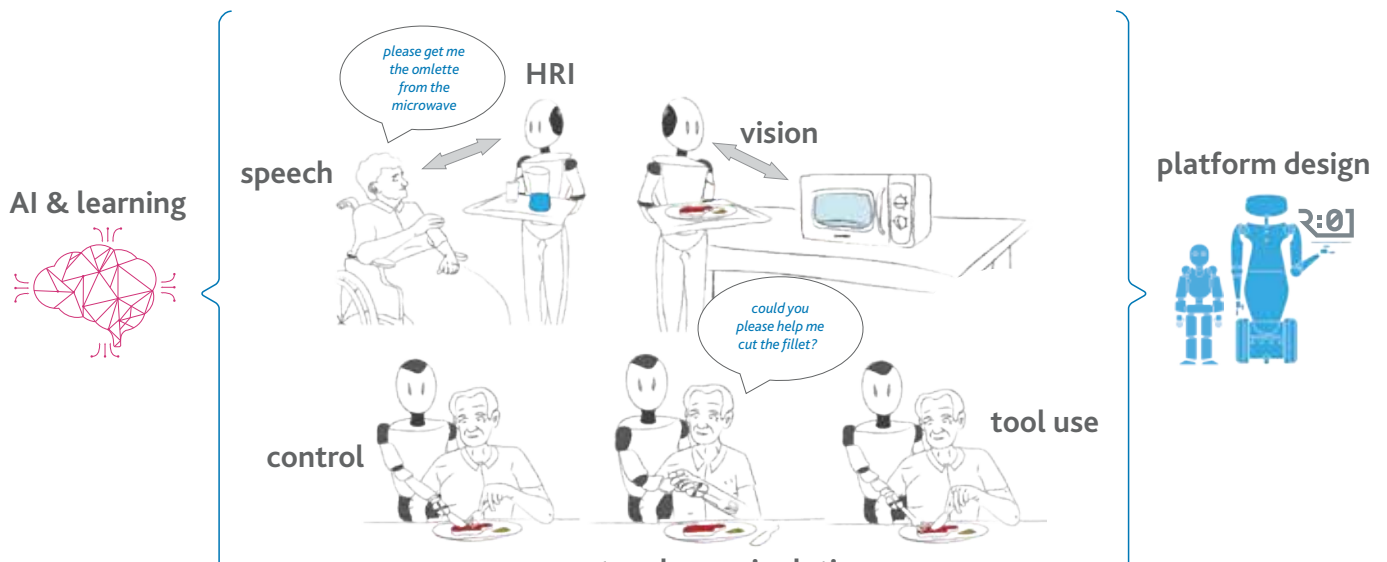
Fig. 3. A cartoon-like representation of the companion research areas.

The iCub humanoid is an example of successful companion robot development. It has been built in 36 copies and is used by researchers as far apart as Japan, Korea, Singapore, and the US. The next major version, iCub 3.0, is planned for release in the first quarter of 2018. It will deliver improved physical performance for the control of whole-body movement (walking while reaching, grasping, etc.), 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), which has also inspired research into graphene-reinforced polymers. 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, increasing its ability to negotiate small obstacles and rougher terrains (within the limits set by the wheels - see Fig. 4).

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 R1; developing new materials that combine biodegradable polymers with 2D fillers (such as graphene); and, with the help of machine learning and AI, simplifying robot programming to support commercial and clinical use.

For the skin system, we will work with IIT's Smart Materials team to develop and manufacture solutions that use graphene on stretchable substrates or conductive silicones. Because of their simplicity (to build and decode), we will design capacitive sensors on new material substrates that exhibit the desired mechanical properties. This will provide high sensitivity and resolution where needed and, generically, low hysteresis. We will prioritize solutions that allow automatic production (e.g., inkjet printing). Improving the skin system will improve the sensing, grasping, and

Fig. 4. The humanoid programs (companion robots).

tool use. In combination with machine learning, this will allow the development of rich representations of objects to support in-hand manipulation and to discover object affordances. For example, recent results on 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.
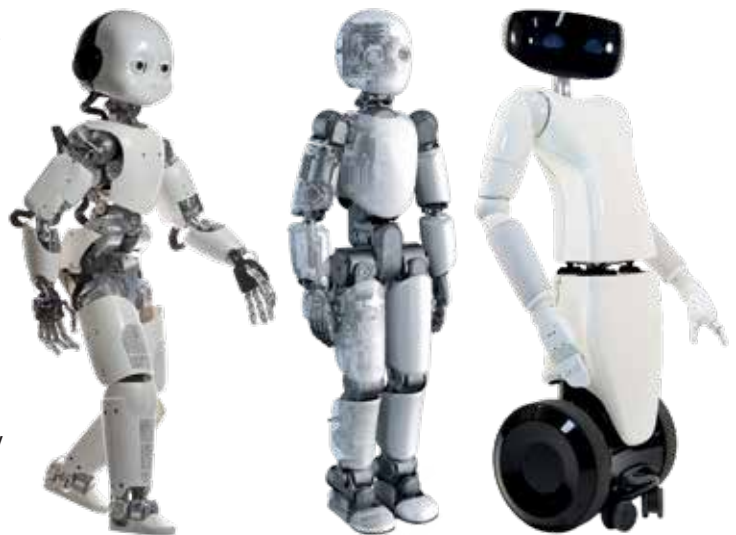
We will work with biodegradable plastics of vegetal origin, enriched by nanofillers to tune their mechanical properties. We will adapt these plastics for the additive manufacture of robot components. The robot will thus biodegrade at the end of its life cycle. We will explore the use of conductive and semiconductive inks to print circuit boards directly onto the robot's scaffold, reducing wiring and simplifying manufacturing. By means of new materials, we also aim to evolve the companion robots 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, 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 non-expert 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 also 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 "Fig. 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 compression (on FPGA or GPUs).

Nanomaterials

Description of the Nanomaterials Research Domain

The Nanomaterials Research Domain is built on expertise in materials science and nanotechnology and on IIT's unique interdisciplinary environment. Research will focus on four priorities (see Fig. 5). The first priority is to develop materials and nanotechnologies to improve the quality of our life and our 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, material 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 and final priority is more fundamental, dealing with curiosity-driven research into new materials such as colloidal nanostructures and 2D materials in the framework of the Graphene FET Flagship program.
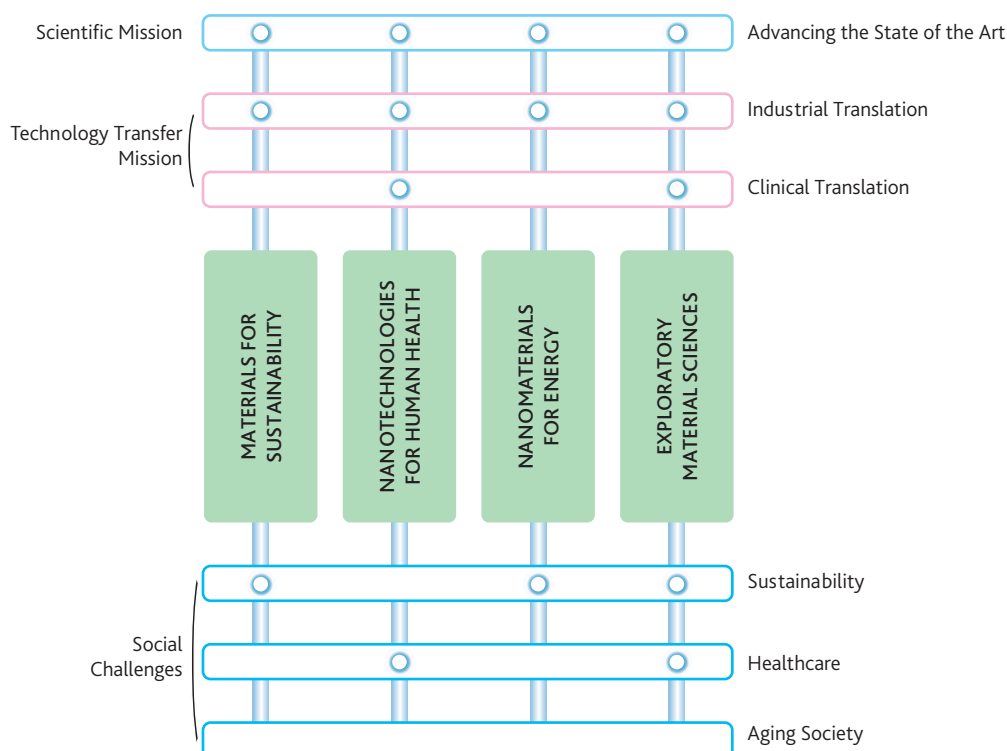

Fig. 5. Priorities of the Nanomaterials Research Domain, contribution to IIT's mission, and impact on the challenges.

