Implantable Microdevices for Real-Time Drug Delivery and Precision Disease Management

Editors

Noor Safaa Abd Mahdi
Department of Medical Equipment Engineering Technology, College of Engineering Technology, Isra University, Iraq

Mohammed Qasem Ismail Jehad
Department of Medical Devices Engineering, College of Engineering Technology, Al-Kitab University, Iraq

Abdalrhman Shehab Ahmed Mustafa
Department of Medical Device Engineering, Al-Kitab University, Iraq

Mustafa Huseen Mahmood
Department of Medical Device Engineering, Al-kitab University, Iraq

Mohammed Haidar Adai Mohsen
Department of Medical Devices Engineering Technology, University of Hillah, Iraq

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Contents

Abstract

Implantable microdevices for real-time dosing impact personalized therapy development via closed-loop control and integration with biosensors. Their intelligent design allows responsive drug delivery rather than fixed pre-programming. Continuous Biosensing, predictive algorithms, and feedback actuators combine to emulate physiological responses and maintain stable internal conditions. Whether miniaturized for intravascular implantation or positioned in direct contact with soft tissue, these responsive biomolecular delivery vehicles enhance safety and efficacy, decrease medical costs, and alleviate patients' disease burden.

Studies assess low-volume areas, such as artificial pancreases for diabetes, automated pain relief, and telemonitored chemical signaling between neurobiological implants. Personalization relies on cloud-based systems that maintain digital twins of patients' bodies; health data platforms enable AI predicted preventive outputs; and therapy-simulating software automate dosing. Regulatory ecosystems support initial product security while ensuring patient autonomy and long-term safety. Future work includes new predictive applications, growth toward nano- and picoscale versions, connection with external indicators, diagnostic-sensory fusion, biohybrid soft-robots, and data-fueled development of implantables requiring external nutrients.

Chapter - 1

Introduction to Implantable Microdevices

Implantable microdevices are small and smart. With ultra-thin structures, multiple functions, nearly total bioresorbability and miniaturization of batteries, they represent the benchmark in high-tech implantable devices. These microdevices can release drugs through microneedle-like elements covering any surface; the amount administered can be controlled by an external command or for a special need of the patient. Real-time feedback systems allowing monitoring of the disease process, and signal processing by AI algorithms with generation of a control signal for the microdevice, can automate its operation. The main objective is to reinforce collaboration between the patient and the healthcare services, dramatically reducing their workload, while still offering remote assistance 24/7.

The use of implantable microdevices is expected to reduce the incidence of unplanned adverse events and complications in patients with chronic diseases by concentrating data in the cloud, analysing them with statistical or AI-based procedures, and automatically adjusting the treatment. Building such an environmental monitoring and remote diagnosis system needs to address several requiring further investigation to ensure safety

and efficiency of this setup, namely the data platform, optimised patient-specific treatment adjustments, and appropriate patient feedback. These three aspects apply also to any other implantable microdevices for treatment or diagnostic purposes [1, 2, 3, 4, 5].

Overview of implantable medical technologies

Continuous health monitoring has gained considerable attention in the last decade and is often considered part of personalized medicine [6]. Personalization involves tailoring treatments to an individual's specific health conditions, medical history, physiology, and obtained results. Implantable microdevices equipped with sensors and micropumps offer the ability to measure important biomarkers continuously and release drugs accordingly, enabling real-time, controlled, and personalized therapy. Several milestones in implantable drug delivery systems have already been achieved, including a fully implantable programmable intravascular delivery system for treprostinil, approved by the Food and Drug Administration [7].

Although personalized, real-time, and closed-loop implants hold great promise, many challenges still need to be addressed to ensure patient safety and intervention effectiveness, such as wireless energy transfer reliability and security, biosensor performance, miniaturization, biocompatibility, and optimal drug release mechanisms. Addressing these challenges is essential for the wide adoption of implantable devices capable of fully autonomous and safe therapy adjustments. The development of responsive drug-delivery microdevices enables feedback-controlled dosing. These devices integrate biosensors for

continuous biomarker monitoring and responsive drug-release actuators.

Evolution from passive implants to intelligent microdevices

Smart implants, also known as intelligent microdevices, autonomously combine a programmable actuator responsible for triggering drug release with a wireless energy source. They are monitored and actuated externally, enabling completely implanted real-time drug-delivery devices. These smart implants represent the latest development stage of drug-delivery implants, also referred to as microinfusion devices or micro-pumps, designed for repeatable, localized, and controlled release of therapeutic agents for various diseases.

They act in response to real-time monitoring of the patient's physiological condition and aim to close the feedback loop by integrating microscale biosensors. Real-time feedback-controlled dosing supported by Artificial Intelligence (AI) offers the possibility of adaptive dosing appropriate for the evolving condition of the patient and any modifiable individual response to the disease. Patient-centric automatic dosing therapy, achieved by combining AI and the Internet of Things (IoT), contributes to personalized medicine [8, 9, 10].

Key motivations: real-time monitoring, controlled drug release, and personalized therapy

Real-time monitoring and control of drug release from smart implants would improve disease management by providing patients and clinicians with valuable information. Furthermore, implants that continuously monitor health parameters and

automatically adjust the timing and dosing of therapeutic agents could enhance patient outcomes while reducing the burden of on-going therapy. Accessibility of these capabilities would be increased by the development of Artificial Intelligence (AI) algorithms for predictive, data-driven, and adaptive treatment recommendations. Prioritizing the patient perspective aiming to improve quality of life, reduce therapy burden, and minimize side effects would deepen the impact across the spectrum of therapeutic areas. With applications in diabetes, pain management, cardiovascular disease, respiratory infections, cancer, neurological disorders, and surgery, the technology would usher in a new era of precision disease management.

Real-time monitoring of health parameters such as glucose and cytokines, coupled with responsive dosing of therapeutic agents, could substantially improve disease management by providing up-to-date information to patients and clinicians. Patient-controlled drug administration offers clear advantages in relieving breakthrough pain, and implants equipped with feedback circuitry would relieve patients of this yet further by mechanically determining optimum therapy. Continuous drug delivery through implants capable of sensing health parameters could enhance treatment outcomes while sparing patients the burden of active therapy. In these applications, externally-processing algorithms implemented in smart wiring would adapt timing, frequency, and dosage to individual needs. The opportunity for personalized, smart, and even predictive treatment fulfills key requirements in several areas of medicine [11, 12, 13].

Ethical and regulatory perspectives

The societal impact, availability, and safety of smart implants predominantly depend on ethical, regulatory, and legal considerations. Patients must be appropriately informed about the concept and technology to provide their consent for data collection, storage, and processing. While invasive medical devices have built-in privacy and security features, a full disclosure to the patient may be impractical. A secure online data platform is required to prevent mishandling of sensitive information when automated machine learning algorithms support an advanced implantable treatment. Such a platform should also be secure against unauthorized access as the system must not be hacked. Regulatory authorities like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) should create transparent and rapid pathways for the approval of autonomous treatment systems, for example, an artificial pancreas that receives continuous data input from a glucose sensor. Informed consent must be obtained from the patient prior to implantation. Algorithms must be carefully calibrated during clinical trials to prevent individual requirements, tolerances, and preferences of the patients and must not alter the normal communication via the nervous system.

Actual and secured health data create new opportunities for computer-aided digital-twin technology, which duplicates a physical object into a virtual version on a cloud computing platform. Various digital twins will be created for different patients suffering from similar diseases. Machine-learning algorithms then adapt the therapy of the real patient in

accordance with recent base readings of his/her digital twin. The first Artificial Intelligent (AI) platform is now applied in oncology to process data from the existing computer tomography images of the patient. The machine-learning algorithms of the AI processing unit detect the tumor and its vicinity in the cloud data network, extract the multi-modal information, classify the tumor, predict its evolution, estimate the possible treatment and consequence, and finally provide the medical staff with an efficient decision support [14, 15, 16, 17].

Chapter - 2

Fundamentals of Microdevice Engineering

Microfabrication techniques (MEMS, NEMS, lithography, 3D printing)

Miniaturization is the key for implantable devices and their micro delivery systems; practical miniaturization of these systems is highly influenced by micro/nanofabrication techniques and methods. Micro and nano-electromechanical systems (MEMS/NEMS), micro and nano-lithography, and micro and nano-manufacturing techniques and methods, such as Three-Dimensional (3D) printing, are well poised to miniaturize smart implants and their systems for the real-time precision management of disease.

Micro and nano-electromechanical systems (MEMS/NEMS) and micro and nano-lithography technologies have become enabling techniques for realizing numerous millimeter- to micrometer-scale devices and structures. Very Large Scale Integrated (VLSI) technology is already well established, with processes automating the fabrication of microelectronic integrated circuits with high reliability and low cost. Such technology has led to the development of other new areas and methods, including Micro-Electromechanical Systems (MEMS),

Nano-Electromechanical Systems (NEMS), CMOS-MEMS, and Nano-CMOS-MEMS technology. The horizontal versus vertical scalability in silicon technologies has extended into the next smaller length scale. The development of micro and nano-lithography techniques, such as X-ray, laser, and deep UV nano-imprint technologies, has allowed novel synthesis and fabrication procedures for one-, two-, and three-dimensional micro/nano-patterned surfaces and structures. The integration of different technologies, especially substrate technology such as glass, polymers, and silicon, is advancing [18, 19, 20].

Biocompatible materials (silicon, polymers, hydrogels, metals, composites)

Biocompatible materials such as silicon, polymers, hydrogels, metals, and composites play a fundamental role in the development of implantable microdevices. The main requirements for these materials include biocompatibility and bioinertness, mechanical properties (stiffness), degradation properties and kinetics, suitability for microfabrication, and ability to integrate with biological components.

Silicon has been the standard material for MEMS technology and is biocompatible. It has also been applied for controlled drug delivery into the gastrointestinal tract with osmotic micro-pumps for a scheduled delivery of therapeutic agents. Organic polymers are essential components in NEMS and have been used in implantable microdevices. Polymeric hydrogels can be biocompatible and bioinert. Poly(lactic-co-glycolic acid) (PLGA) has been used for insulin delivery. Natural and synthetic

hydrogels have been explored for on-demand release from implantable devices. Biocompatible metals, such as gold, iron, titanium, and magnesium, have been tested, with support from advanced composite formulations.

Silicon is characterized by its superior surface microchemistry and electronic properties, essential for typical MEMS functions, but it is not soluble in physiological solutions or body fluids. Polymers are heavily used in microfluidics because they can offer reduced absorption of dyes, low noise levels in PCR assays, and superior chemical compatibility. However, unmodified polymer surfaces generally exhibit strong protein adsorption and nonspecific binding for cellular components. Hence, accelerated biodistribution and clearance are required for nanocarriers based on unmodified polymers. Hydrogel-forming systems constitute the heaviest investigated materials for controlled drug delivery [21, 22, 23].

Power sources and wireless energy transfer

Like all implantable systems, microdevices require energy for sensing and actuation. External power supply via wired connections is impractical due to the increased risk of infection and the impediment to body movement, while batteries have intrinsic limitations of size, reliability, and life-cycle. Therefore, emphasis has been placed on energy harvesting and wireless power transfer. Energy harvesting requires no batteries, prevents the associated disadvantages, and enables operating lifetimes limited only by performance decay of other components. A multitude of energy sources is available *in vivo*: including

electromagnetic radiation, body temperature, mechanical motion, and biochemical reactions in bidirectional and unidirectional forms. Conversion of optical or RF signals into electrical energy by rectennas is commonly applied to RF identity tags and telemetry of implanted devices; piezoelectric converters can transduce organ motion or muscle contraction into electrical energy.

A notable area of development is the harvesting of biochemical energy by biofuel cells, which power microelectronic devices for life-long implantation in a non-functionally altering manner. In particular, the continual oxidation of glucose by the ubiquitous enzyme glucose oxidase can be exploited by immobilising it on an electrochemically active anode; oxygen from the surrounding medium serves as a terminal electron acceptor at a cathode. Glucose biofuel cells show enormous potential as power systems of implantable devices. Long-term and stable assembly and integration of their components with biomedical systems remain a challenge, with the majority of housed studied being incapable of serving the energy needs of true microdevices. Current research is aimed at overcoming the limitations in power density and performance, miniaturizing constituents, developing microfabrication processes compatible with cleanroom and MEMS techniques, and scaling biofuel cell-based microelectronic devices comparable in autonomy to those powered by batteries.

An alternative strategy is to focus on wireless inductive power transfer, a well-established means of supplying energy to implanted devices. The operation of an inductive power transfer

system is based on generating a time-dependent magnetic field in a primary coil; this field is sensed by a secondary coil located in the near field, inducing a voltage in it and thus forming an open circuit. An alternating electric current flowing through the primary coil produces a time-varying magnetic flux in the solenoid, which senses it. Operation for the near field region relies on a short coupling distance; consequently mutual induction of the coils can be neglected and the magnetic circuit model deployed. Importantly, control circuitry may be housed in a transponder located close to the secondary coil, allowing a minimal complexity in the microdevice [24, 25, 26].

Microfluidic control and system miniaturization

Microfluidics is the study and manipulation of small volumes of fluids (nL to pL range), enabling precise control of flow and mixing, analysis, or guiding cells and chemicals. Microfluidic «labs on a chip» enable chemical, biological, and biomolecular reactions to be performed with very small quantities of sample and reagents, while microelectrodes on the chip surface allow electric signals to be read. Microfluidics are also relevant for implantable devices, where fluidic components allow for precise drug administration, either in a controlled manner or in response to detected stimuli.

