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Introduction

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Biomedical Engineering (BE) is a complex applied science that has applications in the fields of medicine concerning diagnosis, therapy and rehabilitation. As in all sectors of technology characterized by complexity, the capability of solving problems and developing new devices for therapy and rehabilitation or to devise innovative techniques for diagnosis and treatment of pathologies requires synergy of various forms of expertise. This need is especially felt in BE where the subject of research is the human body with its complex operations: molecular mechanisms, chemical and biochemical intracellular reactions, control systems, functions of human organs and so on.

Despite the complexity of the biological system that doctors and biomedical engineers must relate to, the elements of which the human body is composed and the functions they perform have a close affinity with the operations carried out in a chemical plant [1] where some raw materials undergo a series of transformations (reactions, separation operations, mass and heat exchanges, etc.) in order to obtain useful products and energy. In the last century, this analogy has led to striking graphic representations of the human body and of its functions as an industrial plant. It is worth mentioning the picture [2] named "Der Mensch als Industriepalast," a creation by Fritz Kahn, a German doctor, science writer and pioneer of information graphics.

Indeed, the human body is composed of a solid structure of support and a casing that encloses a series of organs with functions of mass exchange, synthesis and transformation, and are connected to each other by a network of ducts passed through by fluids. A pumping system equipped with valves has the task of ensuring blood circulation in the vascular circuit. The digestive system, through complex chemical reactions, transforms ingested raw materials into

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useful substances and energy needed for the operation of the whole system. The muscular system can be regarded as a set of actuators responsible for moving several parts of the body whereas the peripheral nervous system supplies sensory stimuli coming from the environment to the central nervous system that supervises the control and processing of various functions in a similar way to what happens in the system of sensors, monitoring and automatic control in an industrial plant.

Beyond this evocative picture, however, the analogy suggests the idea that many sophisticated techniques of chemical engineering (CE) could be usefully applied to face the technical challenges of BE. Since the beginnings of its history, CE has dealt with unit operations for the separation of mixtures, humidification of gases, chemical reactors, mass, heat and momentum transport, properties of materials and so on, on the basis of scientific fundamentals that are phase equilibria thermodynamics, chemical and biochemical kinetics, transport phenomena, automatic control and mathematical tools needed to better understand many complex phenomena and to represent the behavior of equipment through theoretical or semi-empirical models useful for the simulation and the optimization of the process. Therefore, CE can provide skills to the solution of problems that BE has to face and, vice versa by a cross-fertilization process, can receive from BE valuable input for the development of innovative methods and processes deduced from the behavior of biological systems.

The fields where CE can provide fundamental contributions are numerous and range from the macroscale of artificial and bio-artificial organs to the nanoscale of chemical-physical properties of materials of cell micro-reactors. Furthermore, also in the industrial biotechnology and pharmaceutical fields, CE points out its potentiality in the large-scale production of drugs and in sophisticated methods of targeted drug delivery.

Organs like the kidney, liver or heart-lung system have, among their functions, those of cleaning the blood from toxins or excesses of substances and of exchanging oxygen and carbon dioxide. When native organs are not able to correctly perform these functions for pathological reasons, an artificial kidney, artificial liver or lung oxygenation unit can substitute or at least support the damaged vital functions and allow the patient to stay alive indefinitely or, at least, long enough for the possibility of carrying out transplantation or revival of the native organ. Nowadays, ultrafiltration technology by selective membranes is an acquired asset in CE that can provide a key contribution to the development of increasingly effective and low-cost artificial organs. Some chapters of the present book are devoted to artificial organs and their behavior.

However, just separation operations and selective transport are not enough in many cases to mimic the functions of the native organ: complex organs such as the liver or pancreas carry out synthesis functions and biochemical reactions not currently reproducible by artificial systems. This need has led to the development of bio-artificial or hybrid organs in which the artificial

component is coupled with a biological element; that is, a cell tissue able to perform functions not reproducible by a totally artificial system.