Contribution to the first Mission: Advancing the state of the art

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 capability will be enhanced by the new polymer synthesis team, by

establishing new laboratories to investigate matter under harsh conditions (at high temperatures, high pressure, and when exposed to various chemicals and ionizing radiations), by the new ultra-high-resolution electron microscopy system and by a new time resolved electron microscopy laboratory.

Contribution to the second Mission: transferring new ideas to the production system or to clinic

Around half of IIT's industrial projects and 37% 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. For the next years, we forecast strong growth in our translational activity, thanks to a rising number of collaborations of our Joint Labs with several industrial partners. The Nikon Center will be 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 2018, the Nanomaterial RD will start the activity within the Joint Labs with the Camozzi Group (to develop new materials for high-performance actuators) and Directa Plus (to develop water-remediation technologies based on graphene and foams). The Joint Lab recently launched with the Novacart Group will develop sustainable solutions for food containers.

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.

Contribution to the Social Challenge of Sustainability: development of technologies for sustainable production and a safe 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 performances and a lower environmental impact.

Our planet's natural resources are massively exploited by its human inhabitants. Its systems cannot fully absorb, metabolize, or neutralize the waste that we are generating. This has a strong negative impact on the quality of our air, water, and food. For human health and for the environment, the most alarming and harmful type of waste is represented by plastics, electronic and electrical waste (e-waste), endocrine-disrupting chemicals (from e-wastes and plastics), and nanomaterials in general. 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 generates no waste or pollution. Governmental and institutional support for the circular economy is rising. The United Nations' 2030 Agenda of 17 Sustainable Development Goals also reflects growing acceptance of this paradigm. In line with this concept, and in order to fulfil the Social Challenge, the Nanomaterials RD will develop new technologies for water safety and sanitation, new strategies for CO_2 valorization and conversion, and innovative materials made from vegetable waste, food waste, and converted CO_2. These contributions will drive future industrial production, helping to achieve the sustainable development goals. We are targeting 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 towards 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.

Contribution to the Healthcare Social Challenge: Develop technologies for affordable and personalized therapies and diagnoses

By 2020, the World Health Organization estimates that people over 65 will outnumber children under 5, with over-65s making up 35% of the world's population. However, 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 disease origin and progression 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 a 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, 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. The main research lines that we will pursue are the following:

▮ 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.

Description of the priorities of The Nanomaterials Research Domain

Most of the research and technology activities of the Nanomaterials RD will be carried out at IIT's Central Research Laboratory (Morego building), exploiting the four facilities (clean room and nanofabrication, electron microscopy, physical and chemical characterization, and pharma chemistry) and four industrial Joint Labs (Nikon, Camozzi, Directa Plus, Novacart) established there. The Nanomaterials RD is strongly supported by a laboratory network that includes centers at CNI-Pisa, 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 next years the Nanomaterials RD should grow about 10% (staff to date: more than 460 - including 22 PIs and about 35 technicians), with the inclusion of new PIs in the fields of advanced electron microscopy, chemistry and materials science.

Priority 1: Nanomaterials for Sustainability Program

This program will have at its core 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 Fig. 6) 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

Fig. 6. Biopolymer composites from vegetable wastes.

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., agro-waste 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.

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 lines to make packaging: i) more sustainable and cheaper; and ii) more active in preserving food and monitoring its quality. In the first 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 upon 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.

Fig.7. Milk spoilage indicator.

In the second line, we will insert spoilage sensors and indicators directly into the packaging material, significantly advancing the technology of active packaging (see Fig. 7).

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, CO_2, 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 very simple and fully passive (like antennae integrating a sensor), or more complex, comprising a power source, logic circuitry, sensors, and a transmitting module.

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);
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 be addressed also in the 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:

i.   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.
ii. 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 currently an underexplored field. We will integrate microfluidics and advanced nanofabrication techniques in order to deliver a new generation of on-chip bioassays.

Combinatorial nanoconstructs for imaging and drug delivery

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

i.   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 Fig. 8). We will modulate the 4S parameters to modulate nanoconstruct accumulation within diseased tissues and blood longevity in a patient-specific fashion.

ii. 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.
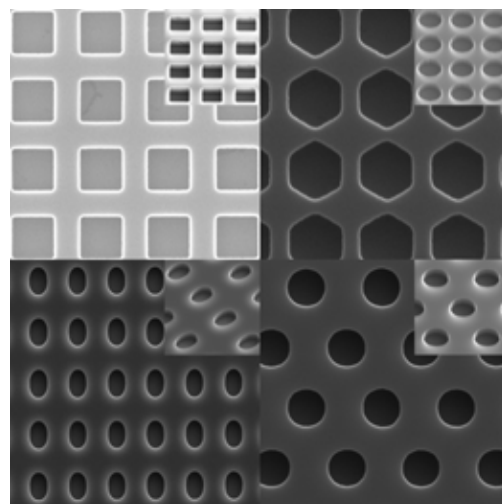

Fig. 8. Tailoring the size, shape, surface, and stiffness (the 4S parameters) of nanoconstructs via a flexible top-down strategy.

iii. 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 (see Fig. 9) 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.
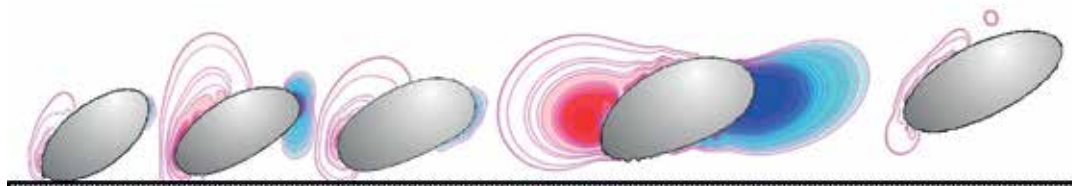

Fig. 9. Computational model of the transport and flow field around a soft elliptical nanoconstruct close to a blood vessel wall.

Organic 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 (see Fig. 10). 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. 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 higher 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.
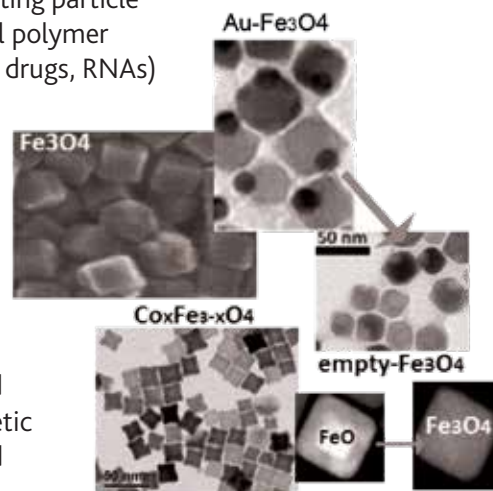

Fig. 10. Shape-controlled superparamagnetic nanocarriers.

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 (see Fig. 11). We will develop scaffolds with specific geometries, 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. 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/nano capsules. 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-inflammatory, and antibiotic performances. Drug release will be controlled by environmental cues such as humidity and pH. Growth factors and electrically conductive inclusions, such as graphene, will be incorporated.