The implementation of small reservoirs and pumps, as well as mechanisms generating the pressure needed for fluidic actuation, have been extensively studied in microfluidics. These microfluidic components can be used in autonomous implantable devices. For example, a miniaturized reservoir supplying oxygen

to cultured cells connected to a micro-needle enabling perfusion was built, demonstrating the ability to manipulate small fluidic volumes in an accurate manner. Smart polymers that expand and induce fluidic pressure for actuation in a microdevice are also available. The use of smart actuating hydrogels as hydrogel-based pumps capable of generating sufficient pressure to discharge the aqueous solution through a microgroove also allowed fluidic control of micro-systems. For long-term implantation, glucose-responsive microfluidic devices were combined with an insulin-producing synthetic micro-organ implant, demonstrating the generation of an insulin-secreting closed control system [27, 28].

Chapter - 3

Physiological Barriers and Implantation Sites

Biological barriers to drug delivery (BBB, mucosal, dermal, systemic)

Therapeutic delivery encounters four biological barriers depending on the route of administration: the Blood-Brain Barrier (BBB), mucosal barriers, skin, and those encountered by systemic delivery. The BBB, consisting of vascular endothelial cells, pericytes, astrocytes, and neurons, maintains homeostasis and protects the brain from toxins, pathogens, and inflammatory responses. Key structural characteristics include tight junctions, low transcytosis, and limited paracellular transport. These restrictive features hinder the delivery of nanocarriers and all types of drugs to the brain. Strategies for overcoming these obstacles include receptor-mediated transcytosis and the use of exosomes originating from mesenchymal stem cells. Modifying the geometry of nanocarriers, employing viral vectors, depleting the receptor for advanced glycation endproducts, silencing specific genes, and using ultrasound or MRI guidance have also been reported as promising approaches.

Mucosal barriers, such as the intestinal epithelial barrier, serve as front-line defenses against environmental pathogens while permitting nutrient and drug absorption. Mucus secreted by goblet cells on the epithelium protects mucosal surfaces but impedes the penetration and permeation of therapeutic agents. The skin is an efficient barrier for many substances. Drugs reaching the stratum corneum are hindered in further diffusion into the deeper layers by the compact arrangement of keratinized cells and the presence of ceramide-rich lipids. Transdermal delivery by nanoparticles is possible when particles are functionalized with penetration enhancers. For systemic delivery, specific techniques have been developed to transiently open tight junctions or introduce nanocarriers through calcium ionophores, indicated for the treatment of various diseases, such as diabetes, rheumatism, allergies, and leprosy [29, 30, 31].

Implantation routes (subcutaneous, intravascular, neural, organ-specific)

The implantation route plays a decisive role in the design of miniaturized implantable microdevices for real-time drug delivery. The selected pathway determines such aspects as access to the target tissue, capacity for local drug-target interactions within the bioactive area, risk of surgical morbidity, and aesthetic considerations. Numerous implants are inserted via a subcutaneous route, providing easy access for device implantation and power supply through radio-frequency telemetry. This solution is often employed in open-loop setups for chronic monitoring, notably of glucose levels in diabetic patients. Controlled release via the blood circulation has been

proposed for multiple therapeutic applications, especially in drug infusions for pain relief. However, the relevant closed-loop systems making use of implanted biosensors and pumps, and even the laboratorial realization of an artificial pancreas have not yet reached a larger-scale clinical application.

Subcutaneous implantation is unsuitable for delivery applications addressing biological obstacles such as the blood-brain barrier, mucosal/dermal transport, or localized therapy. Such configurations require directly inserting into the blood-brain barrier, onto the mucosal surface, or through the dermis, or placing the device in proximity to affected organs (e.g., cardiac anti-inflammatory therapy). Both local treatment and infiltration of digital nerves, however, involve surgical procedures that can present complications. A less invasive solution is to use microneedles concentrated in a patch for epidermic delivery, although these must be coupled to an efficient device for energy supply [32, 33, 34, 35].

Host-tissue interactions and immune response

An unusual feature for implantable devices is biocompatibility, or the capacity to function in contact with living tissues. Implant insertion always causes surgical wounds; these heal and regroup tissue with the first contact but can be considered a failure functionally if chronic. Two well-described processes frequently occur: biofouling layer formation and fibrosis infiltration by fibroblasts that lead to fibrous encapsulation. These responses are the result of complex interactions with tissues that are energetically favorable for the

body. The outcome of the implant-tissue interaction depends on various biological factors (amount of implanted mass and surface composition + shape), the local and systemic immune response, and other parameters intrinsic to the host as well as extrinsic environmental ones.

Systems are desired not only to be biocompatible but also to promote healing. They should desire the local expression of anti-inflammatory cytokines (such as IL-4 and IL-10), and the expression should be attracted, for example, stimulated by the infusion of pro-inflammatory molecules, leading to active and regenerative processes in question. Pharmacological treatment is regularly applied in the preclinical stages to modify stress factors and study immune tolerance and adaptation to implanted stimuli [36, 37, 38].

Strategies to minimize biofouling and fibrosis

A foreign body reaction often arises upon implantation, triggering a series of host responses that can lead to encapsulation of the device. This process not only compromises drug or signal release, but also has the potential to disrupt normal tissue function. Biofouling can be caused by the accrual of proteins, lipids, and other biological moieties at the device surface, often resulting in heightened immune responses and a subsequent fibrotic capsule. Research has focused on biofouling and fibrosis minimization through biochemical modification of the device surface in order to promote tissue integration, modulation of macrophage polarization toward a wound-healing phenotype, and release of anti-inflammatory agents.

To reduce cytotoxic effects, modify the local inflammatory response, and subsequently decrease fibrosis formation around the implant, coatings loaded with anti-inflammatory growth factors or small regulatory RNA (miRNA) have been employed. Exogenous delivery of miRNA-21 has been shown to promote macrophage polarization toward the M2 phenotype while stiff polylactide membranes loaded with fibroblast growth factor 2 have been demonstrated to significantly enhance *in vivo* vascular permeability, thus facilitating material integration and suppressing chronic inflammation. In another approach, a polycaprolactone-based device that releases a pro-angiogenic peptide sequence derived from vascular endothelial growth factor (VEGF165) has conferred pro-angiogenic and pro-vascularized activity *in vitro* while promoting local vascularization and nerve outgrowth *in vivo*, thereby supporting peripheral nerves without triggering adhesion formation [39, 40, 41].

Chapter - 4

Controlled Drug Delivery Mechanisms

Diffusion, osmotic, and electrochemical actuation

Actuation is one of the key aspects in the design of any drug release system, and in particular, those of closed-loop systems. The most straightforward action mechanism is simple diffusion, where the system relies on the inherent concentration gradient in the micro-environment to trigger the release of the therapeutic agent. The primary advantage of this form of drug release is reliability, since no external actuation element is required. However, such micro-reservoirs release their content according to the second Fick's law, which states that the amount of drug released per unit of time is inversely proportional to the distance the molecules must diffuse. Consequently, as the system empties, the concentration gradient decreases and so does the rate. This behavior is often unsuitable for therapeutic purposes. Osmotic systems can be more reliable, relatively simple, and allow for a zero-order release. These systems use an external source of fluid to push the drug solution out of the micro-reservoirs, and can be designed to also control the amount of fluid released. However, an exogenous source of fluid must be provided to the device in order to refill the reservoir, which can be a drawback in some applications.

Another way to enable drug release is to create an electrochemical reaction at the tip of a micro-needle that leads to the discharge of a drug with therapeutic values. Such systems can offer steady release rates, but require an external power source to operate and other mechanisms to control the amount of solution delivered. One potential limitation, shared by electrochemical and osmotic systems, is the success of the actuation. These systems rely on the continuous availability of a certain type of fluid that must be either disposed of, used, or replenished. In the case of an osmotic system, the fluid must pass into the reservoir easily in order to offer any kind of reliability. If one of these operations fails, the local therapeutic delivery cannot be guaranteed [42, 43, 44, 45].

Micro-reservoirs and pump-based systems

address the need for stored drug supply and provide refined release profiles beyond passive diffusion. Micro-reservoir systems consist of multiple compartments where drug reservoirs communicate with the environment through selective release windows (actuation gates) and can aim to maintain stable concentration levels for long periods. The actuation of these gates can be provided by bioaffine bond dissociation (responsive to pH, temperature, antibodies, metal ions, small molecules) or by diffusion of external stimuli in the implant environment (glucose, urea, NO). Micro-reservoir systems are designed for reliable long-term and long-distance delivery of therapeutic agents that require pulsatile administration (hormones, cytokines, analgesics, anaesthetics) or that are eliminated from the body with rapid pharmacokinetic responses (anesthetics, fomepizole).

Pump-based systems contain a drug solution reservoir and use fundamental physical principles (electrochemical, osmotic, piezoelectric) or external energy sources (light, electromagnetic field, ultrasound) to spray or inject drugs into the body. The most elaborated electromechanical micro-pump systems consist of micro-valves that control the fluidic paths, thus allowing complex pumping schemes. Long-term reliability is mandatory for such systems, and operational lifetime testing strategies are being developed to explore the candidate assay and actuator components for vulnerable points in the micro-device. Refill and replacement options are developed to extend lifetime and cure unexpected faults or component failures.

Microsystems, nanotechnologies, microfluidics, bioinformatics, and self-healing materials are being explored to fabricate low-cost intelligent implants for various applications in the human body. These implants are crucial for the management of acute and chronic diseases such as diabetes, heart attacks, cancer, burns, post-operative pain, severe facial injuries, nervous system disorders, and local bacterial infections. Artificial pancreas based on implantable micro-devices with a closed-loop feedback regulation system are emerging to manage blood glucose level in diabetic patients by restoring natural insulin secretion function for controlling glucose concentration in the body fluid [46, 47, 48, 49].

Smart polymers and stimuli-responsive release (pH, temperature, glucose, magnetic, ultrasound)

Smart polymers and stimuli-responsive release systems allow for more sophisticated microdevice designs. Controlled release

through diffusion, osmosis, or actuation by external stimuli is achievable; however, transient responses are more suited to electrolytic and electrospinning-driven modes. Driven by immediate internal physiological changes, acting responses effect release that is not necessarily synchronized with transiting concentrations of the analyte of interest.

These materials and systems broaden the design space for smart, polymer-based devices. pH-responsive chitosan/gelatin/ Fe_3O_4 trilayer membranes, magnetic- and ultrasound-triggered core-shell spheres from PDMAEMA/PEO copolymers, i-Encoding systems combine pH- and temperature-responsiveness, and dual pH- and glucose-sensitive nano-hydrogels leach insulin. Biorthogonal click reactions have enabled smart microgels with spatiotemporally-dynamic releases of multiple therapeutic agents.

Real-time feedback-controlled dosing

Closed-loop systems that respond to real-time feedback from biosensors promise to offer an optimal dose of a drug whenever necessary. Beyond the application of artificial pancreas devices, monitoring and dosing for the treatment of chronic pain constitute a further immediate domain in the real-time control of disease management by intelligent implants.

Controlling the release of drugs from implanted microdevices in a smart manner is another pertinent topic. aims al precision disease management and concern the integration of biosensors and actuators inside a single implant. The integration of biosensors for continuous monitoring of physiological

parameters that influence disease activity such as glucose, pH, cytokine levels, and hormone concentrations for real-time feedback-controlled dosing of pharmaceuticals constitutes a promising short-term direction. These approaches build on laboratory-bench studies demonstrating closed-loop-control of microfluidic insulin-delivery devices in response to physiological glucose concentrations and drug delivery in the treatment of pain as a further application area. A sound conceptual understanding of closed-loop systems, their architecture, the design of the individual components and their integration, as well as the algorithms for managing data flow, processing, calibration and patient-specific fine-tuning provides an appropriate knowledge basis for future design activities [50, 51, 52].

Chapter - 5

Sensing and Feedback Systems

Integration of biosensors for continuous monitoring (glucose, pH, cytokines, hormones)

Seamless integration of biosensors for continuous monitoring with actuators represents one of the key enablers for personalized autonomous medicine. Advanced biosensing technologies are now capable of routinely monitoring a wide range of physiological parameters, including glucose, pH, temperature, lactate, hormones, mRNA, cytokines, and immune metabolites. One of the next milestones in smart implant development is linking these sensing elements with drug-delivery units to achieve closed-loop pharmacotherapy for a variety of diseases. The architecture of such systems is relatively simple; it involves a biosensor that continuously measures the analyte level in the body, a signal-conditioning circuit that pre-processes the sensor output, an algorithm that issues control commands on the basis of established relationships between the analyte concentration and drug dose for that specific patient, and the actuator that releases the desired amount of drug.

Closed-loop therapeutic systems have been demonstrated for glucose monitoring and insulin release in the form of an artificial

pancreas. These implants consist of a miniaturized glucose sensor based on Amperometric, potentiometric, or Optical techniques and an insulin-release unit that is triggered by the sensor output. Similar architecture has also been explored for pain management, where multiple detection and release channels are connected to a central control unit. The biofouling problem is critical for closed-loop systems for cytokine detection and medication against inflammatory diseases and remains an open challenge in smart implant research. A key advantage of combining actuators and biosensors in a smart implant is the ability to shift the paradigm from a patient-centered treatment strategy to the emerging idea of preventive medicine, implemented by catering for therapeutic needs even before symptoms occur [53, 54, 55, 56].

Closed-loop control algorithms

Feedback-controlled dosing of drugs and other therapeutics constitutes an advanced therapy paradigm that can help maintain health status at an optimal range. The system architecture used for real-time, closed-loop control of drug dosing is composed of an actuator, a biosensor, and a signal processing module (see Fig. 1). The actuator provides a stimulus and a micro-/meso-reservoir to deliver the therapeutic; the biosensor provides continuous monitoring of a health biomarker; the signal processing module determines the release rate from the reservoir to keep the biomarker at a target set point. Control algorithms govern the actions of both the signal-processing and control modules.

A variety of control algorithms can be applied, including feed-forward control, feed-back control, PID control, and

advanced-data-driven adaptive predictive control. Application of predictive algorithms, such as predictive-adaptive control or model predictive control, requires an underlying process model for prediction of the monitored signal. The model can be identified through system identification methods, or physiological models can be used when available. Data-driven algorithms, including reinforcement learning algorithms, utilize both simulated and field data for training. Classical control methods for low-dimensional system generally provide satisfactory results. For closed-loop control, predictive models are not mandatory; feedback control using PID or state-space feedback methods is sufficient [57, 58, 59].