Therefore, hybrid organs are characterized by the presence of a kind of bioreactor where cells are kept in the optimal conditions for their survival and, in particular, to perform the functions of which they are responsible. The use of living cells as engineering materials is the basis of the so-called *tissue engineering* [3] where chemical engineering, material science and life sciences skills are involved. In the field of tissue engineering, the scaffold or support technology provides an important step in the growth and differentiation of the desired tissue. Even in this case, chemical reaction engineering and theory of reactors, the typical hallmarks of chemical engineers' activity, play a fundamental role in modeling, designing and properly running the bioreactor used for growing the new tissue.

A technology still under study is the development of an artificial pancreas. The purpose of this device is monitoring and properly releasing insulin, a hormone produced by β cells of the pancreatic islets of Langerhans, that regulates the absorption of glucose from blood and its conversion into glycogen or triglycerides. If β cells do not work, insulin can no longer be synthesized or secreted into the blood resulting in a high blood glucose concentration (type 1 diabetes). In order to solve this problem, chemical engineers are working on a computerized device able to monitor continuously blood glucose levels and to actuate micro-pumps for delivering insulin contained in a small reservoir. Chapter 5 of the present book is devoted to the artificial pancreas.

A well-known field of CE deals with scale-up techniques; that is, similar criteria needed to develop an industrial plant from information on the behavior of a pilot or bench scale plant. In the past, these techniques have already provided fundamental results for designing and running plants devoted to manufacturing products essential to human health. A typical early example is the process of producing penicillin on an industrial scale, suggested at the end of the World War II by Margaret Hutchinson Rousseau [4], a young chemical engineer. The industrial production process is based on an aerobic submerged fermentation. When penicillin was first made, the fungus *Penicillum notatum* was used and the yield of the process was about 1 mg/dm^3. Nowadays, using a different mold species (*Penicillum chrysogenum*) and by improving fermentation operating conditions and downstream processing, such as extraction techniques, a yield of 50 g/dm^3 is reached.

The opposite side of the coin is represented by scale-down techniques; that is, by the techniques to implement micro-devices [5, 6]. These devices are composed of a network of microchannels connecting micro-reactors, mixers, pumps and valves contained in vessels whose dimensions are in the order of micrometers with controlled volumes down to picolitres. At this scale, fluid transport in capillaries is laminar and the resulting very high surface area to volume ratio affects mass and heat transfer rates and catalytic reaction rates that depend on the interface area. Microfluidic devices (lab-on-chip assemblies)

are increasingly used to carry out chemical and biochemical reactions for applications in the genomic field, immunoassays, sensors, drug discovery, new catalyst development and many other forthcoming uses.

Properties of materials is another field where CE together with material science can provide an important contribution to BE. Scaffolds used in tissue engineering have to be biocompatible and biodegradable [1] to allow their use in contact with biological material and their absorption by the surrounding tissues when scaffolds are used in implantable devices. In any case, the degradation rate of the support must be compatible with the rate of making new tissue and with the integration of this one with the surrounding tissues. A very important property of the scaffold is its porosity and the distribution of pore sizes to allow three-dimensional tissue growth. A fractal geometry approach has proven to be useful for the characterization of these properties.

The knowledge of rheological properties of biological fluids [7] is another essential requirement for a proper design of extracorporeal devices. Blood is a suspension made of an aqueous solution (plasma) of electrolytes, sugars and proteins and of a corpuscular part composed of erithrocytes, leucocytes and platelets. Plasma is a Newtonian fluid with a viscosity of $\mu_P = 1.16 \div 1.35 cp$ at 37 °C. Whole blood, on the other hand, shows non-Newtonian behavior ranging from Bingham to pseudoplastic fluid behavior depending on the value of the shear stress. Non-Newtonian characteristics are clearer in the thinnest ducts as capillaries.

These rheological properties make the modeling of blood flow particularly complex [8, 9] in the various blood ducts, especially if one wishes to account for the transient behavior of the flow due to heartbeat and for non-stiffness of blood vessels. Moreover, in the case of blood circulation in extracorporeal devices, a non-negligible feature to take into account is the possible damage that shear stresses in circulation ducts and even more in pumping systems can cause to corpuscular part of the blood and to proteins [10].