Fig. 11. Biomedical devices made of natural polymers loaded with active principles.

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, likely due to complex aspecificity issues (e.g., LAMP and NEAR). We will also seek to develop novel reactions by combining the particular physico/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

This program will tackle important challenges related to energy conversion and storage. It comprises three main research lines, which tap three areas of expertise at IIT:

i. halide-perovskite-based solar cells;

ii. Li-ion batteries and supercapacitors based on 2D materials;

iii. technologies for capturing, purifying, and converting CO_2 into fuels and useful chemicals.

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

Building on recent IIT 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 the 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. In tandem, we will develop materials processing for large-area deposition. This must preserve the efficiency already achieved, while targeting environmental 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; to deliver novel device concepts; and to convert the proofs of concept into large-area modules and flexible PV devices with enhanced performances. Through a collaboration with an external industrial partner, we will develop 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.

Low-dimensional materials for Li-ion batteries and supercapacitors

This activity targets at 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, 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 the attempt to develop hierarchical (2D and 3D) electrodes to improve their performances. On a similar footing, 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 CO_2 into fuels and useful chemicals

This line will combine our consolidated activities with that of new teams established in 2017. The main activities will be:

Development of new materials and methods for CO_2 capture

These will include:

i. ionic liquids derived from natural sources;

ii. use of deep eutectic solvents;

iii. polymeric solutions functionalized with CO_2-philic groups;

iv. 3D-printed polymeric structures composed of CO_2-philic materials acting as sorbent membranes.

New catalysts for CO_2 reduction

We will search for efficient catalysts that can reduce CO_2 in the presence of H^2 or other reducing agents that use thermal-, photo-, electro- or biologically mediated reactions. We will use different synthesis techniques to fine-tune 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 CO_2 conversion will be supported by extensive computational modelling.

Efficient electrochemical reduction of CO_2 into fuels and useful chemicals

Here, we will address two scenarios:

i. a low-cost, high-efficiency, grid-connected reactor, producing reduced forms of CO_2 from concentrated streams;

ii. 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 CO_2, 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 non-photosynthetic 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 thermal- and electro-catalytic routes. Combining experimental and modeling tools, we will focus on two families of materials: supported bimetallic nanocrystals 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

Exploratory Nanomaterials Science encompasses the most fundamental research done by IIT in the field of Materials Science and Nanotechnology. It is based on the considerable expertise of IIT in materials synthesis and advanced characterization. This area, traditionally focused on colloidal nanomaterials, has recently been expanded with the constitution of new teams working on novel 2D materials and polymer synthesis. The behavior of materials at the nanoscale is strongly connected with these themes, as understanding the fundamental physical and chemical processed in nanoscale materials is an essential step for their successful integration in many technologies. This whole 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/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, laser hyperthermia, and smart windows; 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 the use of various chemicals (including in the gaseous phase) that can directly react with the nanocrystals 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.

Study of transformations in nanomaterials under extreme conditions

Researchers are still in the very 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 postsynthetic transformations in nanomaterials. The main objectives are:

i. to develop new sets of experimental tools to investigate chemical transformations in nanomaterials;
ii. to understand the role of irradiation in the fate of surface ligands and in 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 allows 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 powder X-ray diffraction and single crystal electron diffraction on nanocrystals. The latter will be specific to investigating unknown crystal grains and solving their structure.

2D Materials

IIT is one of the leading partners in the European FET Flagship Graphene. In this context, IIT will target the production, investigation, and device application of a wide portfolio of 2D crystals (see Fig. 12). Two main lines will be pursued:

i. synthesis of 2D topological insulators and novel 2D materials;
ii. solution processing of novel 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. In the second line, we aim to develop solution-processable functional materials, understand their (opto)electronic and electrochemical properties, and develop self-powered wearable devices, nanocomposites with on-demand properties, and energy

Fig. 12. A selection of 2D-crystal-based inks developed by IIT.

storage and conversion technologies. We will obtain 2D crystals 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.

Description of the Technologies for Life Science (LifeTech) Research Domain

The Technologies for Life Science (LifeTech) Research Domain will focus on three Priorities as shown in Fig. 13. The first Priority (Neuroscience and Brain Technologies) originates from IIT's traditional core activity of neuroscience. The plan is to develop new optical, computational, optogenetic and molecular tools to efficiently monitor and manipulate brain circuits at multiple organizational and spatio-temporal scales and to continue to study the fundamental processes at the basis of brain activity. 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 within this Priority are curiosity-driven, and are being carried out by several PIs finishing their tenure track in 2018-2019 (evaluation expected by the end of 2018).
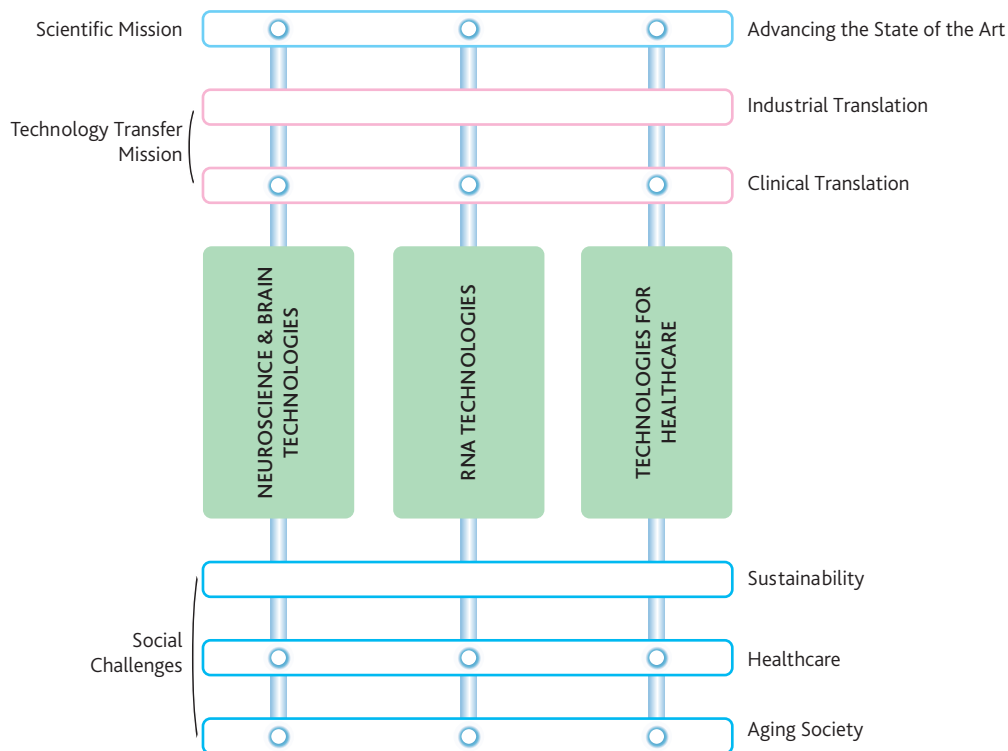

Fig. 13. Priorities of the LifeTech (Technologies for Life Science) Research Domain, contribution to IIT's mission, and impact on the challenges.

The other two Priorities involve an evolution from a purely fundamental life science domain to a technological approach to life science which is characteristic of IIT:

i. RNA Technologies: a post-genomics approach dealing with the genome's non-protein-coding portion. We will study the role of non-coding RNAs (ncRNAs) and repetitive elements in the physiology and dysfunction of the human brain. We will also investigate how these molecules can be exploited for a new generation of innovative theranostics in personalized medicine. While based on fundamental science, this Priority is likely to have a strong technological and translational impact.

ii. Technologies for Healthcare: this Priority is a unique outcome of the multidisciplinary knowhow of IIT. It deals with 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 Laboratories 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 (such as mechatronic hands and artificial retina), robots for physical and neurological rehabilitation, and sensing technologies for blind patients.