Data acquisition, signal processing, and calibration

Closed-loop control systems rely on real-time data to predict disease state and therapeutic demand. Implementation of predictive, patient-specific algorithms requires continuous data acquisition and storage, through either a central device or external wearable devices linked to implantable microdevices. A cloud-based digital health platform that stores historical health data for all patients in a centralized database can facilitate the implementation of patient-specific control. To optimize closed-loop systems for artificial pancreas and pain management applications, data collected from multiple patients is examined along with the corresponding prediction-output data from control algorithms to create a hyper-heuristic framework for automated control tuning.

Real-time delays in dosing systems can be compensated by

data-driven predictive algorithms that utilize historical glucose concentration data to anticipate timely adjustments in insulin dosage. In an adaptive control network, the health status of each patient is compared, and the prediction information on the patient status or the control output is then used to tune the corresponding controller. Data-driven predictive and adaptive control algorithms enable dynamic change in closed-loop control according to the current patient-neighbour data, ultimately facilitating individualized control. Digital twin technology can support accurate, patient-specific simulations of therapeutic strategies and enable personalized optimization of dosing systems [60, 61, 62, 63].

Examples: Artificial pancreas, pain management systems

An artificial pancreas is arguably the most successful example of real-time drug delivery. Extra- and intra-cellular glucose concentrations are monitored continuously using broadband fluorescence measurement of glucose at the surface of a nanosensor based on Plasmonic nanoparticles, implanted sub-cutaneously. Detection of hypoglycemic or hyperglycemic episodes triggers the release of insulin or glucagon, respectively, from miniaturized electrochemical actuators based on palladium membranes loaded with the appropriate peptide. Parallel work focuses on a less demanding application involving feedback control of paracetamol dosing in patients with painful sores. Continuous monitoring of inflammatory interleukin-2 and interleukin-10 enables delivery of the appropriate amount of an anti-inflammatory agent.

These examples illustrate the cornerstone of closed-loop insulin dosing: real-time monitoring of glucose concentration using a blood-level independent nanosensor with response times ≤ 3 s; responsive pulsatile release by a smart actuator; and a patient-specific control algorithm tuned and validated offline using simulation [64, 65, 66].

Chapter - 6

Wireless Communication and Powering

Near-field and far-field wireless telemetry

Telemetry enables periodic or continuous monitoring of internal parameters by transmitting information wirelessly to an external receiver. Depending on the propagation range, these techniques can be classified as near-field (usually sub-metric) or far-field (over a meter). Near-field telemetry typically takes the form of a bi-directional communication link between an external reader and a transponder or tag placed within the host, providing power and/or data through Electromagnetic (EM) coupling. Because of the limited range, such systems can be designed to meet low-power requirements, consuming significantly less energy than far-field telemetry. At the same time, the very short standoff distance allows the direct connection of sensors to the transponder without long-distance electrical feedthroughs. This integration simplifies packaging and enables higher reliability. The periodic exchanges of information may also be fully authenticated, reducing security concerns.

Far-field telemetry is required for systems that need to transmit well beyond a meter radius from the subject. These systems rely on wireless communication technologies, such as

Radiofrequency (RF) Identification (RFID), Bluetooth, Wi-Fi, ZigBee, and other similar technologies. In order to enable more efficient RF communication between implanted transceivers and external routers, micro- and minified antennas should be used. However, for large-scale applications where inexpensive sensors should be distributed and freely floating in the environment (e.g., for a smart city), miniaturization is not an issue. On the other hand, the energy costs of far-field telemetry must be taken into account when designing real-time feedback-controlled implantable systems. Patients are usually willing to accept a certain level of energy consumption, as long as the system does not require frequent recharging. To prevent excessive depletion, continuous monitoring of impeller parameters is usually limited by yet another battery embedded in the RTX. By incorporating an electrically charged supercapacitor, it is possible to deliver long-duration continuous readings even during the short recharging intervals. Security is critical when far-field telemetry is used to transmit sensitive patient information over wireless networks [67, 68, 69].

Energy harvesting methods (RF, piezoelectric, biofuel cells)

Energy harvesting methods are essential to ensure long-term, autonomous operation of implantable microdevices that are capable of complex functions, including real-time monitoring, closed-loop control, and multi-drug delivery. To achieve sufficient autonomy, new approaches are required that go beyond the use of conventional batteries, which offer limited energy density and lifespan. Several alternative energy supply technologies have been explored, including RF identification

systems, RF and ultrasound-based wireless powering schemes, piezoelectric devices implanted in the body, and biofuel cells that utilize glucose or other biomolecules present in the human body.

RF-powered sensors have been reported that provide near-real-time sensing of temperature for health monitoring; body temperature information for insulin delivery; glucose and PH levels for a diabetes management system; and the detection of a wide variety of biomarkers, including cytokines and hormones. In these devices, miniaturized sensors harvest the RF signals generated by an external reader, then stimulate one or more electrochemical sensors that can be interrogated by the same or a different external reader. However, RF devices generally cannot operate in a typical far-field configuration, and extra care must be taken to ensure security and privacy.

Piezoelectric generators can provide power autonomously from motion and could be combined with other microscale generators (internal and external) to ensure long-term implant operation. These devices generate AC voltages that can be rectified and used to charge capacitors, or to power different units in a sequential manner. Biofuel cells are an interesting complementary technology for implantable microdevices. They convert physiological substrates, such as glucose, urea, or lactate, into energy and water. Most research has focused on glucose biofuel cells capable of using glucose from blood or tissues as fuel. Such generators can provide sufficient power even for relatively large systems [70, 71, 72].

Data transmission security and encryption

When using implantable microdevices capable of wireless near-field or far-field data transmission, ensuring transmitted data security is essential. Potential threats include unauthorized access to a device's signal and leakage of sensitive data such as physiological measurements, drug dosage information, and medical conditions, especially if the device is used over a prolonged time period. Therefore, data encryption mechanisms should be included in any device that represents an attractive target for exploitation.

Introducing any form of encryption modifies the input-output relationship, complicating the signal detection by unwanted receivers and turning the implanted device into a secure transmitter. Wireless encrypted communicate signals present particular characteristics, enabling a near-field implanted device equipped with a small microcontroller to share secure data in a packet with longer data from an external controller. The military-inspired a.k.a. VENETIAN protocol can be adapted for biomedical purposes, allowing a rapid and highly secured packet transmission between the two smart devices, thereby enhancing the privacy and safety of the information [73, 74, 75, 76].

Battery-free implant designs

Ultrasmall implantable microdevices can be powered via near-field telemetry, eliminating the need for batteries or biocompatible energy cells. Most applications rely on external control and monitoring devices, such as a smartphone or computer, that activate the system when the operation is needed.

Battery-free microdevices can also feature an on-board sensing unit or connect to such units in the vicinity, performing closed-loop measurements and actuating after detecting an appropriate condition. Miniaturized low-power implants can provide continuous feedback over a longer distance via far-field telemetry, but their small size usually limits on-board processing. The system sends periodic measurements to the external device, which extracts the pertinent information, such as a binary pattern of a safety circuit. Although such designs do not qualify as smart implants, the implementation of a smart bracelet enables continuous monitoring over a period of time.

Battery-free implants that employ low-frequency RF energy also depend on the location of the receiving antennas, as the electromagnetic field decays with the cube of the distance. However, the operation principle implies that the sensor and the actuator magnet are usually placed far apart, and combining the telemetry and control in a single device can help reduce the overall dimensions. Integration with an external power source is a simple solution to advance the smart concept in the near future, and the interaction and integration with an adaptive wearable powered by a biofuel cell may enable fully autonomous functionality. Even though using rifampicin and isoniazid with predetermined cycles, a recent study introduced a more complex system combining inductive coupling with additional smart functionalities through Bluetooth connectivity [77, 78, 79, 80].

Chapter - 7

Microdevice Fabrication and Packaging

Cleanroom processes and microassembly

Satisfactory operation of smart implants for prolonged periods relies on appropriate hermetic sealing and surface modification. Sealing techniques have been adapted from traditional packaging of microelectronic and optical components. Simultaneously, microassembly of the individual elements is either performed in cleanrooms or by state-of-the-art automated systems. In-house microassembly may leverage individual user preferences and may therefore not need to comply with large-scale production processes suitable for mass devices.

Closed-box hermetic encapsulation prevents pollution of the inner device volume, while sealed-box hermetic encapsulation enables refilling through a microvalve. Both methods use silicone as the sealing material. The advanced silicon-silicon bonding technique relies on deep reactive-ion etching and low-temperature bond activation. The additional application of a silanol layer prior to bonding can enhance the sealing for dielectric-potential components. Sealing for REF systems has also been achieved by low-temperature bonding with developed nanoporous adhesives. Processes by which external microvalves

were integrated into the device structure have also been applied for RF-powered implants, smart aspiration probes, and smart MEM-control systems.

In addition to protecting actuation elements from biofouling and hydrolysis, coatings have been employed to prevent or biomimic protein adsorption, protease activity, and cell adhesion; to prolong the functional lifetime of implanted photonic components; to contribute to guided tissue regeneration; and to promote synergistic neuroinhibition and regeneration. Hybrid 3D-printed devices have been obtained by a combination of laser-assisted and glue- and UV-assisted assembly approaches.

Sterilization of microdevices prior to implantation is paramount for patient safety. Special care must be taken to preserve their functional performance after sterilizing treatments. Information is thus required on the effects of different standard sterilization techniques on specific devices and how to maintain sterility during *in vivo* implantation [81, 82, 83, 84].

Hermetic sealing and encapsulation materials

Integrity, durability, and functionality *in vivo* require hermetic sealing of microdevices and their active components. A cleanroom environment and automated handling processes aid in the assembly of encapsulated microsystems. For implantable devices, hermetic encapsulation is generally achieved using glass frit bonding, epoxy sealing, or soldering. Other materials used for encapsulation include epoxies, polymers, and metals; these are selected according to the respective application.

Devices in contact with highly corrosive body fluids, for

example, are usually coated with precious metals. Considering tissue response, an inert and biocompatible coating layer is often deposited to promote long-term stability. For example, silicon-based ceramics, such as silica and silicates, have been successfully used for the encapsulation of sensitive parts of implanted neural microsystems. These layers help to prevent diffusion of ions as well as hydration of the underlying sensitive parts and to facilitate long-term operation of the neural microsystem in aqueous solutions. Moreover, by choosing appropriate processing parameters, it is possible to minimize the effect of these packing layers on the performance of the integrated microsystem in terms of time constant, diffusion sensitivity, and electrical characterization [85, 86, 87, 88].

Sterilization methods and their effects on performance

The majority of implantable medical devices must be sterilized prior to implantation, typically through one of three techniques: ethylene oxide sterilization, gamma irradiation, or steam sterilization. Ethylene oxide sterilization can be used to sterilize a wide variety of samples, including multi-material devices, but can require a long de-gassing phase. Gamma irradiation is usually applied to single-material devices, preferentially those composed of hydrogels. Steam sterilization is the cleanest method but is limited to silicon devices, as other materials are degraded in the high temperatures or moisture. Following sterilization, potential adverse effects on drug delivery performance should be carefully evaluated, such as altered cytotoxicity or difusion characteristics. When *in vivo* studies do not conform to the reproducible implantation and testing

protocols of other study environments, such as *in vitro* testing or accelerated ageing studies, special precautions for the testing phase must be considered.

Sterility during *in vivo* studies is generally maintained through the adoption of implant polymers that are either non-degradable or well-integrated within tissues (e.g., hidrogels and metals implanted in contact with tissue). For organ implants or non-permanent penetrative implants (such as electrode-based devices), the use of drugs is usually the only strategy available to meet sterility needs. Local application of selected antibiotics shall be planned in advance and the response of the drugs against the specific infection monitored [89, 90, 91, 89, 90, 91, 92].

Reliability and lifetime considerations

Reliability and lifetime of implantable devices during service in the human body, expected failure modes, and a life-cycle approach to device management are vital for their long-term safe use. Evidence of short-term device failure comes from examples of withdrawn commercial products, and several case studies address failure modes, such as bone degradation issues detected in a wireless stimulator implanted in sheep. Data from a neural implant in the parkinsonian monkey suggest a long mean time to failure of 110 months, similar to that of pacemakers. However, these data are too scarce to allow generalization. The need for a reliability plan that considers the entire life cycle of the product has been emphasized, highlighting that current research for the development of enhanced service life and risk mitigation is often neglected.

Despite the crucial impact on patient health, costs, and quality of care, the reliability of small surgical implants has received little attention compared to larger more expensive medical devices. Reliability modeling and testing techniques traditionally developed for other fields have been proposed to increase the knowledge available in this area. Such innovative studies should also promote lifetime test methods to accelerate the data available on this critical aspect of small surgical implants. For drug-delivery systems, lifetime reliability is particularly challenging since, in addition to the factors affecting mechanical reliability in general, biofouling has a significant detrimental effect on performance and therefore poses a risk of premature malfunction.

Chapter - 8

Biocompatibility and Biointegration

Cytotoxicity, genotoxicity, and hemocompatibility testing

Cytotoxicity, genotoxicity, and hemocompatibility are essential tests in the assessment of biocompatibility for all medical devices, as defined by ISO 10993-1. Cytotoxicity tests determine the effects of leachables from completely extracted devices on cell viability. Genotoxicity tests assess the potential of leachables to induce DNA damage or gene mutations, either *in vitro* during direct contact with mammalian cells or *in vivo*. Hemocompatibility tests show whether blood can pass over a device without spontaneous coagulation. In incipient devices, the testing of materials without any additional surface treatment serves to identify materials that are unsuitable, whether due to inherent properties or surface treatments such as coatings.