These features cannot properly be accounted for without the knowledge of momentum transport that is one of the typical expertise areas of CE.

Another significant CE contribution can be found in the increasingly sophisticated techniques that are being tuned for an effective and safe administration of drugs or for their targeted delivery. The development of controlled drug delivery strategies has the purpose of assuring a precise drug dosage and of avoiding the risk of insufficient dosing or of over-dosages that can appear in conventional methods of delivering (ingestion or injection). Some of these new methods have been developed at MIT in the 1970s by chemical engineer Robert Langer and his colleagues [11, 12] by exploiting the property of some highly porous structures (mixtures of hydrophobic polymers and proteins) impregnated with the drug to release it in slowly and controlled way under appropriate conditions. Such a device, in the form of an implantable wafer, has been successfully tested in delivering, with small side effects, a potent chemotherapy drug to brain cells attacked by glioblastoma.

Glucose-sensitive hydrogels can be used for the controlled release of insulin to diabetic patients. A system based on this kind of materials has been developed at the Purdue University by the team of chemical engineers coordinated by Nicholas Peppas [13–15].

Overdoses of many antitumor drugs are dangerous for healthy tissues and organs. This drawback has started up an intensive research activity in the community of chemical and biomedical engineers for the development of targeted delivery systems of chemotherapy drugs, that is for the drug delivery in the sick tissue. Attempts have been made by the encapsulation of the drug in carriers as liposomes, nanoscaled C_{60} fullerenes or entrapping it within a hydrogel matrix. These kinds of methods allow a reduction of drug degradation by the digestive system and avoid attack from the immune system if the carrier surface is properly masked. Using specific peptides or, in particular, monoclonal antibodies attached to the external carrier surface allows the drug to be led to target cells where it is released as a consequence of internal or external triggers such as pH, temperature, enzymes, ultrasound or magnetic signals. For example, hydrogels swell under different environmental conditions so that they can release a drug entrapped by changing the pH or the temperature. Furthermore, since hydrogels are stable in acidic environments, they do not undergo any degradation by passing through the stomach. Even in this BE field, CE fundamentals concerning mass transport phenomena and chemical and physical properties of polymers play a paramount role.

Finally, a few words about *synthetic biology* [16] to which a chapter of this book is devoted (Chapter 6). As the human body with its organs can be seen as an industrial plant, so cells can be considered as nanomachines on the molecular scale. The advances in biology indeed allow cell mechanisms to be described as an ensemble of biocatalytic reactions resulting in handling mass, energy and information. This consideration has induced researchers to use the molecular mechanisms of living matter for thinking up models, techniques and devices aimed to the development of new strategies of diagnosis and therapy more effective than the traditional ones. A typical example is the fight against infection, since increasing resistance to antibiotics has made their use partly ineffective.

This approach has led to the origin and evolution of the synthetic biology that is an interdisciplinary field of science based on the use of fundamentals of biology and engineering for the achievement of new and smart methods and devices useful in diagnosis and therapy.

Some examples in the field of therapy are:

- bacteriophage-based therapy that exploits the very specific action of the phages for killing infectious microorganisms;
- synthetic probiotic therapy based on the controlled and confined release under specific conditions of drug-molecules by engineered bacteria in the form of synthetic probiotics.

Similar strategies are evolving also in the field of diagnostics. In particular, a diagnostic technique is emerging based on the ability of specific bacteriophages to identify a particular bacterium on the basis of their ability to clear it.

These considerations clearly show that, as synergy between CE and BE has produced key contributions to the development of tools useful to human health by using typical methods of engineering, we are able to formulate promising achievable ideas. Ever-closer cooperation between these branches of engineering allows us to foresee that results obtained so far are only the tip of the iceberg and that, in the near future, currently seeming science fiction achievements can become reality.

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