The two new Priorities of the LifeTech RD merge the traditional neuroscience knowledge of IIT with those of Priorities 3 and 4 of the Robotics RD (*Social Cognition and Human Robotics Interaction and Biomedical Robotics*), as well as 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 unforeseen technological innovation. The success of this 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.

Contribution to the first Mission: advancing the state of the art

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 these into interpretable neurophysiological events or models that can help us understand how the brain works in health and disease. This limits the development of new diagnostic tools and identification of new targets to treat neurodevelopmental diseases (NDVDs) and neurodegenerative diseases (NDGDs). This crucial "explanatory gap" drastically limits the return on investment of the world's various human-brain-mapping initiatives.

The first Priority of Fig. 13 aims at reducing such an explanatory gap between the detailed neural circuits studied in animal models and their translation to human brain function and dysfunction. To this purpose, 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) computational methods to integrate studies of different scales, to study the brain's functional organization, to identify disease causes, and to make predictions about potential cures; iii) genetic and molecular technologies to exploit the non-coding portion of the genome; and iv) interdisciplinary combinations of these techniques.

Concerning the second Priority, IIT will study ncRNAs and repetitive elements in brain transcriptomes and genomes. Large genomic projects (e.g., the ENCODE and FANTOM Consortia) have enormously 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 non-coding 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 are 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.

Contribution to the second Mission: Creating large-scale infrastructure for Human Technologies and transferring new ideas to the clinic

The third Priority of Fig. 13 is expected to impact substantially on the transfer of IIT technologies to healthcare. To this aim IIT will set up new comprehensive infrastructures dedicated to Human Technologies (the Center for Human Technologies - CHT - at the Erzelli building). The goal is to assemble a collaborative network of Joint Labs

and research/university hospitals. In the start-up phase, CHT will be 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 S. 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 1 p. 33). 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;

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.

After the start-up phase, the initiative will 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.

Contribution to the Social, Healthcare, and Aging Society Challenges: Precision medicine for NDVDs, NDGDs, and other diseases

IIT seeks to develop technologies to address different categories of diseases including Neurodevelopment Diseases (NDVDs) and Neurodegenerative Diseases (NDGDs), blindness, sensorimotor impairment, and physical impairment due to ageing. All carry staggering social and economic costs. 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, with individual lifetime costs exceeding 3 €M 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 177 €billion.

In this context, IIT plans to:

❚ increase knowledge of the biological processes involved in NDVDs and NDGDs;

❚ transfer and co-design technological innovations to diagnose and treat these diseases.

This strategy starts by considering that several major issues go unrecognized in traditional clinical settings and drug development. First, we cannot molecularly classify patients in a satisfactory manner, and we have no molecular signature that can distinguish patients from healthy subjects. Importantly, these diseases are extremely heterogeneous. In sporadic NDGDs, the lack of molecular-based stratification may cause clinical drug trials to fail because they involve a limited number of patients with varied genetic backgrounds. In NDVDs, many genetic mutations have been found in just a tiny number of cases. Additionally, for both NDVDs and NDGDs, integrated searchable records of clinical and genetic data are generally very poor, if they exist at all, and involve a small number of patients scattered across different institutions. To date, genetic-association studies have sought to analyze genomic DNA from blood, ignoring the potential role of somatic mutations. The primary focus has been the genome's exome portion, particularly the protein-coding genes. But this neglects the potential role of regulatory elements, lncRNAs, and repetitive sequences. Additionally, the genomic analyses have been performed on a large number of cells, ignoring cell-to-cell variability.

To address this, we aim to establish precision medicine for NDVDs and NDGDs. We will classify patients according to genomic sequences associated with a group of symptoms, with special emphasis on the analysis of ncRNAs and repetitive elements. This will allow us to better understand the disease mechanisms and develop new treatments using innovative diagnostic and nanodelivery devices.

Contribution to the 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 classic approach to biomarkers and drug discovery may not be successful for precision medicine in the long term. Classic drug discovery sees 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 therapeutics available.

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 non-coding 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.

Description of the priorities of the research domain Technologies for Life Science (LifeTech)

The LifeTech RD seeks to develop new technologies and knowledge to understand how the brain functions. 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 activity will continue at the Morego building and the Center for Synaptic Neurosciences, located in the IRCCS S. Martino-IST (Genoa). Strong support for the LifeTech RD will come from IIT's network of laboratories, including CNCS-Trento, CTNSC -Ferrara, CGS-Milan, and CLNS-Rome.

In the next years the LifeTech RD should grow about 10% (staff to date: more than 360 - including 21 PIs and 46 technicians), with the inclusion of new PIs in the fields of single cell transcriptomics, RNA structures, aptamers for delivery.

Below, we describe the main research and technology activities of LifeTech's Priorities, as summarized in Fig. 13.

Priority 1: Neuroscience and Brain Technologies

IIT will develop new techniques and gather crucial data to identify the key molecular, cellular, and genetic 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 neural circuits studied in animal models, and their translation to the human brain.

Brain technologies

IIT plans to develop new materials and technologies for brain interfaces to obtain a dynamic picture of the brain in action.

Novel multifunctional neural interfaces

We will use optical, thermal, and chemical techniques, which will be integrated into innovative implantable probes and which will use neural activity indicators and actuators. With these, we will interface deep brain regions, including subcortical structures (e.g., thalamus, basal ganglia, hippocampus), which the current technologies cannot directly access at high resolution. We will develop a new class of versatile, minimally invasive, and fully integrated optical and optoelectronic devices. These will be used to simultaneously control and monitor neural activity in

deep brain regions at unprecedented spatial resolutions by combining multiple functionalities (optical, electric, thermal, and chemical functions) in a single, minimally invasive device. This will allow us to achieve multipoint control and readout of neural activity and neurotransmitter concentration in mammalian brains. We will use tapered and nanostructured optical fibers to correlate electrical and chemical signaling in the brain, helping to answer longstanding questions about the brain's functional connectivity.

Bioelectronics for drug screenings and large-scale brain interfacing

NBT has established a large-scale electrode array technology by converging expertise in micro-/nano-structuring, CMOS circuit design, and computation for data analysis. IIT's CMOS-based high-resolution bioelectronic technology and experimental know-how can be applied in research instrumentation to study neuronal networks and brain circuits, and to develop disease models to investigate safety and toxicity in drug discovery. This offers great potential for next-generation preclinical screening programs of human-derived cellular systems, and for implantable therapeutic and prosthetic biomedical devices based on high-resolution implantable CMOS-probes. For *in vitro* assays, IIT aims to: increase experimental throughput by developing multiwell CMOS platforms; integrate capabilities for single-cell intracellular manipulation and molecular profiling (neuroplasmonics and microfluidics); and adapt technologies to monitor bioelectrical and biochemical signals in 3D human-derived cellular systems (neurospheres, organoids) with sub-millisecond time resolutions. In the push for implantable bioelectronic devices, we will develop standalone, integrated systems with embedded data transmission and power solutions. In parallel, we will explore microfiber/nanofiber electrode arrays and carbon-based materials for large-scale 3D sensing and actuation with sub-threshold brain tissue damage.

Synaptochips

The Synaptic Neuroscience Team of IIT in collaboration with Plasmon Nanotechnologies (RD Nanomaterials) plans to develop hybrid connections of neurons with artificial synapses. Neural plasticity is generated by network activity, and relies on information transfer at synapses. With their ability to 'remember' the total electronic charge that passes through them, memory-resistors (memristors) can be considered 'artificial synapses'. The goals are to realize nanomemristors with enhanced sensitivity, and to achieve hybrid intra/extracellular connections with live neurons, allowing a bidirectional information transfer between live and artificial synapse networks *in vitro*. The main deliverables will be to:

❚ develop neuron-friendly nanomemristors for inter/intra-cellular live interactions;

❚ understand the interactions between the bio-logic of neuronal and memristive networks;

❚ define the learning capabilities of memristor-based devices when instructed by patterns of neuronal activity;

❚ investigate the plastic and computational properties of the hybrid neuronal-memristor network;

❚ extract information to develop a new generation of neurocomputers.