Cytotoxicity and genotoxicity data are obtained from an accredited laboratory using cell lines from suppliers that characterize the cell lines according to published guidelines. ISO 10993: Part 5 outlines the cytotoxic effects of leachables on V79 cells, which are normally pig kidney cells; Part 3 lists chemical materials commonly used in medical devices and describes how these materials can be screened before further tests on other cell

lines. Blood is considered a biological environment that uses blood flow to protect implants, and the ISO 10993 standard part for hemorrhage addresses the passage of blood over a surface in contact with a cardiac prosthesis. In these tests, blood is normally taken from healthy rabbits, and other laboratory animals provide blood samples for different genotoxicity testing purposes [93, 94, 95, 96].

Long-term tissue integration and healing response

Long-term interactions between implantable microdevices and the host tissue are crucial for ensuring device stability and performance. During healing, several phenomena may lead to undesirable effects:

i) Foreign-body response, an innate immune reaction characterized by the recruitment and activation of macrophages and the possible formation of multinucleated giant cells;

ii) Biofouling, the undesirable adsorption of biomolecules on the implant surface, which in turn promotes cell growth and tissue encapsulation; and

iii) Fibrosis, a complexity of the foreign-body response that causes the formation of a dense fibrous capsule around the implant, potentially affecting sensing or release performance.

While these processes normally evolve over a few weeks, the risk of damage or failure exists for a longer period, especially for systems that require reopening of the surgical site for refilling or maintenance.

Design strategies to promote long-term tissue integration mostly consider the development of advanced coating or surface-functionalization procedures. These approaches exploit known biocompatibility-inducing molecules, undergoing covalent or non-covalent interactions with the implant surface or being incorporated in a polymeric shielding layer. Examples include the use of dextran sulfate, chitosan or heparin. The addition of coatings based on poly-n-alkylcyanoacrylate (for improved biocompatibility) or sulfonated poly(ether-ether-ketone) (for improved hemocompatibility) have also shown promising preliminary results. Surface modification through layer-by-layer assembly offers another possible strategy. Although still in its infancy, the application of improved integration strategies to this field should facilitate the realization of device concepts that take tissue interaction into account [97, 98, 99, 100].

Coatings and surface modifications

Durability, long-term integration, and biocompatibility hinge on effective control of biofilm formation, nutrient transport, mechanical strength, and drug diffusion. Surface coatings and modifications that remodel topography, roughness, wettability, charge distribution, or hydrophilicity lessen fibrotic response and improve tethering. Disease-specific coatings supporting local micro-environmental cues relative to diabetes, neurological disorders, cardiac disease, and tumors.

Metal and polymer components can be functionalized for biofouling protection. Hydrogels further enable recognition of pH, glucose, enzymes, and temperature. Sandwiched between

magnetic particles, peptide-functionalized thermo-reversible hydrogels loaded with anticancer drugs and magnetic nanoparticles reduce hyperthermia-associated side effects in local tumor recovery. Peptide- and pH-sensitive nanocarriers release anti-inflammatory drugs at sites of active inflammation, alleviating postoperative complications in oral squamous cancer [101, 102, 103, 104].

Case studies of successful implant biocompatibility

Long-term interactions between implants and host tissues can trigger adverse immune responses that inhibit normal healing, promote device rejection, or compromise functional capabilities. Biocompatibility of implantable drug-delivery devices therefore needs to be carefully examined in accordance with established standards. Four representative systems designed for different therapeutic targets and drug classes demonstrate the successful prospect of long-term biocompatibility and highlight the relevance of screening methods for future implantable microdevices.

An implantable polymeric microdevice for the localized delivery of insulin, wound-healing compounds, and antibiotics to diabetic patients utilizes silicone as the main elastomeric frame and polycaprolactone as the release matrix. Release kinetics during long-term immersion in phosphate-buffered saline have been studied and long-term implantation in a diabetic rat model has confirmed the absence of severe tissue inflammation.

A micromachined silicon device for local, continuous infusion of chemotherapy agents against pancreatic cancer

including its bioinert silicon-silicon and silicon-titanium interfaces has been tested for 30-day *in vivo* compatibility in rats. The studies demonstrate viability and tolerability of the implant in surrounding tissues.

An implantable microdevice for the sustained release of neuropharmaceutical compounds demonstrates versatility for different active substances and copes with the immune response of the central nervous system. Bioactivity of neurotransmitters, glutamate and magnesium in particular, is preserved during controlled release *in vitro*; qualitative histological evaluation at 30-day implantation confirms low tissue reaction and connectivity.

An implantable microinfusion system for local delivery of antibiotics to prevent biofilm formation on orthopedic implants highlights the need to demonstrate biocompatibility for sustained release of several drug classes. Sterilization by ethylene oxide has no significant detrimental effects on device performance; bioactivity of gentamicin and vancomycin released *in vitro* is preserved. Evaluation in a rabbit model shows tolerance of the release system after 2 weeks of subcutaneous implantation [105, 106, 107, 108, 105, 106, 107, 108].

Chapter - 9

Real-Time Drug Delivery Platforms

Implantable insulin delivery systems

Numerous implantable systems for insulin delivery have been reported, including semi-active and active solutions. The first category consists of passive devices that rely on glucose-induced, patient-triggered, or external-control discharge without real-time feedback, largely mimicking native function. In contrast, active systems provide real-time glycemia readings with closed-loop release, forming a biocompatible artificial pancreas. The latter technology exemplifies smart biosensors-actuator pairs the next-generation implants transforming passive therapy into adaptive treatment for diabetes, pain, and potentially any disease requiring pharmacological or bioactive modulation. Independent blood-glucose monitoring via continuous glucose monitoring, Becker's bioelectric glucose sensor, or other glucose-sensitive techniques enables autonomous full closed-loop operation without patient involvement.

In addition to glucose, feedback-controlled insulin release has also been induced using pH-based or photo-thermal glycemia-responsive systems. Other locally implanted technologies maintain sub-therapeutic blood concentrations in

parallel with localized treatment. Furthermore, euglycemia can be combined with external stimuli, such as near-infrared light, for anti-inflammatory modulation. Within the area of diabetes management, parallel therapy for chronic pain via multiple peripheral delivery has also been investigated, thus emphasizing the wide-ranging capabilities of these developing devices.

Chemotherapy microinfusion devices

Four decades ago, implants for continuous release of chemotherapeutics were introduced. These devices exempted cancer patients from the stress and discomfort of multiple intravenous administrations while maintaining effective drug concentrations and minimizing exposure of healthy tissues. The infusions were performed through subcutaneous skin ports and catheters that reached the target tumor sites. Attention has moved toward fully implantable devices that gradually infuse sizeable amounts of chemotherapeutics locally through implanted catheters, thereby also allowing tightening of the therapeutic window.

Such systems are indeed indicated for intratumoral delivery of anticancer agents in breast cancer patients. Two devices have been developed: a patient-friendly, remotely controlled version that infuses different agents into a single tumor, and a temporary solution that administers chemotherapy through multiple catheters and works by diffusion of the drug cocktail buried within stable biodegradable scaffolds. In addition to chemotherapy, local delivery of antibodies is also possible, and pain control is another area of application.

Neuropharmaceutical implants

are under development for long-term delivery of antidepressant, antiepileptic, and neuroprotective agents in chronic neurological conditions, with promising early results in animal models. Depression affects around 350 million people and is associated with a twofold increase in suicide risk; drug therapy plays a major role in current treatment but two-thirds of patients do not respond to the first antidepressant trial. For the one-third of patients diagnosed with treatment-resistant depression, available therapies are ineffective. Neuromodulation techniques, including electroconvulsive therapy, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation, are also ineffective amid poor tolerability and high dropout rates. Moreover, antiseizure medications are ineffective for 30% of patients, making surgery the only alternative. The delivery of pharmacological agents to modulate brain activity may be an effective strategy for treatment-resistant cases.

Antidepressants act on serotonergic and noradrenergic systems to reduce inflammation. Multiple doses or long-term infusion of ketamine exert rapid and lasting antidepressant effects and restore synaptic plasticity and myelination in stressed and depressed rodents, while the NMDA receptor antagonist memantine has also shown neuroprotective properties. In a rat model of Alzheimer's disease and depression, scopolamine-associated inflammation is ameliorated by the reversible MAO-A inhibitor harmine. Neuroinflammatory activity is also fivefold more pronounced in patients with temporal lobe epilepsy, while the potential anticonvulsant role of anti-TNF-α therapy offers

real prospects for combined treatment. Neuroinflammation has been reported to play a key role in temporal lobe epilepsy, and associated neuroprotective and anti-inflammatory approaches may offer clinical benefits [109, 110, 111].

Antibiotic and anti-inflammatory local delivery

Localized delivery of drugs for the treatment of antibiotic infections or inflammatory diseases represents another important application area for implantable devices. In the case of antibiotics, the promise of limiting abuse in people and farm animals has driven research aimed at combating bacterial resistance. Local or prolonged delivery has the potential to mitigate cytotoxic side effects and remain effective in areas of local impeded blood circulation (e.g., ulcer, burn or decubitus lesions). Antinflammatory agents, essential for the postoperative control of inflammatory responses, have likewise been embedded into biodegradable or bioerodible polymers, opening up possibilities for local administration over both short and extended periods.

Control of diabetes, neurological disorders, cardiovascular diseases, cancer and pain are the currently recognized areas of application broached in the context of closed-loop microdose delivery systems. Such devices monitor relevant parameters online and automate physiological drug adjustment, delivering higher doses only as necessary. Development efforts in this therapy-optimizing direction are currently based on system designs featuring multilayer integration of actuators and wireless data transmission. The concept focuses on transferring control

algorithms from laboratory, research or clinical use into end-user medical settings in other words, toward the precision of automatic control sharing information with the healthcare digital cloud, providing healthcare professionals with a full overview of the patients' evolution, and incorporating the patients' friends, relatives or caregivers into the process. Patience-oriented optimization is derived from both predictive algorithms and accessibility of up-to-date information [112, 113, 114, 115].

Chapter - 10

Precision Disease Management Applications

Diabetes and metabolic diseases

What to mention here?

- Smart implants for continuous glucose monitoring, insulin release, and closed-loop control
- Potential to provide an artificial pancreas for T1DM patients
- Other microdevices for diabetes and metabolic diseases (e.g. infarct repair, localized treatment)

Diabetes mellitus is a metabolic disorder with severe long-term complications, caused by insufficient insulin supply (type 1 diabetes mellitus, T1DM) or secretory dysregulation (type 2 diabetes mellitus, T2DM). Patients with T1DM depend on exogenous insulin delivery for survival, and suffer recurrent hypoglycemic episodes, while hyperglycemia is associated with long-term damage. Therapeutic alternatives include islet transplantation and bio-artificial devices, the latter combining intra-body artificial organs with cellular sensing and control.

Microdevices with integrated glucose-responsive actuators can continuously monitor the physiological level of this crucial

metabolite and provide real-time feedback-controlled ISO-registered response. This capability is particularly important for T1DM patients to avoid both hypoglycemia and hyperglycemia. The combination of such devices with closed-loop control algorithms therefore paves the way towards an artificial pancreas. Other metabolic diseases, especially those involving local tissue injury (e.g. myocardial infarction) or inflammation (e.g. diabetic foot ulcer) also benefit from long-term implantable microdevices that continuously release drugs directly into the affected area [116, 117, 118, 119].

Precision medicine has emerged as a new paradigm for disease management and is already strengthening efforts to reduce the societal burden of diabetes and related metabolic disorders worldwide. The need is acute. The World Health Organization estimates that 422 million people are living with diabetes, making it one of the leading causes of disability and mortality globally. Even more concerning, the adult prevalence of diabetes has nearly doubled between 2000 and 2016, indicating an escalating disease burden that shows no signs of abating; yet diabetes is just one complication of a much broader epidemic of metabolic disease that threatens human health and well-being. According to the CDC, almost half of U.S. adults (47%) have obesity or are overweight, and many more suffer other noncommunicable metabolic disorders such as hypertension and fatty liver. Metabolic disease is associated not only with diabetes but also with increased risk and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, yet another impetus for accelerated action. Large-scale mitigation efforts have not only failed to arrest but also

accelerated the growing diabetes and metabolic disease burden. The limited success of past initiatives highlights a critical need for new management paradigms. Precision medicine can help meet these needs, targeting the causes of the pandemic rather than just the sequelae of the disease. Individualization could avoid ineffective one-size-fits-all approaches, facilitate accurate diagnosis and timely treatment, and enhance the overall effectiveness of drug development and repurposing. As knowledge of disease mechanisms expands, precision medicine is evolving from theory and conjecture to practical clinical applications [1].

Precision medicine, also referred to as personalized medicine, is an approach in health and healthcare that allows routine individualization of care by accounting for patient variability in genes, environment, and lifestyle [2]. The ultimate goal of precision medicine is to tailor medicine to each patient to maximize the benefit of interventions while minimizing the risk of adverse effects. The adoption of precision medicine in diabetes and diabetes-related metabolic disease, the most prominent update to medicine and management in the past century, is timely, because diabetes has evolved from a rare disorder to a common, chronic, and progressive disease. Precision medicine in diabetes focuses on the pathogenetic mechanisms of hyperglycemia and their molecular pathways, insulin resistance and pancreatic beta-cell failure, and the emerging recognition of non-biochemical metabolic disease manifestations of diabetes. The availability of commercially effective CGMs, novel drugs with established mechanisms of protection or effect on glucose homeostasis, and anticipated safe and effective drugs have positively impacted therapy and compliance [3].

Despite their unique and distinct characters, the search for accurate classification and causal understanding of diseases now often rests on either observational discrimination among the heterogeneous or problematic common or obvious characteristics known about them, whether by traditional or screening means, or, on the diverse types of available relatively coarse, microscopic, or spectroscopic data on specimen, by graphical routines still mostly confined to the collection of coarse characteristics, unless afforded a major advance in the theory and practice of statistical experiment design which allows the acquisition of a full biochemical halo of information on normal patients that and diseases.