Multiscale neuroscience

IIT seeks to understand how higher functions of the brain (e.g., sensory perception, motor coordination attention) arise from the coordinated activity of largescale (from hundreds to million units) cellular networks. To this end, we will study basic functions of the nervous system and develop new technologies to record brain activity at different levels of organization.

The targets are:

❚ to integrate genomics data in order to rigorously test hypotheses about the molecular basis of neural networks, and how they are controlled by epigenetic mechanisms and neural genome heterogeneity;

❚ to elucidate the structural and functional organization of synapses;

❚ to understand how higher brain functions arise from the coordinated activity of large populations of neurons;

❚ to provide experimental data, recording techniques, and computational methods for large-scale neuronal recording and manipulation with high spatiotemporal resolution;

❚ to complement the Computation and Data Science effort by providing cutting-edge computational methods to advance the discipline of systems neuroscience; and

❚ to translate knowledge from animal model systems to the human brain.

Single-cell genomics. The current challenge in genomics is how to monitor gene expression at the single-cell level and how to study single-cell genomic variants. IIT plans to set up a single-cell genomics laboratory in collaboration with the European Bioinformatics Institute (EMBL-EBI, Cambridge, England) and RIKEN (Yokohama, Japan). This will be especially relevant for studying the brain, given its staggering complexity in terms of neuronal cell types. Single-

cell profiling will help us understand the heterogeneity of neuronal networks and the molecular basis of neuronal electrophysiological properties. This knowledge will also support the RNA Technology Priority 2, LifeTech RD in identifying cell-type-specific targets and membrane molecules for use as specific markers for nanoparticle homing. IIT will also pursue a new generation of spatial transcriptomics and genomics technologies:

▌ New technologies will be developed for the simultaneous image processing of a large repertory of nucleic acid molecules. The goal of this interdisciplinary effort is to study gene expression, genomic structural variants, and chromatin organization in vivo;

▌ As discussed in "Plasmonic Ultra-High Sensitivity Biosensors" (Priority 2, Nanomaterials RD), a plasmonic-based readout for a nanopore sequencing platform will be coupled to tissue preparation and imaging to develop a new high-throughput sequencing system for tissue transcriptomics.

Shaping neural genomes

Repetitive elements comprise almost 50% of the entire human genome. They are crucial to regulating chromatin status. Long Interspersed Nucleotide Element-1 (LINE-1 or L1) is the most abundant and the sole autonomous retrotransposon still active in the human genome. By exploiting the expression of a reverse transcriptase, L1s replicate with a copy-and-paste mechanism, which gives rise to Copy Number Variation (CNV). L1 mobilization occurs in the germline, during early embryonic development, in neuronal precursors, and in postmitotic neurons, leading to somatic mosaicism. Altered retrotransposition has been demonstrated in NDVDs, NDGDs, schizophrenia, and cancer. IIT plans to develop sequencing-based technologies to identify genome structural variants in neurons in humans and mice. To better define the role of somatic heterogeneity in brain function and dysfunction, we will investigate the behavioral and electrophysiological changes in wild-type mice and genetic models of NDVDs and NDGDs, when the expression and mobilization of repetitive elements are altered. We will also deploy several paradigmatic behavioral tasks to evaluate how neural CNVs are established and their functional significance. Finally, for NDVDs and NDGDs, we will investigate differences in the content and distribution of repetitive elements in discordant monozygotic twins.

Synaptic Plasticity of Inhibitory Networks

The ability of the brain to process information relies on the versatility of synaptic signaling. Indeed, synapses are believed to influence neuronal activity, microcircuit function, and, ultimately, behavior. It has recently emerged that the "regulated" Brownian diffusion of proteins at synapses is a determinant that can shape the synaptic signaling properties. IIT aims to understand how synaptic protein diffusion affects synaptic function at the nanoscale and mesoscale levels. This knowledge will help us understand higher-level computational capabilities at synapses. In the long term, we will investigate how the diffusion of synaptic proteins correlates with the animal's behavioral brain states. To visualize the trajectories of diffusing receptors, we plan to develop a device that exploits recent advances in fast focusing in order to track GABAA receptors in somata of cultured neurons in an extended axial range. IIT plans to optimize this device so it can track receptor diffusion in brain slices where neurons are organized in a 3D architecture. This technology will significantly improve our knowledge of receptor lateral diffusion at synapses in an in-vivo-like environment.

Local Micro-environment and Brain Development

Basic research on cortical development has provided evidence that the extracellular space of a given developing brain cell also contains other developing cells (cellular environment). These cells influence one another through different extracellular factors. Thus, what is relevant for a developmental process at a particular time and in a particular brain area may not be significant at another time or place, due to the different cellular environments. This has tremendous conceptual consequences for the treatment of NDVDs. By studying the different cellular environments during brain development, researchers may eventually identify specific therapeutic windows for addressing aberrant neuronal development with drastically reduced side-effects. In previous studies on animal models of NDVDs, NBT demonstrated that subtle alterations during brain development can have long-lasting effects on behaviors later in life.

In collaboration with the Nikon Center we will perform quantitative nanoscale investigations of protein complexes, which comprise molecules that are essential to physiological cortical development and that have been linked to NDVDs. The goal is to identify potentially converging pathways in NDVDs to identify new druggable targets. Emerging sample-preparation techniques (i.e. expansion microscopy) will be combined with cutting-edge biophysical tools, such as single-molecule localization, super-resolution techniques, and light-sheet illumination microscopy (as integrated in the liquid tunable microscope).

By definition, NDVDs begin in embryonal and/or postnatal life, so therapies would ideally begin then. However, this carries the risk of side effects with long-lasting noxious sequelae for the developing brain. Therefore, NBT will explore different therapeutic approaches. In particular, RNA interference coupled to viral-vector-mediated *in vivo* delivery will be assessed for its efficacy in treating cognitive impairment in DS. Another approach uses CRISPR-Cas9 gene-editing technology to manipulate, *in utero*, specific and possibly converging gene networks in neuronal progenitors of DS mice. This approach will be evaluated for its ability to recover brain development and cognitive deficits later in life.

Cracking the neural code

To survive, organisms must accurately represent stimuli from the outside world, and use that representation to generate beneficial behavior. However, we still do not understand the basic neural mechanisms underlying these processes. For example, when we see an object, hear a sound, or smell an odor, this generates precise spatial and temporal patterns of electrical activity in neuronal networks in specialized areas of the brain. This electrical representation of the external stimulus is believed to mediate our perception of the sensory experience. However, little is known about how we encode information about the external stimulus in the spatial and temporal dimension of sensory-evoked activities. We also do not know which specific feature of the evoked network dynamics then drives our behavior. Moreover, even in the same apparent state of vigilance, sensory-evoked activities are highly variable. Repetition of the same sensory experience produces different network dynamics. What does this variability mean for sensory experience? Do these different network dynamics carry different information about the stimulus? Or does the brain encode the same information coming from the outside world in multiple and equivalent ways?

The long-term objective is to understand the computational principles of brain networks during perceptual decisions. IIT will develop advanced optical systems for largescale neuronal recording and manipulation with high spatiotemporal resolution. The goal is to target hundreds to thousands of cells at cellular resolution. To pursue this goal, IIT will recruit experts in the field of perceptual behavior quantification using various approaches in rodents, from the application of complex external stimuli to the use of virtual reality. Using these new optical technologies, we will map endogenous patterns of cortical circuit activation during sensory stimulation. These activity patterns will be replicated to investigate how precise spatiotemporal patterns drive circuit dynamics and behavior.

Deconstructing intrinsic brain activity using perturbations with fMRI and computation

Perturbation approaches will be used to understand which fundamental neural elements govern the establishment and derangement of intrinsic network activity. Using rs-fMRI recordings of cell-type-specific chemogenetic and multipoint optogenetic manipulations, we plan to elucidate the drivers of macroscale coupling, such as the role of different classes of inhibitory or excitatory cells. These 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 dynamics.

Computational methods to analyze brain activity at multiple scales

To optimize the information obtained from multiscale data, we will develop information theoretic and machine-learning tools to extract sensory- and decision-related information from simultaneous recordings of large-scale single-cell populations and mass signals from different brain areas. We will also develop graph-theoretic methods to assess the effects of neuropsychiatric conditions on the brain connectivity at multiple scales. To pursue this goal, IIT will recruit computational neuroscience experts to model recordings of the human brain in terms of the underlying cellular mechanisms, thereby leading to a closer interaction and transfer between basic neuroscience, genomics, and clinical research.

Priority 2: RNA Technologies

Manipulating RNA expression *in vivo* is a new strategy for molecular therapy in the brain. This 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 of 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 the physiological amounts of the target protein would, in principle, be curative.

In this priority, special efforts will be devoted to foster interdisciplinary collaborations. Contributions from "Advanced Multiscale Modeling of Biomolecules" (Priority 1, Computational Sciences RD) will provide the mathematical and computational knowledge to dynamically simulate and predict RNA secondary structures. 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 Priority 2, Nanomaterials RD.

RNA Biology

Dietary RNA

Exogenous sRNAs (ex-sRNAs) have been detected in mammalian plasma and serum. These ex-sRNAs are derived from the microbiome, the diet, or both. This raises the possibility that they mediate the trans-kingdom regulation of gene expression, prompting a paradigm shift. In particular, plant-derived dietary ex-sRNAs have been associated with immunomodulation, cancer prevention, and protection from viral infection in humans. They directly interact with human endogenous RNA interference and pattern recognition receptors (PRR) of the innate immune system. Thus, in addition to indirectly mediating epigenetic modification in recipient cells, nutrients may also directly affect biological processes by providing bioavailable and bioactive ex-sRNA species. Exosome-encapsulated miRNAs in breast milk may play a crucial role in the development of the newborn's immune system and in the "epigenetic priming" of the baby. These findings have major implications for our understanding of diet-gene interactions and for preventive nutrition. They could also provide new directions for developing and optimizing RNA therapeutics.

Here, IIT will investigate the function, bioactivity, and biodiversity of dietary ex-sRNAs. We will focus on the functional relevance of their posttranscriptional modifications and tertiary structures. Major challenges will include routes for ex-sRNA delivery, strategies to bypass intracellular surveillance mechanisms, and the actual amount of dietary ex-sRNAs needed for biological action. We will investigate their cross-kingdom signaling, health-promoting, and immunomodulating properties. This information may then be useful for designing highly stable and active RNA drugs.

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 IT 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 multiwell CMOS programs from human-derived cellular systems for RNA sequence optimization.

IIT also plans to develop new tools to optogenetically modulate the transcription and translation of neural genes involved in NDVDs.

RNA Sensing

The complexity of the RNA world has increased massively, which raises questions about the classic approach to studying RNA expression. This classic 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). In this context, it is also highly desirable to visualize 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-RNAs interactions in 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. These may be potential biomarkers and/or effectors of diseases, including those of the nervous system. In general, RNA expression can be used as biomarkers 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 exosome biochemistry, we can produce them 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.

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 to the brain is to hijack BBB-crossing mechanisms. Optogenetic tools will tune BBB permeability via the reversible perturbation of claudin-claudin interactions. Using molecular biology and molecular dynamics simulation techniques, we will engineer chimeras of peptides fused to light-sensitive modules. Furthermore, as part of the European Graphene Flagship, NSYN will also investigate to what extent and by which mechanisms graphene materials can cross the BBB.

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 HTS strategies are available and under development, which can be used 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

A key lesson in clinical translation is that technologies for healthcare should not only be designed for users, but also with users via a cross-disciplinary process of co-design and co-development. IIT will confront this challenge by bringing together and enhancing expertise in technologies for life sciences, robotics, nanomaterials, and computational science. Partnering this expertise with that 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 (Priority 1, LifeTech RD), as well as initiatives arising from other RDs. We also envision the establishment of translational projects based around technological innovation developed by RNA Technologies (Priority 2, LifeTech RD). 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 close 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 G. Gaslini Children's Hospital for NDVD patients and with S. 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 ncRNAs 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 non-coding 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 machine learning and AI. We anticipate a strong synergistic effort with the RD Computational Sciences in particular with the research activities *Advanced Multiscale Modeling of Biomolecules*, and *HPC Algorithms for Extremely Large-scale Data Analytics* (Priority 1), with *Machine Learning Theory and Algorithms and Deep Learning, Data Science, and Artificial Intelligence* (Priority 3) and with *Computer Vision for Life Science* (Priority 4). Furthermore, we plan an aggressive campaign to recruit experts in big data analysis in this domain. We will thus obtain information through genomic analysis, machine learning, and AI algorithms. This information will be translated into precision medicine tools and protocols that can be applied to many individuals in collaboration with the network of clinical research institutes and research hospitals mentioned before.

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. Its 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, as well

as 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 non-coding regions, including repetitive elements and retrotransposons. In this context, we are currently establishing a collaboration with a world leading company for the next generation sequencing devices.

Nanomaterials for multifunction 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 2, Nanomaterials RD), a repertory of nanoparticles and soft materials is synthesized for the detection, imaging and therapy in 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 are aiming at facilitating 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 (Priority 2, LifeTech RD) will support even further this translational initiative providing novel molecular tools for patient-specific therapies.

Nanosparks and artificial retina

In the last 5 years the Nanotech teams of the IIT center in Milan and the Neuroscience team of the IIT at S. Martino University Hospital in Genoa, have developed a new neurointerface with conjugated polymers that photo-activates neurons and rescues visual sensitivity in a rat model of Retinitis pigmentosa. In short time this technology has evolved from a proof-of-principle stage to a real prosthesis which has been implanted first in rats and then in pigs, to optimize the surgery procedures in view of its application to humans. Currently IIT is waiting for the Ministry authorization for clinical trials in humans and has gathered the interest of international investors to move towards the market in case of successful tests. In addition, IIT will target macular degeneration by scaling photoactive devices down to cellular size. The plan is to engineer and test: (i) subcellular-sized nanoparticles comprising conjugated polymers that may accumulate in contact with inner retina neurons; (ii) amphiphilic photochromic moieties that incorporate into the plasma membrane and induce light-dependent modulation of the electrical state of inner retina neurons; and (iii) develop new architectures with conjugated polymers as multilayered devices or nanosheets for microinjection of graphene to improve the stimulation efficiency of optoneural interfaces. Preliminary tests of such technologies are in progress in animal models of retina degeneration to demonstrate their feasibility and potential transferability to humans.

Rehabilitation technologies and prosthetics

IIT is investing considerably in research into high-performance prosthetic limbs and rehabilitation systems. The road map of the Joint Laboratory with INAIL in this field is to expand the reach of these activities and fully realize their potential to alleviate the effects of stroke, paralysis, and physical injury. 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.

Theranostic robotics

In healthcare, robots have long been used to assist individual users with physical functioning. Thanks to rapid progress in AI and cognitive robotics, there are new possibilities to assist individuals with cognitive and social functioning. This line will develop innovative robotic technologies to assist the diagnosis and treatment of autism 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 NDVDs

IIT will use advanced computational methods to identify the motor signature of autism and other NDVDs. Accumulating evidence indicates that early diagnosis, followed by appropriate intervention, is critical to optimizing outcomes for children with autism. But it is complex and difficult to diagnose autism in children before the age of five. Recently, motor abnormalities have been identified in young children who are later diagnosed with autism. This presents a new target for early assessment. IIT's goal will be to identify and quantify disorder-specific changes in movement patterns. 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 autism 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 autism based on human-robot interaction. Atypical movements in autism 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 autism 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 autism 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 autism (phase II). If successful, testing will be extended to the national network of IRCSS (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 mechanisms of social cognition such as joint attention, recognition of facial expressions and communicative gestures. We will design novel human-robot interaction protocols, which integrate a humanoid robot with cognitive neuroscience methods (EEG, eye tracking, and physiological markers). The humanoid robot will be programmed to evoke and enhance social cognition mechanisms in the human user at various stages of brain development. The mechanisms include, but are not limited to, joint attention, recognition of facial expressions and communicative gestures. With the use of such methods, we will monitor the development and improvement of mechanisms of social cognition, nonverbal communication, and learning in typically and atypically developing individuals.