In the early stages of diabetes epidemiology, a continent-wide communication by PEA estimates the risks associated to diabetes in different age strata on men, women and total. An example of the epidemiological searches undertaken with the collaboration of national societies of tuberculose is the mapping of tuberculose morbidity in three sub-populations of a same city whose spatial distribution of insudectors would yield an estimation of the coefficient of environmental decay expected over and above the immediate effects of soiling; the clues resulted in modifying above a kilometer from an artificial nucleus [2].

Precision Disease Management (PDM) applications are grounded in a set of established concepts and tools aimed at characterizing the determinants of health and disease at the population and individual levels [2]. PDM incorporates

i) Multi-omics profiling and high-dimensional phenotyping to stratify populations by disease mechanisms,

ii) Scalable digital health technologies and data integration pipelines to enhance accessibility and broaden user involvement, and

iii) Advanced clinical decision support systems to facilitate the interpretation, clinical utility assessment, and during-the-visit integration of multidimensional health data [1].

Omics technologies such as genomics, transcriptomics, proteomics, and metabolomics have enabled unprecedented characterization of biological systems in health and disease. Based on multi-omic and high-dimensional phenotyping data, populations can be stratified according to underlying disease mechanisms or physiological dysfunctions, paving the way for tailored prevention and therapy.

Digital health innovations smartphones, wearables, and remote monitoring devices are rapidly proliferating and generating unprecedented volumes of behavioral, physiological, and social data. Digital data can be converted into clinically relevant insights, yet complicated data ecosystems and limited interoperability hamper widespread implementation.

Clinicians are often swamped with accumulating information; analogue methods (e.g., guidelines and textbooks) can no longer cope with the deluge. Without intelligent interpretation tools, data access can quickly overwhelm the user. Advanced clinical decision support systems that embed multi-modal digital health data into existing workflows are therefore

essential. The interpretation of complex health data is inherently uncertain; elegant frameworks are available that quantitatively and qualitatively characterize not only the health insights but also the uncertainty surrounding them. Such frameworks foster clinician-patient collaboration, align expectations, and promote informed and shared decision making.

Precision medicine combines modern technologies to outline disease progression and define treatment course for the patient, thereby replacing the traditional one-size-fits-all approach with a system better aligned to patient typology and needs. These applications in diabetes and related disorders use patient data to refine system models, improve clinical diagnostics, and better predict the progression of disease [4]. Metabolic diseases can be stratified by identifiable subgrouping mechanisms correlated with individual genotypes and phenotypes, such as the classic allyl dimethylcarbinyl acetate (ADCA) linked to the Green Leaf Volatile (GLV) status that has no impact on yield under either intermediate or long-term stress of exposed hydrophilicity and length [5]. Cancer has been stratified using precision medicine for decades, but diabetes widely regarded as a metabolic disease has not gained similar attention. These models consist of related glucose amounts and peak times at different stages of the post-harvest time of inoculation coincided with iso-volume transformation forming long and stable interconnected tubules across plants under multiple hydrophilic and long-chain situations, where subgroups can be further parsed.

Digital health encompasses the application of digital technologies to address health challenges and encompasses a

wide array of tools, solutions, and applications designed to improve health care. These may be broadly grouped into M-health (mobile health), E-health, E-care, health care apps, telemedicine, telemonitoring, telecare, E-counselling, smart wearables, and digital devices [6]. Digital health tools can influence the prevention, diagnosis, treatment, and monitoring of diabetes and related diseases and can support health care workers, patients, and affected individuals. Digital tools may support home treatment, self-treatment, preventive interventions, risk factors monitoring, and chronic disease management.

Data pertaining to health and the environment arises from numerous sources: clinical laboratories, outpatient and inpatient facilities, wearable devices, smartphones, patient-reported outcomes, sensors, accelerometers, health- and lifestyle-related websites, and social media. Different sources generate diverse data types, including demographics, clinical assessments, audio, image files, free text, GP interrogation, genomics, metabolic reports, family histories, food intake, and inquiries. Digital health platforms collect, transmit, log, and display these diverse and voluminous data streams in real time [7]. Data analytics can track patients, individuals, cohorts, communities, and populations. Effective analytics enables diabetes prevention and relies on good health data aggregation and integration techniques. Data-driven systems, decision pathways, and the choice of digital health agents depend on data access, analysis, interpretation, integration, and compatibility with user needs.

Clinical Decision Support Systems (CDSS) assist healthcare teams in interpreting and acting on individual patient

characteristics by providing tailored recommendations, alerts, and educational materials [8]. These features, combined with a foundational capability for aggregate data synthesis, facilitate a collaborative knowledge exchange that helps clinicians and patients better understand the rationale behind proposed actions and the uncertainties they entail [1]. With the rapid expansion of diabetes precision medicine, the mainstream implementation of relevant CDSS would help strengthen, or even catalyse, existing initiatives and investments in this area.

The historical aim of diabetes management to achieve normoglycaemia has evolved into a more nuanced understanding of the diverse benefits associated with the prevention and amelioration of hyperglycaemia, in the context of a broader vision of optimal metabolic, cardiovascular, and overall health. Despite the high mark assigned to glucose metrics in this evolving hierarchy, current measurement and reporting paradigms nevertheless remain substantially oriented towards the blood-glucose-centric view, severely hampering practitioners' attempts to navigate a multimodal landscape. In parallel to the development of multimodal outcomes frameworks, concerted efforts are under way to enhance the analysis, integration, and interpretation of quintessentially blood-glucose-centric data across distinct dimensions: time, place, frequency, and modalities.

An evolving Precision Disease Management (PDM) framework enables the consideration of patient heterogeneity, underscoring the need for a precision approach to diabetes and metabolic disorders [2]. The diabetes spectrum includes a variety

of immunological and metabolic forms. Type 1 Diabetes (T1D) manifests with autoimmune and multiple immunological targets, Type 2 Diabetes (T2D) is characterized by diverse metabolic phenotypes, and Gestational Diabetes (GDM) requires risk stratification and individualized intervention. Even as diabetes treatments become increasingly individualized, PDM applications extend beyond diabetes to encompass metabolically related conditions, such as obesity and non-alcoholic fatty liver disease, that require early management to avert further complications [1]. Substantial opportunity exists to enhance current diabetes and metabolic disease management systems through the implementation of precision approaches across PDM-focused domains.

With the recognition that Type 1 Diabetes (T1D) is heterogeneous, the 2021 Diabetes Care Precision Medicine article on immunotherapies for T1D emphasizes the need for personalized immunotherapies that consider temporal involvement of autoimmunity, genetic predisposition, environmental risk factors, and the preservation of endogenous insulin secretion [9]. T1D-predictive autoantibodies (AAbs) against β-cell proteins develop years before clinical onset and remain detectable from months to decades thereafter. Autoantibody profiling thus becomes the principal monitoring strategy for immune-modulating therapies during the preclinical, early, or late stages of T1D.

With the advancement of Insulin-Producing Cell (IPC) devices that restore metabolic control in patients with autoimmune T1D, monitoring AAbs against glucagon, C-

peptide, proinsulin, and GAD65 constitutes a rationale for assessing the risk of recurrent β-cell autoimmunity in IPC recipients [10]. AAbs against specific β-cell proteins develop sequentially and have been associated with specific HLA genotypes. Therefore, establishment of a personal profile based on the combination of first AAb detected and current HLA genotype may assist in anticipating additional AAb positivity. An extensive combinatorial and temporal profiling of autoimmunogenic markers would enable highly personalized immunotherapy against T1D before its clinical onset, yet no immunotherapy has been successfully approved for clinical use therefore far.

Type 2 diabetes is defined by a heterogeneous, complex pathophysiology. To aid in the stratified treatment of type 2 diabetes, patients can be divided according to the different metabolic and pathophysiological components of their hyperglycemia. These components include β-cell dysfunction and insulin resistance, as well as non-metabolic factors. A wide variety of treatment options are available to target the different metabolic contributors to hyperglycemia and to reduce the incidence of diabetes-associated complications. Individualization of treatments according to metabolic patterns contributes to optimizing management [11].

Gestational Diabetes Mellitus (GDM) affects approximately 1 in 7 pregnancies globally and is associated with risks for both mothers and babies. Optimizing treatment could improve outcomes, but current approaches are largely standardized despite substantial heterogeneity in GDM. A precision medicine

approach might enable risk stratification and earlier, more effective therapy. Routine clinical measures such as prior GDM history, body mass index, and blood glucose levels at diagnosis can help identify women needing escalation of pharmacological treatment. Further research is needed to identify additional sensitive markers, including complex individual-level data, and to assess their feasibility in practice [12].

Metabolic diseases beyond diabetes constitute a substantial part of a significant health burden. Precision disease management has started to garner attention in these conditions, focusing on patient stratification for targeted prevention and intervention.

Obesity and metabolic syndrome are major public health issues, with multifactorial physiological and environmental causes contributing to individual risk and preventive strategies. Conventional prevention approaches focus on universal recommendations that often fail to drive behavior change. Precision disease management proposes strategies to estimate obesity risk or metabolic syndrome status with long-term perspectives and to guide personalized lifestyle and pharmacological interventions.

Non-alcoholic fatty liver disease (NAFLD) has become an important form of chronic liver disease worldwide, posing a significant health and economic burden. Precision disease management aims at patient-level risk stratification at the time of diagnosis; while steatosis status is routinely assessed, the long-term risk of progression and underlying biological patterns remain largely uncharacterized. Identifying such markers can

enable the definition of targeted interventions to prevent disease evolution.

Rare and monogenic metabolic disorders are characterized by specific clinical traits and typically occur early in life. Precision disease management emphasizes the identification of existing treatments that target underlying molecular mechanisms and of additional criteria required to guide treatment selection in other congenital conditions. For monogenic diabetes, less than one in five cases is diagnosed, and increasing deployments of accessible gene-sequencing technologies could facilitate case confirmation. Equally, the availability of pathway-targeted or metabolic drugs to guide therapeutic decisions including associated biomarkers may improve the feasibility of precision approaches in suitably defined populations [2].

In developed countries, obesity and metabolic syndrome have gathered the status of an epidemic and a pandemic, respectively. Consequently, personalized prevention is becoming more important in stopping the emergence and spread of these two diseases [13].

Applying the concepts of metabolic syndrome and obesity, it is possible to define distinct patterns of risk and individual responses to each lifestyle- intervention regimen at the pre-obesity stage. These responses can be assessed experimentally via intervention trials or retrospectively via population cohorts. Behavioural experimentation and behaviour-context modelling can be tailored to fit such patterns of risk and response, and thus aid personalized prevention [14].

Metabolic diseases associated with type 2 diabetes, such as non-alcoholic fatty liver disease (NAFLD), obesity, and metabolic syndrome, share similar risk factors, pathogenesis, and disease progression patterns. NAFLD spectrum ranges from benign steatosis to non-alcoholic steatohepatitis with or without fibrosis, progressing to cirrhosis and end-stage liver disease. Although management of NAFLD remains less established than for diabetes, lessons learned from precision approaches to diabetes therapy optimization can inform NAFLD management [15]. Precision risk stratification utilizes demographic, anthropometric, laboratory, and clinical data to guide screening and patient-level management strategies [16].

Individuals with type 2 diabetes are at increased risk for NAFLD and require timely risk assessment to initiate appropriate follow-up. Clinicians should measure alanine aminotransferase and gamma-glutamyltransferase both at diagnosis and periodically during routine checks to screen for progression to advanced liver disease. In patients with fibrosis-4 index or a Hepatic Steatosis Index score greater than the set threshold, additional screening with ultrasonography or elastography is recommended. Various diabetes medications are being evaluated for their effects on hepatic lipid content and markers of disease progression, providing opportunities for targeted management. NAFLD has emerged as a major cause of liver transplantation in the U.S. and contributes significantly to hepatocellular carcinoma, highlighting the urgency for monitoring and intervention in at-risk patients.

Monogenic forms of metabolic disorders represent clear targets for precision management: their underlying biology is

understood, clinical features associated with different genotypes are established, and several targeted therapies are available. Because monogenic disorders account for a very small fraction of cases, targeted molecularly guided interventions are confined to rare, intractable, and severe forms of the disease that offer the prospect of substantial improvement [2, 17].

Pharmacogenomics principles can be applied to antidiabetic medications, enabling genotype-guided selection and dosing in patients with reduced response or increased risk of adverse effects. The pharmacogenologues of major classes of oral and injectable antidiabetic drugs are summarized, highlighting target genes and their clinical implications. Guidance for implementing pharmacogenomic testing for diabetes at the population level is also outlined [2].

Molecularly targeted therapeutics and combination modalities derive from profiling of tumor specimens, liquid biopsies, or circulating biomarkers and inform selection of agents or drugs in metabolic cancer precision therapy preliminary evidence for the druggable metabolic targets, pathways, and combined agents; the importance of biomarkers or surrogate variables indicative of the response to treatment remains prominent; and γ-aminobutyric acid and riboflavin drive selection of these agents and drugs in a specific molecular context [1].

Microbiome-targeted therapies arise from defined microbiota signatures implicated in metabolic diseases. Microbiota are linked to the regulation of carbohydrate, lipid, and amino acid

metabolism, and weight, with implications for targeted interventions, including prebiotics, probiotics, postbiotics, fecal microbiota transplants, and specific antibiotics now under investigation.

Pharmacogenomics in antidiabetic medications

Pharmacogenomics aims at DNA -based therapy selection and dose individualization while anticipating adverse drug reactions for safer and more efficacious therapy [18]. Pharmacogenomics of metformin, sulphonylureas, thiazolidinediones, and GLP-1-GIP receptor agonists-DPP-4 inhibitors represents key precision initiatives. Pharmacogenetic variability underlies inter-individual response to antidiabetic agents and metformin's pharmacokinetics [19]. Various loci influence glycaemic response to first-line agents (1-3 and 1-4) and second-line medications (1-5). Dual gene-modulating metformin-tolerability-combination regimens sulphonylurea, thiazolidinedione-site-matched addition together with approach-parent or GIPR improve safety and therapeutic regain. DPP4-sulphonylurea-facilitated retrieval proves glycaemic control amenable to triple-polygenic targeting and guides liner-initiated gain back of earlier-stage management. Functional variants have been associated with increased risk of glycaemic deterioration when dipeptidyl peptidase 4 inhibitors be initiated in type 2-diabetes patients on metformin monotherapy. Extensive research is warranted for a comprehensive pharmacogenetic framework that elucidates the combined influence of multiple-drug and drug-gene interactions and clarifies new candidate biomarkers per antidiabetic agent and modality.

Emerging type 2 diabetes therapies target pathways disrupted in a given patient. These agents are often combined to address multiple dysregulated pathways, and biomarkers of target engagement or on-target pharmacological effect predict patient response. Metformin-induced changes in lactate pathway metabolites predict responsiveness to adjunctive dual therapy, which dramatizes these concepts [2].

Recent efforts have focused on agents modulating the renin-angiotensin system, such as Angiotensin Receptor Blockers (ARBs) and neprilysin inhibitors (NEPi). ARBs and NEPi in type 2 diabetes jointly regulate multiple metabolic pathways, including glucose- and lipid-dependent hepatic steatosis, biogenesis of dysfunctional islet and enteric gluco-lipid metabolites, and SGLT-2-independent global and local glucose metabolism. Emerging data indicate pro-inflammatory, DPP-4 and GLP-1-independent, protective mitochondrial-signalling overlaps with metformin; coadministration potently augments GLP-1-GLP-2 analogue effects [18].

Specific gut microbiota signatures are associated with diabetes and metabolic diseases, and microbiome−metabolome studies indicate links between the microbiote and metabolic regulation. The gut microbiota also influences drug metabolism and antidiabetic drug response. Thus, microbiome-informed strategies to reshape the gut ecosystem represent potential therapeutic approaches in metabolic disease. Interventions tailored to gut microbial composition enable early-stage diabetes management and type-2 diabetes treatment strategies. Ongoing research is exploring the bi-directional relationships between gut

microbiota, their metabolites, and antidiabetic therapeutic agents, aiming to facilitate precision-targeted management of metabolic disease [20, 21].

Precision medicine in diabetes and metabolic diseases aims to tailor therapies according to individuals' characteristics, enhancing effectiveness and minimizing side effects. Several typologies stratify diabetes and metabolic disorders according to underlying pathophysiology and patient characteristics. Stratified approaches for precision guidance cover type 1, type 2, and gestational diabetes, obesity and metabolic syndrome, non-alcoholic fatty liver disease, and rare or monogenic metabolic diseases. Emerging precision therapeutics, such as pharmacogenomic-guided treatment, pathology-targeted drugs, and microbiota-informed dietary modulation, are also in development [2].

Long-term, real-world data collection is necessary to monitor the execution and outcome of precision diabetes and metabolic-disease management. Monitoring precision diabetes management entails documenting the timely initiation of target-modulation strategies as well as the periodic assessment of the trajectories of key biomarkers and associated clinical events. Monitoring precision metabolic-disease management involves tracking the implementation of tailored prevention, intervention, and follow-up plans and collecting relevant clinical outcomes. In both cases, micro-level indicators of the execution of stratified prevention, intervention, and follow-up interventions are needed and can be derived from routinely recorded data. Lastly, the development of aggregate indicators to capture the overall extent of executed precision-medicine approaches is a priority [1].

Long-term outcome tracking remains an ongoing challenge. There is a tendency for diabetes precision medicine datasets to be predominantly cross-sectional; securing longitudinal data is of paramount importance and requires dedicated collection efforts [7]. For diabetes, the health outcome metrics typically pertain to rates of diabetes complications (retinopathy, nephropathy, neuropathy, etc.), glycaemic control parameters such as HbA1c, weight and Body Mass Index (BMI), as well as supplementary clinical notes. These metrics are pertinent to long-term monitoring of diabetes precision medicine strategies [6].

Shared decision making and patient engagement highlight two crucial aspects of precision disease management. These concepts emerge from clinical interactions, during which patients' unique life situations shape priorities and influence management approaches. Firms in many sectors engage with consumers to ensure offerings align with needs and preferences. Like firms, health services shape their offerings based on consideration of consumers' requirements; however, these exchanges often complicate delivery. Instead, market leaders closely interact with consumers. Such approaches reflect higher engagement and admiration, characteristics seen in shared decision making [1].

Initially, patient engagement signified consumerism in the health sector; the advent and impact of the internet amplified the bid for active consumer participation in health care and health portfolio decisions. Such trends gradually matured to become patient engagement, a shared concern for active participation during clinical consultations and precision medicine [22]. Shared

decision making reinforces this personalised health engagement. In decisions on medication, either chronic or acute, patients remain invested and actively involved, contributing useful insights while gaining a sense of ownership of their personal health [23].

Rapidly advancing digital technologies have created new opportunities for data generation and integration, enabling healthcare systems to better characterize patients and identify those most likely to benefit from a given intervention. While personalized and precision medicine respectively emphasize tailoring interventions to the individual and targeting subgroups defined by shared disease mechanism or treatment response, discerning meaningful and clinically actionable precision indicators for diabetes remains an ongoing challenge [1]. Moreover, the increasing generation and availability of large-scale datasets particularly those associated with genomics, transcriptomics, proteomics, and metabolomics has the potential to deepen understanding of the epidemiology of diabetes, its aetiologies, and associated complications [24]. Clinically relevant clarifications of existing knowledge gaps are therefore essential to achieving effective integration of precision medicine data into diabetes prevention and control efforts.

Although the advent of computing technologies capable of generating increasingly large and complex datasets has stimulated investment in genomics, epigenomics, proteomics, metabolomics, and even transcriptomics, large datasets focused on physical activity, cellular activity, sleep, diet, and social environment are equally applicable to diabetes. In addition to

patient characteristics such as risk factors and physical, biological, stress-related, clinical, and demographic characteristics, context data about health care institutions, social determinants of health, and governmental public health policies remain equally critical. A comprehensive analysis of such datasets enables identification of data features consistently associated with diabetes across various cohort studies, geographical regions, health care systems, and diverse populations, thereby illuminating potential targets for intervention.

Precision Disease Management aims to address critical implementation challenges in diabetes and metabolic disease. Priority challenges include establishing data interoperability and common standards for effective integration of diverse datasets supporting disease management [1]; increasing equitable access to stratification pathways, interventions, and necessary skills and infrastructure [2]; and clarifying regulatory frameworks guiding the incorporation of multiparametric, including digital, patient data into decision-support systems and precision guidelines.

Data interoperability remains a major barrier shaping the characteristics of metropolitan and semirural clinics and centres, the link to primary care, participation in data-science initiatives, and broad implementation of precision approaches throughout diabetes care. Supporting interoperability within clinics requires the establishment of a core record; attention to transmission formats, coding, and ontologies; and availability of the necessary skills, support, and hub agreements. Out-of-clinic initiatives would benefit from widely adopted data and disease-

management standards comparable to the common guidelines for diabetes systems and technology.

Precision Disease Management is transforming the implementation of precision medicine from principle to practice in diabetes and metabolic diseases. The approach links innovative digital health ecosystems that deliver rich patient data outside traditional healthcare visits, with Artificial Intelligence operating at the crossroads of multidisciplinary clinical and biomedical data to generate tailored recommendations.

The concept of precision medicine encompasses interventions informed by individual characteristics such as genetics, environment, or lifestyle [7]. The paradigm delivers more precise risk assessments, diagnoses, prognoses, and treatment strategies compared to conventional, class-based approaches. Diabetes and metabolic diseases major threats to population health worldwide are prime candidates for precision approaches at different stages of the care pathway. An increasingly urgent need is the early identification of individuals at high risk of developing type 2 diabetes, obesity, or non-alcoholic fatty liver disease [25]. Identifying such individuals and estimating their likelihood of progression supports targeted preventive actions, as do precision approaches to the monitoring and management of gestational diabetes. One of the largest longitudinal cohorts of type 2 diabetes patients in a real-world setting highlights the risk of substantial morbidity and mortality even when patients achieve sufficient glycaemic control, and exemplifies the case for stratified care.

Access to disease management tools is a major goal of precision medicine. Evidence suggests that patients using diabetes devices achieve lower blood glucose [26]. Yet device access is often limited for underserved communities. For Type 1 Diabetes (T1D), patients are expected to start using devices soon after diagnosis, anywhere from 5 days to 6 weeks post-diagnosis. T1D is best managed using a Continuous Glucose Monitor (CGM), smart insulin pen, or hybrid closed-loop insulin delivery. Unfortunately, there is a noticeable under-prescription of these devices among Black, Hispanic, and other underrepresented groups with T1D. Prior studies have shown wide disparities in access to diabetes technology for Type 2 Diabetes (T2D) as well, despite overall greater engagement following the COVID pandemic [1].

Regulatory agencies play a crucial role in driving the translation of precision medicine in diabetes and metabolic disorders into clinical practice. The Technical Framework for the Integration of Health Informatics into Digital Public Health describes the design principles and key parameters of public health digital health strategies. The European Medicines Agency has identified and proposed several studies within the Adaptive Pathways initiative. The U.S. Food and Drug Administration has released a framework for real-world evidence. In diabetes, analyses led to U.S. and European regulatory approvals for Glucometer (LifeScan, 2001) and the first user-applied Continuous Glucose Monitoring system (Dexcom, 2016). Similar initiatives on health data integration, use, and governance

for addressing data richness, connectivity, and interoperability are relevant.

The growing burden of diabetes and metabolic diseases demands innovative approaches, yet conventional efforts toward individualizing therapy remain fragmented, restrictive, or inadequate. Precision Disease Management integrates diverse data on pathophysiology, etiology, and disease progression to holistically characterize patients; predict complications, comorbidities, and therapeutic responses; and tailor management accordingly. Strategies enable applications in type 1 diabetes, type 2 diabetes, gestational diabetes, obesity, metabolic syndrome, non-alcoholic fatty liver disease, and rare or monogenic metabolic disorders [22]. Further progress in the field requires multidisciplinary collaboration, expanded datasets, standards for data-sharing and integration, policies that enhance accessibility and affordability, sustained monitoring of real-world outcomes, and increased awareness among healthcare professionals.

Precision Disease Management represents a transformative advance within the precision medicine landscape. Continued exploration may yield critical insights into diverse health challenges across the ages, unlocking new opportunities and providing enduring benefits to patients, clinicians, and researchers worldwide.

Neurological disorders (Parkinson's, epilepsy)

Neurodegenerative disorders such as Parkinson's Disease (PD) affect millions annually. These conditions necessitate

continuous dosage management of hormones and neurotransmitters. PD treatment involves periodic drug administration; however, prolonged sinus node stimulation and dopamine release can harm the organ or cause side effects. Consequently, constructing parallel implantable smart microdevices enables responsive insulin/cytokine secretion and close-loop control of neural nucleus stimulation (without skin piercing) and subsequent dopamine release. Epileptic seizures are primarily treated with antiepileptic medications that maintain blood concentrations between the toxic and effective ranges. Artificial intelligence predicts seizure onset through continuous electroencephalogram monitoring and controls a closed-loop antiepileptic delivery implant to release a precise drug quantity before a seizure. These AI-driven predictive algorithms apply to harmful environmental conditions, thereby automatically adjusting functional layer thickness. Diabetes and neurological disorders illustrate near- and far-field wireless telemetry for feedback-controlled drug delivery, respectively [120, 121, 122, 123].

Cardiovascular conditions (hypertension, heart failure)

Cardiovascular diseases affect more than a quarter of the US population, with two-thirds of these conditions attributed to hypertension. Current treatments involve invasive procedures such as stent implantations and bypass surgeries, along with a range of drugs. Despite the widespread availability of antihypertensive medication, nearly half of individuals receiving it continue to have uncontrolled hypertension, often due to non-adherence. Although a closed-loop system has been demonstrated for a complete feedback system, including blood

pressure control, it currently requires the implant of an electrochemical actuator. Local injection of antihypertensive drugs represents a feasible and less invasive approach for hypertension population. The development of biodegradable and biocompatible closed-loop devices offering a drug release according to specific patient conditions would certainly facilitate patients' adherence, thus improving the management of hypertensive patients. Recent studies on drug delivery systems capable to respond to specific biological signals suggest the feasibility of a similar approach in controlling the hypertensive process.

Heart failure is a growing epidemic worldwide, due to an ageing population and increasing rates of diabetes, hypertension, and ischaemic heart disease. Heart transplantation, although scarce, remains the gold standard of care for advanced heart failure, with the development of total artificial hearts and long-term left ventricular assist devices helping towards this goal. A novel therapy for the management of heart failure with preserved ejection fraction consists of the selective administration of pro-inflammatory cytokines to induce transient left ventricular contractile improvement in conjunction with bilateral thoracic vagal stimulation. Such a strategy requires the ability to deliver a wide panel of cytokines in a time-response manner, thus ideally suited for a closed-loop system that would exploit the natural phe-nomenon of circumferential cardiac nerve fibres around the left atrium in the delivery of a cytokine mixture in an automated manner based on the patients need [124, 125, 126, 127].

Oncology and chronic pain management

Local delivery strategies have been explored for the treatment of various diseases, including diabetes, neurological disorders, cardiovascular diseases, cancer, and pain. Patients with diabetes may benefit from implantable devices capable of releasing insulin or anti-diabetic agents from reservoirs replenished using minimally invasive procedures. Discomfort from certain chronic pain conditions could be alleviated via the localized release of pain-relieving agents, for example, through an artificial closed-loop system that employs a microelectromechanical glucose sensor for monitoring and a microinfusion pump for glucagon-like peptide-1 administration, which activates insulin release.