Sensory technologies

Building on studies on 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:

❚ improve the motor, spatial, and social skills of visually impaired children and adults;

❚ foster learning skills at school (e.g., mathematical and geometrical skills);

❚ 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 (Joint Lab with Istituto Chiossone; ANIOMAP, CIP, FIRR, IRCCS Stella Maris, IRCCS Bosisio Parini, IRCCS Mondino, IRIFOR, MAISOLI, PAIS,

PHILOS, UIC) and private companies (Vodafone, Linear, Geomobile, Ateknea).

Robot-assisted microsurgery

Robots can offer assistance to microsurgeons by enhancing their levels of precision and dexterity, making the control of surgical tools easier and more intuitive, and improving the access and visualization of difficult-to-reach parts of the anatomy. In cooperation with IRCCS S. 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 Micro Surgery (μRALP). One great challenge in the coming years 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)	IRCCS Medea (Lecco)	IRCCS Mondino (Pavia)	IRCCS Don Gnocchi (Milan)	IRCCS Stella Maris (Pisa)	Galliera (Genoa)	Centro Protesi INAIL (Budrio)	Istituto Chiossone (Genoa)	Other Institutes*
Clinical Genomics	●	●	●		●				●			
Low cost, disposable, ultra-high sensitive diagnostics	●											
Nanomaterials for multifunction drug delivery	●	●		●					●			●
Medical Chemistry	●		●						●			●
Nanosparks and artificial retina		●									●	
Rehabilitation technologies and prosthetics	●	●							●	●		●
Theranostic robotics	●				●		●			●		
Sensory technologies	●					●		●	●		●	
Robot-assisted microsurgery	●	●										

Table 1. Overview of the translational initiatives contributing to Priority 3: Technologies for Healthcare (LifeTech RD).

*Other Institutes: including Istituto Ortopedico Rizzoli (Bologna), Fondazione Toscana G. Monasterio (Pisa), Ospedale Santa Corona (Pietra Ligure).

Computational Sciences

Description of the Computational Sciences Research Domain

Massive computation and the emerging exascale infrastructures will have a major impact on IIT's Strategic Plan. Two major developments in computational science are: i) massive simulations of physical systems, 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. The second development is playing a major role in artificial intelligence (e.g., for robotics) and genomics. Both areas need informatics infrastructures, including high-performance computing (HPC), big data storage, and cloud computing. HPC will be crucial for computational life sciences and material sciences. 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 2018-2023 Computational Sciences RD is to establish a dynamic interplay between HPC and big data analytics. We will achieve this by developing a new portfolio of HPC codes, ranging from new tools for multiscale simulations to machine-learning and deep-learning algorithms.
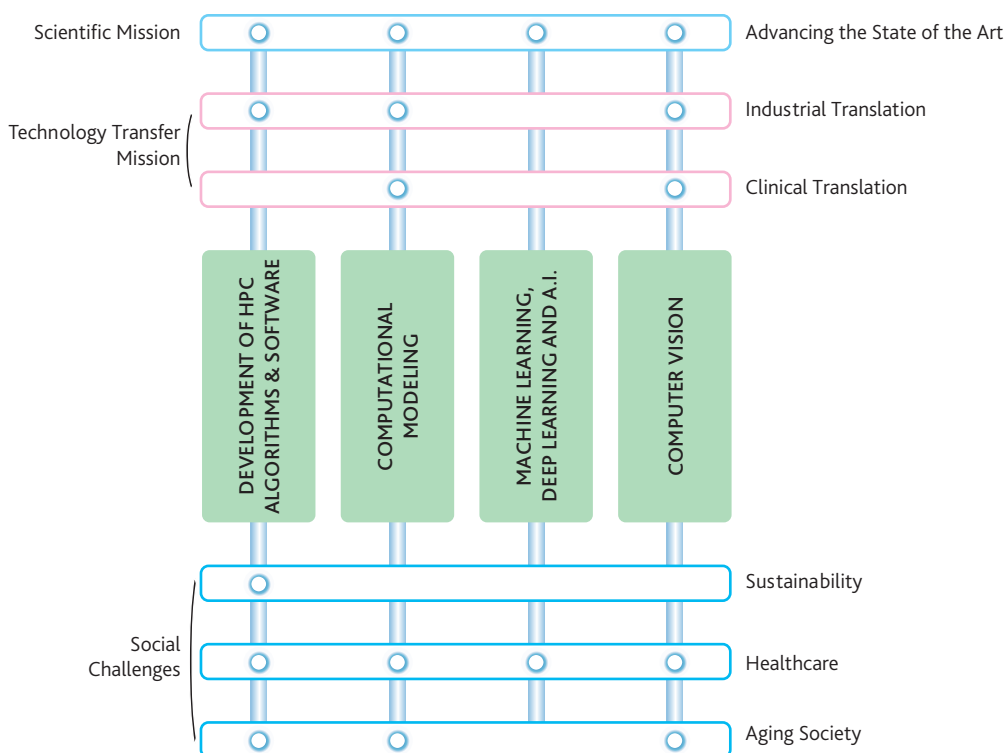

Fig. 14. Priorities of the Computational Sciences Research Domain, contribution to IIT's mission, and impact on the challenges.

The Computational Sciences Domain will focus on four computational priorities in the fields of life sciences, material sciences, and data science for robotics and health. 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. Machine learning and deep learning are the focus of the third priority. This priority will be dedicated to novel theories and models to develop next-generation algorithms and codes for artificial intelligence and bioinformatics. Finally, the fourth priority will concern computer vision for novel in silico tools for robotics and pattern recognition techniques, with applications ranging from ambient intelligence to health. It is important to remind that the Computational Science RD originates form the small Compunet team launched by the previous Strategic Plan. Though small, the Compunet has been a successful intuition of IIT, generating high return on the

IIT research and becoming a transversal driver of multidisciplinary innovations, from Robotics to chemistry. Clearly the Strategic Plan 2018-2023 aims at creating a world class Computational Sciences facility in IIT, with the double goal of boosting the research of all other RDs domains (from AI to Bioinformatics) and of generating autonomously new frontier research fields. For this reason, the Computational science RD will need important investments and the recruitment of a few highly skilled PI.

Contribution to the First Mission: advancing the state of the art

Computational Sciences will integrate data science and computation to achieve two objectives. First, we will develop new theories, algorithms, and software for life sciences, material sciences, 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., machine learning, deep learning). 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 bioinformatics 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 exascale computing. At IIT, we will develop and optimize codes for HPC, providing the end user with flexible and efficient tools, enabling the full exploitation of state-of-the-art computing architectures. In the period 2018-2023, large 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 in collaboration with the Italian supercomputer center CINECA (or any other European HPC facility).

Contribution to the Technology Transfer Mission: designing and developing new codes and software, and creating an infrastructure for big data storage and HPC

The technology transfer 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 material sciences. 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 technology transfer 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 codes and software for machine learning (for genomics and robotics) and quantum chemistry (for material sciences). Developing professional codes 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 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 close collaboration with CINECA, which has extensive experience in HPC and code refactoring for cutting-edge hardware architectures.

Contribution to the Healthcare Challenge: designing and developing a data storage facility and novel HPC 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 illness, particularly 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.