Local drug delivery could also lessen the side effects associated with systemic treatments. Such a strategy is particularly appealing for the treatment of cancer, where chemotherapy is often accompanied by severe adverse events. Microinfusion devices have thus been proposed for the continuous delivery of gemcitabine, 5-fluorouracil, or cisplatin into pancreatic, colonic, or bladder cancer tissues, respectively. To combat bacterial infections, deterioration of tissue implants, or inflammatory diseases, microchips capable of delivering anti-inflammatory agents and antibiotics have been developed. A closed-loop fully implantable system for the pharmacological treatment of epilepsy has also been reported, with a microelectromechanical pH biosensor for real-time monitoring and an integrated electrochemical stimulator delivering a cocktail of antiseizure drugs [128, 129, 130, 131].

Chapter - 11

Artificial Intelligence and Data Analytics Integration

AI for predictive dosing and adaptive control

In addition to enabling real-time monitoring and delivery, implantable microdevices hold promise for closed-loop control through prediction, feedback, and adaptive adjustment of the dose. These approaches rely on biologically relevant data or surrogate physiology to anticipate the dose a capability shared with a similar artificial pancreas concept. AI-driven predictive dosing represents an exciting direction within this context.

An AI-based predictive dosing approach has been demonstrated for an implanted drug delivery device for epilepsy. A combination of monitoring data from an external wearable; a cloud database of all health data; prediction of future biosensor signals through an LSTM network; an online adaptive Kalman filter; and Monte Carlo simulation produced a digital twin of the patient. With this twin, a predictive dosage of disulfiram a drug that reduces the frequency of seizures was achieved, minimizing both the average amount delivered to the patient and the number of days of high-dose treatment.

Underlying these developments is a shift from conventional repeat-biosensing-regenerate routes toward forward-looking prediction-adaptation strategies that closely resemble the predictive functional behavior in all biological entities. Similar concepts can be developed for adaptive control of the implant; that is, adjustment of the control algorithm to compensate for caused degradation or changes in the bioenvironment. Such calibration can be aligned with the health-check program for the patient [132, 133, 59, 134, 135].

Machine learning models for patient-specific optimization

The ongoing revolution in artificial intelligence is transforming most areas of industry and research, including healthcare. Within this sector, emphasis is being placed on the year-on-year increase in health data generated by patients. Such a large volume of information can be used in preventive and predictive algorithms that allow anticipating such health events. The patient's own record can also serve as a basis for end-to-end treatment optimization, taking into account the characteristics of the disease together with biological and environmental information. Symptoms and possible risks can therefore be inferred. Moreover, prediction of the best combination and dosage of drugs to use during treatment increases the chance of a successful application with minimal side effects.

For example, in the case of diabetes, the glucose concentration in the blood has important physiological consequences. Moreover, inappropriate insulin concentrations produce hyperglycemia and hypoglycemia episodes, both of

which cause damage and can even lead to death. The whole process can be addressed from a daughter machine-learning model that builds on a dataset of insulin-glucose pairs obtained during the normal evolution of diabetes. Another approach would use predictive models that not only minimize classical training errors, but also consider risk functions defined over the outputs.

All this means that the therapy development using such implantable smart microdevices can no longer be limited to the use of expert knowledge. As for many other applications, patient-specific optimization is now an increasingly important demand, leading to the deployment of data-driven approaches [136, 137, 138, 139].

Cloud-based health data platforms

The cloud-based platforms provide a centralized repository to continuously store and share patient health data, including information from wearable sensors. Such platforms can be used to create digital twins that mimic the response of an individual under various conditions. Clinical data generated during monitoring are valuable and can be used to parameterize digital twins and simulate patient-specific responses. In combination with AI-based predictive algorithms, data driven digital twins can help optimize treatment strategies prior to implementation in the patient. Predictive models allow testing patient therapy with different scenarios to minimize side effects or maximize efficacy of the treatment over time. Testing therapeutic strategies on non-actual digital twins can be done from any developer, such as independent researchers, companies, or public institutions.

Hence, therapy can be optimized faster, cheaper, and independent of physical limitations of developing real-time and real-condition experimentation. Digital twins can be used as templates during bench-to-bedside therapy development when applied in general with patients groups and can help generate initial hypotheses, or shortcuts when there can be data scarcity for modeling.

AI techniques applied monitor a patient on the actual time, learn the optimal control policies of an adaptive disease model or digital twin, and automatically modify the controlled variables of the patient in real time without the need of understanding the patient full physiopathology. Algorithms requiring fewer data to provide controlling solutions are of particular interest and decrease the time and money involved for model parameterization. The combination of different data sources, such as wearables, implantables, and traditional means, is relevant, as any source can monitor the pathology state. The amount of data provides different perspectives, and appropriately fused data improve reliability and completeness. The synergy enhances the modification of treatment devices implanted for additional therapy, or implement preventive strategies as alerting and alerting-fuzzy control [140, 141, 142, 143].

Digital twins and simulation for therapy planning

Online platforms aggregating cloud-based health data facilitate the use of patient-specific digital twins that predict responses to various treatment options including predictive biostatistics, patient-specific dietary and pharmacological regimens, and digital transformation of dosage regimens.

Coupled with accurate simulations, this drives custom-made solutions. The answers yield insight into the most suitable treatment strategy, indicating the necessary control-engine structures, devices, and optimally tuned set points required for achieving effective and robust closed-loop drug-release control.

In digital health, patient data stored in databases on the cloud can be accessed anywhere worldwide. Cloud-based processing at affordable costs allows the design of digital twins that respond accurately to control inputs over realistic time frames. Digital twins are increasingly used in healthcare to predict the patient-dependent outcome of a wide range of clinical interventions. Such online databases provide the opportunity for a patient to choose an optimized and personalized dietary or pharmacological regimen to achieve a specific objective. When combined with an accurate simulation tool, they provide answers that allow the identification of the most suitable therapy and the determination of the dosing regimen. In the digital-twin framework, health record data become part of the software for predictive biostatistics.

In the specific case of the digital twin associated with feedback-controlled drug release, the cloud-based automated solution provides information about which control engines are necessary to achieve effective control and which set-point operations need to be implemented. Digital twins and online simulations thus allow the prediction of closed-loop drug-release profiles using external eHealth wearable sensors [144, 145, 146, 147].

Chapter - 12

Clinical Translation and Human Trials

From bench to bedside: Regulatory pathways (FDA, EMA)

The progression of an implantable microdevice from conception to routine clinical use entails the meticulous execution of several well-defined stages. The initial phase, commonly referred to as "bench testing," involves *in vitro* experimentation supported by computer simulations to establish proof-of-concept and assess performance and effects associated with use. Microfabrication and packaging are subsequently optimized to ensure proper hermeticity. After successful initial testing, the device undergoes further evaluation in animal models, with the objective of "first in man" trials. Following the completion of such trials, the final hurdle consists of the underlying regulatory procedures, which can be particularly demanding. Depending on the region of the world, the relevant approving authority may be the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). While these processes are distinct in their details, they share many similarities, requiring careful preparation and preparation if time delays and higher costs are to be avoided.

The FDA process recognizes several classes of medical

device, each subject to progressively more stringent requirements. Any implant that involves active electronics is at least Class II, necessitating filing of a 510(k) premarket notification demonstrating equivalence to an existing implant that has already completed the review. Submission of a Premarket Approval (PMA) application is required for the highest-risk devices, demanding far more extensive clinical data than the 510(k) procedure. These implants are subject to more intense "post-marketing" surveillance than their lower-risk counterparts. The European Medicines Agency (EMA) is the relevant body for member nations of the European Union (EU) and the European Economic Area (EEA), which have a shared approval process for module-based pacemakers and sensing devices. Within that framework, the National Institute for Health and Care Excellence (NICE) in England provides additional coverage [148, 149, 150, 151].

Preclinical testing and animal models

The successful and extensive application of implantable microdevices in humans requires a comprehensive and rigorous verification and validation process to ensure that all potential risks are mitigated, that safety is adequately compared with conventional solutions, and that the intended therapeutic benefits are realized. A significant portion of this evaluation might be carried out during preclinical testing with appropriate animal models, allowing assessment of the therapy in a closely matching physiological environment, although regulatory approval for clinical trials will ultimately depend more on the effectiveness and safety of the complete system rather than solely the implantable microdevice itself.

Animal models of the disease, involvement of standard-of-care treatment, or New Approach Methodologies (NAMs) to assess human physiology and potential risks and benefits are preferred. The research team thus needs to establish a strong rationale for using a specific animal model. For example, an artificial pancreas implanted in a pig could provide a valuable experimental ground prior to human trials because of the similarities in size and blood glucose level response between pigs and humans, the porcine anatomy being well-defined, and the availability of diabetic pigs. Animals are used to validate the release rate, therapeutic efficacy, and safety of implanted microinfusion devices, such as a system for the local perfusion of complex chemotherapy formulations in orthotopic tumor models. Subsequent trials follow with other animal models closer to the target population. Any cytotoxic effect of polymeric reservoirs used in the controlled release of anti-inflammatory drugs is evaluated during screening of suitable materials with a co-culture of human peripheral blood mononuclear cells and either fibroblasts or keratinocytes [152, 153, 129, 154].

Human clinical trials: Design, ethics, and outcomes

Planning human clinical trials for novel therapeutic devices is a systematic but complex process. Medical need, device risk, approach to therapy, and technology requirements all contribute to trial design, which encompasses nonclinical research, clinical risk analysis, and preparation of a Clinical Investigation Plan and Investigational Testing Application. Evidence generated in the early animal and human studies and their relevance to later full-scale trials, including the regulatory strategy relative to standard

drug development, are assessed. A detailed example of the end-to-end process illustrates these aspects in relation to neural stimulation and sensing devices.

While the design process is universal, its particulars differ for active devices and other technologies. The need for nanobiohybrid devices to replace nonresolving drug-delivery approaches has already been established; however, there are important biological tests and other nonclinical development aspects that must be specific, relevant, and adhered to. The fundamental engineering challenges are also being addressed: what type of reservoir and release mechanism should be utilized, and what actuating signal properties are required? Further clinical trials, especially for therapy personalization, require a thoughtful perspective. Predictive and adaptive algorithms using dedicated datasets can prove crucial because, in a clinical setting, each patient is atypical and may present a multifaceted, hierarchical disorder [155, 156, 157, 158].

Challenges in large-scale manufacturing and standardization

Mass production of implantable smart microdevices demands robust, fast, reliable, and economical processes that yield consistently high-quality products. Most current technologies remain ill-suited for commercialization. Batch processes such as MEMS and NEMS fabrication may be too slow and expensive for mega-scale production. 3D printing has considerably shortened individual-process time, but full systems often still require assembly by specially trained personnel unavailable at all times in developing countries. Technologies allowing rapid,

flexible, and low-cost production of truly integrated devices will therefore be needed.

Global masses of implantable microdevices will also require industrial standardization and quality assurance, as performed by government agencies, acknowledged laboratories, or international organizations. Such standards should specify quality parameters of fabrication procedures, performance tests, and methods for validation and assurance through the complete life cycle, covering also materials, batch monitoring, long-term operation, residual risks, and end-of-life management. Economic prosperity relies upon the careful integration of these aspects. The currently strongly emerging concept of digital twins offers exciting new opportunities in this field [3, 159, 160, 161].

Chapter - 13

Regulatory, Ethical, and Security Considerations

Data privacy and cybersecurity in connected implants

The integration of real-time biosensors, actuators, and data analysis in implants presents novel perspectives on disease management and personalized therapy. The collection, storage, and processing of sensitive personal health data raise concerns about patient privacy and data security. Cyber-attacks on implants may compromise sensitive information or damage the devices, resulting in severe health consequences. Various aspects of data protection are considered, including informed consent, data ownership, the potential for future utilization, data handling by third-party entities, network security, resilience against cyber-attacks, and post-market surveillance.

The use of Artificial Intelligent (AI) systems for data analysis raises additional ethical issues, as the assigned power to an intelligent agent may compromise patient autonomy and independent decision-making. Systems equipped with AI capability are often labeled as “black boxes,” which creates uncertainty regarding their recommendations. Consequently,

developing standards that define AI collaborations in concurrent and adaptive control is essential. Automation and predictive capabilities need to be balanced with patient safety, and strong authorizations are necessary to mitigate risks. It is essential to retain patient trust and to support the clinical use of these automated systems. However, digitally-controlled closed-loop devices also have significant advantages for patients if the associated risks are correctly handled [162, 163, 164, 165].

Informed consent and patient autonomy

One principal aspect of any clinical experiment or therapeutic approach is informed consent. Information about the device, its proper functioning, possible adverse events, and the potential benefits should be clearly stated for the patient before implantation. Patients participating in data collection or clinical experiments must also consent to share their data with the manufacturers. The device and data are continually transmitted to the manufacturer through a cloud platform, and thus the system can potentially collect information from several patients for further improvements. The risks, advantages, and disadvantages of sharing data must be explained to the patient, with emphasis placed on the possibility of having the information utilized for both marketing and improved treatment. A cloud service presents a major risk of data security, and any data leak could affect the patients. This requires strong data protection protocols to ensure confidentiality and directed access to authorized personnel only.

The devices require baseline data for feedback control algorithms and further patient-specific tuning and optimization.

These can be performed during practice sessions before implantation. The algorithms may also need adjustments after any significant physiological change (e.g., hormone changes in women, weight changes, stress) for optimal patient-specific control. All of these concepts lead to a need for minor surgeries and implantations in various types of patients with different attributes. These needs can be solved through the creation of an "adaptive digital twin," a novel concept that consumes information storage for every individual patient, identifying essential features and thus needing fewer data samples. The requirements for implementing specific algorithms for individual patients must be communicated clearly to each patient at the beginning of the therapy system [166, 167, 168, 169].

Risk management and liability

Real-time monitoring and closed-loop control allow predictive and adaptive drug management for specific disease states. However, new ethical risks arise from data security and privacy concerns, the carving out of data-access rights, and involuntary changes of treatment parameters. Although patient autonomy can be safeguarded through functional data ownership by the patient, other facets must be underpinned by ethical guidelines. These aspects and their connection to the process of informed consent during the installation of a feedback-controlled medical device have implications for data-sensitive investigations. Existing laws and requirements defined by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and the Clinical Trials Directive (CTD) can be extended to facilitate human trials. The establishment of

standardized therapeutic procedures with real-time control reduces trial risk. The predictive-human-adaptive control concept helps brace for the implications of nonlinearity and catastrophe. Proactive third-party data-protection and cyber-safety systems render digital connections less vulnerable to exploitation, while general cybersecurity architectures enable intelligent real-time data protection.

Novel developments in predictive, responsive, and patient-specific drug therapy enable considerable risk reduction. However, the very nature of feedback control, which can destabilize behavior in vulnerable anti-control zones, implies the remaining possibility of unsafe operation. Autonomy remains unaffected, since the actual configuration of the drug therapy also remains under patient control. The new risk phase was heralded by the establishment of a true artificial pancreas, complete with control functions, and has now advanced to the point of near completion of a reliable pain-management system. The internal border wiring of the control function trajectory is merely a matter of time. As long as the physiological model is well tuned around the actual physiological operating point, the method remains proactively enabling for patient safety and comfort [170, 171, 172, 136].

Post-market surveillance

Despite extensive premarket testing, the safety and efficacy of a new implantable microdevice still need to be monitored after regulatory approval to assess potential risks stemming from previously unconsidered aspects or its combination with a specific patient profile. Long-term consequences of implanted

devices may originate from design flaws, unpredicted kinetics, failure to accommodate patient heterogeneity, effects beyond the initiation of therapy, or, generally, any aspect overlooked during preclinical assessment. The incorporation of biosensors into microdevices allows continuous collection of individual data that can be securely transmitted via telemetry to a centralized database, enabling analysis of multiple devices in real-world conditions. Advanced data processing can identify potential links between device function and adverse reactions, enabling corrective actions either in later-production appliances or through proper patient training for early detection and management of complications.

Novel approaches, artificial intelligence, and personalized medicine often evolve through clinical testing with volunteers affected by the treated disease. of microdevices based on these concepts offers a unique opportunity to monitor patients receiving chronic therapy and adapt treatment depending upon response, improving safety and efficacy. However, clear insertion and replacement protocols, both for active devices and adjunct external sensors, still need to be established in order to adequately support the required bench-to-bedside transition [173, 174, 175, 176].

Chapter - 14

Emerging Technologies and Future Trends

Nano- and pico-scale drug delivery systems

Research interest in novel drug delivery systems is expanding down the spatial scale, as major advances in materials science enable drugs to be delivered for specific therapeutic applications from volumes that approach single molecule and nanoparticle quantities. Recent advances include nano- and pico-scale carriers designed to load and catalogue drug. Many exploit the drug itself as the active ingredient in biodegradable carriers that are created *in situ*, as for example, with the self-assembled hæmoglobin-containing protein-lipid nano-containers for the delivery and release of nitric oxide for the treatment of vascular diseases. These pico-scale systems can operate with massive excess volume but lost drug through biotransformation. Topical delivery of the therapeutic enzyme trypsin is achieved by topical intradermal application of biodegradable polymeric nanocarriers functionalised with a homing peptide that, assisted by the tryptic enzyme, crosses the dermal barrier toward a fibrous nidus in the deep dermis-superficial subcutaneous. Polyethylene glycol (PEG) drug conjuagates are being developed to overcome

phospholipidic barriers by the combination of high drug-carrier activity ratios with a slower biotransformation through the protic environment below the major barrier, PEG-lipid self-assembled surfactants to enclose and translocate chemotherapeutics through the blood-brain barrier, and PEG-targeted-photodynamically active nanosized liposomes for cancer therapy [177, 178, 179].

Picoliter volume drug units have been proposed for the more sustainable management of acute benign lesions of human and animal skin and mucosae, as well as of local infections. These medicine-free units have no one-to-one relationship with drug-symptom pairs. PICOs, very short for picoliter construction, are made solely of PEG, have a mean internal free-volume lower than single-molecule size, and can harbour surfactants or droplet-growth modifiers. They adapt their chemical environment to any applied drug sufficiently concentrated and are catalytically active against drug degradation that is, inhibitors promote drug inhibition rather than catalyse action. Data for the five major anti-infective classes, which have several multimolecular-symmetric antidotes, point to a considerable decrease in the volume of penetrated solution when the penicillin unit is added. An adjusted PIC formula pointing to MIC-unit superposition indicates that a broad variety of surfactants could be suitable additives to enhance their action against delicate tissues. These propoals open up new avenues for healing practice: the aim is no longer a drug with a corresponding, active-molecule concentration, but the smallest non-free-drug volume that generates enough local drug by catalytic slow release.

Soft robotics and biohybrid implants

Recent advances in materials science and engineering have enabled the development of soft robots for use in sensitive environments, such as the human body. The design principles of these devices are similar to those for biohybrid systems and implants. Research in these areas has primarily focused on drug-delivery applications, highlighting autonomous operation in closed-loop systems. Current bottlenecks are sensor integration, long-term operation, and reliable trials in living organisms.

Current investigations also include nano- and pico-scale systems and implantable devices for personalized autonomous therapy. Soft robots are mainly composed of elastomers or hydrogels; their mechanical properties ensure that operation is gentle on fragile items. The soft-living hybrid design finds application in flying robots controlling air-swarming behavior with feedback from living sensors, such as fish. Many of these interruptions also rely on closed-loop control. Programming bleeding behavior could enable control over the movement of a soft robot in an aquatic environment. Integrated automated surgery remains unreachable, but these principles provide inspiration.

Biohybrid actuation powered by energy sources from living organisms paves the way for novel exploratory robotic devices with long operational times. These ideas have naturally been brought to the field of drug delivery, where a self-powered system that integrates chemical sensing, chemical actuation, motion control, and error detection remains in the conceptual stage [180, 181, 182, 183].

Self-healing and biodegradable devices

Biodegradable materials minimize environmental pollution and reduce the long-term risk of implant failure. Conversely, self-healing components are crucial for long-term operation, particularly in implantables for the central nervous system that cannot withstand repeated implantation. The two approaches have now converged, enabling the development of self-healing, biodegradable electronic-coated hydrogel membranes. Such devices could potentially be integrated into or placed within the body for long-term monitoring of chemical species such as glucose, pH, and cytokines.

Nanoparticle-assisted evaporating self-assembly has been used to fabricate free-standing and self-healing multilayer hydrogel films. The approach utilizes saccharide-chemistry-derived hydrogel and nanosilica at the surface of a saline droplet that evaporates. Hydrophilicity, mechanical property, and electrolyte permeability shear velocity determine the anisotropic swelling behavior. Surface chemistry prediction on the basis of free energies of adsorption places hydrophilic polyols with higher osmotic pressure at the hydrogel-solution interface during swelling. The self-repair can be triggered by physical stimulus (e.g. gap closure) or chemical factors [184, 185, 186, 187].

Integration with wearable and external sensors

Seamless integration between implantable microdevices and wearable/external sensors paves the way for enhanced closed-loop control as well as for more specific control algorithms (e.g., predictive or adaptive). Wearables have shown great promise for

non-invasive and continuous monitoring of various physiological parameters. Data gathered from wearables can also be integrated with cloud-based health data platforms and used by specialized algorithms (including artificial intelligence) to predict future values of monitored parameters (e.g., blood glucose concentration). Similar modeling-based predictive approaches can also be applied to improve biological parameters associated with wound healing, and data generated by models can be used to reproduce desired glucose concentration profiles in artificial pancreas systems. Information-sensing and biosensing wearables serve multiple functions, including monitoring of glucose, urea, sweat compounds (e.g., lactic acid), bilirubin, hormones, blood pH, ECG, and EMG. The timed release of insulin, drugs, or nutrients can be further optimized by examining variations in the environment and adjusting the response of drug delivery systems. Smart wearable designs based on radio-frequency identification technology have enabled the continuous tracking of body temperature, perspiration, and heart condition.

The concept of digital twins, in which the behavior of biological systems is replicated in simulation, has been playing an increasingly important role in personalized medicine. Benchmarking data are being employed in tandem with cloud-based health data to create digital twins that are as close as possible to the real system. These digital twins are then utilized to define the personalized behavior of biological systems, including the prediction of blood glucose concentrations. Such methodologies can therefore be employed to assist closed-loop systems in mimicking the natural response of human bodies, thereby contributing to active disease management [188, 189, 190, 191].

Chapter - 15

Conclusion and Outlook

Lessons from current developments

Successes in developing intelligent implantable microdevices demonstrate their benefits for specific diseases. However, from a broader perspective, such systems are yet to be widely deployed, indicating risks and challenges that must be confronted for mass adoption. These insights may inform future development efforts for implantables that enable closed-loop control and predictive algorithms, aligning with the real-time disease management paradigm.

Despite numerous publications and demonstrations, autonomous closed-loop control remains scarce. In most cases, the implant responds to independent external inputs rather than leveraging biological measurements for decision-making and feedback control. Even fewer systems incorporate adaptive algorithms. Thus, although autonomy offers significant patient-centric advantages, its current frequency of implementation and level of intelligence do not reflect the system's technological maturity. The disjunction highlights both design complexity and acceptance barriers. A deeper understanding of the specific

mechanisms involved in the process and their functions may improve patient acceptance, leading to a natural shift toward autonomous systems. Key implementations in closed-loop control and predictions, especially those using artificial intelligence-driven predictive dosing or adaptive algorithms, can serve as valuable examples when positioning future designs toward autonomous real-time control. In particular, the literature on predictive algorithms for closed-loop systems is rich and serves as an excellent resource for the development of intelligent implants.

Analysis of the ethical and regulatory aspects of these microimplants is equally essential to their deployment. Closing the loop from biosensor to actuator represents a critical step in managing human health with medical implants. Exploring the potential for supervise-free medical administration of implants is tentatively proposed. Such a digital twin of the human body has major implications for systematic action, patient autonomy, and even social interaction. At the same time, ethical dimensions and perspectives must be clearly understood and addressed before realization can become a true focus of progress. Data management, privacy, security, patient consent, and caregiver involvement during the healing process are highly sensitive. Choice logging and continual monitoring are essential touchpoints that reinforce confidence and altruism. Finally, combining all these elements with the subsequent feedback-control path to further qualify implanted or medical-device action ensures holistic patient harmonization.

Challenges to overcome for mass adoption

Despite the rapid progress and numerous demonstrations of real-time monitoring, closed-loop control, and biosensor-actuated release, implantable microdevices remain relatively uncommon in clinical practice. Scaling up manufacturing and establishing standardized protocols for MEMS and NEMS would decrease production costs, promote wider use, and reduce engineering time for novel devices. In many applications, however, electronic miniaturization is limited: implant volume is constrained by the volume of available batteries, while extensive use of wireless data transfer incurs the cost of communication security. Efforts to provide wireless power or battery-free operation reduce miniaturization requirements, impose new constraints on device operation, and presently limit deployment to low-power systems. In addition, although key release components are commercially available, miniaturized adaptations of liquid pumps and reservoirs are less common.

Regulatory pathways and preclinical testing protocols, designed for traditional, visible-scale implants, may not suitably address the challenges of closed-loop systems. Digital data sources and predictive algorithms introduce new responsibilities for physicians and patients alike. Predictive therapy driven by artificial intelligence raises questions of patient autonomy and responsibility; possible breaches in algorithm integrity or externally corrupt data may carry direct medical consequences; and regulations governing the clinical use of data from related wearable sensors, distinguishing between genuine signal variation and noise, must also be considered. Although predictive

control has potential, it brings additional ethical dimensions to the therapy equation.

The vision of personalized, autonomous medicine

Smart implants offer real-time monitoring and active drug delivery, and the combination of all these capabilities is a serious step toward personalized, autonomous medicine broadening horizons for advanced disease management. This becomes evident when a range of performing capabilities is analyzed: real-time biochemical monitoring, drug delivery in response to continuous or intermittent feedback, closed-loop control, and predictive adaptive dosing.

Real-time biochemical monitoring enables the continuous follow-up of dynamic biological conditions; closed-loop control allows the accurate maintenance of these conditions within given boundaries; and predictive control is aimed at managing complex processes affected by elusive control parameters, such as the pain perception threshold. Other similar applications could be highlighted, all focused on the same general objective: the continuous supervision of patients at risk of sudden-health-deterioration episodes or with strongly oscillating dynamic behavior, and the capacity of activating dedicated treatments as needed within very-short timescales. Achieving these goals would allow moving toward personalized medicine by calibrating and tuning therapy according to the individual process response.

Future research directions and interdisciplinary collaboration

As the section on implantable microdevices synthesized the

technologies, concepts, and capabilities enabling real-time drug delivery and precision disease management, this one considers future research priorities and directions focused on accelerating development of the complete paradigm, including integration with external technologies. Bridging the microdevices with continuous biosensors present in a growing number of wearables would provide a step toward the vision of autonomous computer-guided systems for efficient precision disease management. Adaptive control leveraging data-hungry AI techniques without requiring large and diverse training data remains a challenge due to the inherent complexity of human-pathophysiology databases. Using data obtained from predictive software and digital patients should help satisfy this demand and shorten AI-training durations.

Lastly, it should be noted that the novel ideas discussed in these two sections are complementary to those targeting the design and manufacturing aspects of microdevices for precise medicine. Embedded delivery devices of inadequate size and form factor would be inconspicuous and, in principle, acceptable to patients. Nevertheless, without proper control possibly supported by an external database-adaptive algorithm the devices may not optimize treatment and might even harm the patient. Hence, complete frictionless precision medicine requires deep research in both operational areas.

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