Contribution to the Aging Society Challenge: big-data-driven polypharmacology

Neurodegenerative disorders, including Alzheimer's and Parkinson's disease, almost exclusively affect elderly people. No effective cure exists for either disease, so new drug discovery approaches are needed. In this context, multi-target-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. In particular, we will develop new computational tools based on machine learning and/or deep learning 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, machine learning, 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.

Description of the priorities of the Computational Sciences Research Domain

The Computational Sciences RD will be organized in four programs that cut across the other RDs. As shown in Fig. 15, the Development of HPC, Algorithms, and Software Program will be crucial for fully exploiting modern computational infrastructures and for optimizing code and software for bioinformatics, genomics, and material sciences. 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 sciences and nanosciences, primarily dealing with statistical mechanics, ab initio models, and multiscale simulations for broad application. The Machine Learning and Deep Learning Program will be instrumental in robotics, life science (genomics, clinical data, and personalized medicine), and artificial intelligence. 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). As shown in Fig. 15, the dynamic integration of these two areas, traditionally running on separate tracks, is one of the biggest challenges in 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.

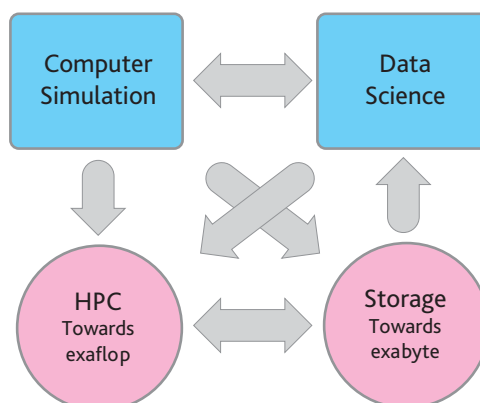Dynamic interplay between data analytics and HPC simulation

Fig. 15. 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.

Most of the Computational Sciences research and technology will be developed in the new Center for Human Technology in the Erzelli building, supported by CNCS-Trento, CBN-Lecce, CNI-Pisa, and CNST-Milan. In the next years the Computational Sciences RD should grow about 50% (staff to date: more than 120 - including 12 PIs and a few technicians), with the inclusion of new PIs in the fields of Analytical Modeling of nanosystems, Bioinformatics, Quantum Chemistry and Data Sciences, AI and machine learning for genomics.

Additionally, in 2017, IIT in collaboration with the University of Bologna and Milan Polytechnic launched a new PhD School in Data Science & Computation. This major European PhD school is also 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 include the International School for Advanced Studies of Trieste (SISSA for the doctoral program), EPFL (for computational material science), ETH, and USI. Indeed, a memorandum of understanding was recently signed between IIT and USI, which covered joint computation and data science activities.

At Erzelli, we will create a Data Storage Facility for the Center for Human Technologies. 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 PBytes) to store raw data and aligned sequences in databases (possibly along with clinical records); and iii) a large external infrastructure of more than 100 PBytes 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 mid-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 GPUs clusters and strengthen our strategic collaboration with CINECA. Massive data storage and HPC will be key infrastructures for IIT's 2018-2023 strategic agenda.

Priority 1: Development of HPC Algorithms and Software

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 tens (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, as 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 a 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 take into account 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 for 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 to treat neurodegenerative diseases 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 the approximations for the exchange-correlation (XC) energy functional and, in the case of orbital-free DFT (OF-DFT), the 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 meta-generalized 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 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 huge 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, machine-learning 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 machine-learning methodologies to handle large amounts of data and to unlock the full potential of massive computations in life sciences and material sciences. This will result in a dynamic interaction between data analytics and HPC simulations, as illustrated in Fig. 15 (p. 36).

Priority 2: Computational Modeling

Computational drug design, discovery, and delivery

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

Additionally, we will focus on in silico drug delivery, as it has recently been 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 material sciences

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

i. 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 the 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 help 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 such devices will be pursued in the context of nano-gap 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.

ii. 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 monoxygenases 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.

iii. We will continue the Graphene Flagship activities started during the Core1 phase, focusing on two cutting-edge research activities. 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' 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. In collaboration with 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 Deep Learning

Machine-learning theory and algorithms

The objective of the program is to develop new machine-learning and deep-learning algorithms for artificial intelligence (AI) and data science. 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 technologies for AI and robotics.

In the past few years, machine learning (ML) has played a major role in data science. 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 ever more complex tasks; ii) study learning frameworks that allow knowledge from previously learned tasks to be transferred to solve new tasks more efficiently; and iii) develop a theory of deep learning. To tackle these challenges, we will focus on modern ML algorithms, such as those based on representation learning, multi-task 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 its 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.

Deep learning, data science, and artificial intelligence

The progress in collecting huge amounts of data from all branches of engineering, natural sciences, and medicine opens new 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 sciences 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 deep-learning (DL) approaches have strengthened ML. DL has been extensively used in a large range of data science applications, and DL networks are now the premier class of ML approaches. They can cope equally well with static data (images), using convolutional neural networks and auto-encoders, and with data sequences (videos, speech, strings) 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, 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 possible 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 create automatically 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 ultimately 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

Like machine learning, 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 with ad hoc models and prior knowledge of the data (e.g., 3D images, graphs).

Computer vision for robotics

In robotics, scene understanding is crucial (see the Robotics RD section). For example, in the security and surveillance domains, 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, 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. We will focus on behavioral analysis and the understanding of 3D scenes, with special attention paid to nonverbal (human) behavior and social interactions. In addition, we will combine audio data with video data for scene understanding. Augmenting the data sources should result in more informative representations and improved comprehension abilities. This is particularly true in complex cases, where audio or visual information alone is not sufficiently discriminant. 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 & answer. This research will allow us to efficiently tackle generic

scene understanding (including people and object recognition, and behavior recognition). This will be important for applications in domains such as industry, robotics, and healthcare.

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 machine learning 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 in order to analyze the overt behavioral manifestations of certain mental disorders (e.g., schizophrenia, autism). By analyzing electrophysiology, and structural and functional brain imaging data (and possibly 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 automatically extracted (i.e. learnt) from data using deep learning. 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 an important tool for investigating behavioral pathologies (e.g., autism spectrum disorder, schizophrenia) and neurodegenerative diseases (e.g. Alzheimer's and Parkinson's disease, 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.

Appendix: Acronyms

2D	Bidimensional materials
AD	Alzheimer's Disease
AI	Artificial Intelligence
AuNP	Gold nanoparticles
CABHC	Center for Advanced Biomaterials and Healthcare - Naples
CBN	Center for Biomolecular Nanotechnologies - Lecce
CCSL	Center for Computational and Statistical Learning - Cambridge (USA)
CGS	Center for Genomic Sciences - Milan
CHT	Center for Human Technologies
CLNS	Center for Life NanoScience - Rome
CMBR	Center for MicroBioRobotics - Pontedera (PI)
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
D3	Drug Discovery and Development ((grouping IIT pharmachem research lines)
DS	Down syndrome
EIC	European Industrial Council
EM	Electron Microscopy
ERC	European Research Council
EU	European Union
FPGA	Field-programmable gate array
GPU	Graphics processing unit
HPC	High Performance Computing
IEO	Istituto Europeo di Oncologia
IFOM	Istituto FIRC di Oncologia Molecolare
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)
LIFETECH	Technologies for Life Science
lncRNA	Long non-coding Ribonucleic acid
Moog@IIT	IIT-Moog joint laboratory
MSCA	Marie Skłodowska-Curie Actions
NANOMATERIALS	Nanotechnology and Materials
NIC@IIT	IIT-Nikon joint laboratory
NIR	Near-infrared

NMR	Nuclear Magnetic Resonance
NSYN@Unige	Center for Synaptic Neuroscience - Genoa
PCE	Power conversion efficiency
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PV	Photovoltaic
POC	Point of Care
PI	Principal Investigator
RD	Research Domain
TT	Technology Transfer
WHO	World Health Organization