# Chapter 3
# Brief Introduction to Biomedical Microsystems for Interacting with Cells

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**Abstract** Understanding how cells behave and interact with surrounding cells, tissues, microorganisms and all types of biological, biochemical and biomechanical cues from their environment, constitutes a relevant research challenge and requires the support, not only of advanced manipulation and imaging technologies, but also of specifically designed biomedical microsystems with micrometric and even nanometric details for enabling interactions at a cellular and molecular level. These types of microsystems, together with the use of advanced design and manufacturing strategies for their efficient development, constitute the core topic of present Handbook. Among the biomedical microsystems aimed at interacting with and studying the behavior of cells, it is important to mention the following areas of research and application: microsystems for disease management, microsystems for understanding cell activities, scaffolds for tissue engineering, cell-based sensors and actuators and microsystems for modeling life by controlling cells using microfluidic environments. This chapter provides an introduction to these different types of biomedical microdevices and to the related basic concepts, to which we will get back in subsequent chapters linked to design, manufacturing, biofunctionalization and testing strategies and to the complete development of different cases of studies linked to the aforementioned families of biomedical microdevices. Main current research trends are also outlined.

## 3.1 The Challenge of Interacting at a Cellular Level

Natural materials, tissues and organs are consequence of an evolutionary process, amidst a changing environment, in which resources are limited, aimed at the fulfilment of several complex functions, including survival, structural stability, access to and processing of nutrients, elimination of debris and waste, protection against

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external dangers, communication, overall energetic efficiency and even self-regeneration. In fact, the whole process can be seen as a multi-objective dynamic optimization for enhanced performance facing several, mainly energetic, constraints and contradictions (i.e. improved mechanical strength may require more nutrients, organism speed can be opposed to mechanical endurance, and superior adaptability to environmental changes may need lighter materials), hence bearing some resemblance with most engineering problems and related design solutions. Therefore, resulting geometries of living organisms are highly complex (Place et al. 2009), as a consequence of the several functions and constraints to be accomplished; non-intuitive, as solutions provided by Nature have not followed human hypotheses and simplifications, used for "methodical" development processes, neither our mistakes, consequence of limited knowledge of natural phenomena; and extremely varied, accounting for the wide set of macro and microenvironments that surround their materials, tissues and organs.

Tissue engineering and regeneration faces the ambitious challenge of recreating in laboratory the natural processes of cell expansion, differentiation and tissue formation, for improved diagnostic approaches and personalized therapeutic solutions, benefiting from the replacement of damaged or lost tissues, and pursues the overwhelming task of reconstructing entire organs. Pioneer developments in the field of tissue engineering have been based on very simple devices and geometries, aimed at solving very specific problems, such as supplying a drug in an enhanced way, regenerating small portions of damaged tissues or in vitro addressing cell response against toxic agents, pathogens or medicines. Biodegradable polymeric discs or planar substrates, microspheres, and woodpile structures marked the dawn and first years of tissue engineering, although more complex porous foam-like geometries have also been used since the beginnings of such recent research area.

In many cases, biodevices with quite simple geometries work properly for their desired purposes, such as studying cell behavior and fate for a deep understanding of life, and are more likely to reach market than other much more over-engineered products. However, to promote further developments in tissue engineering and cell biology, the complexity of biomaterials has to be adequately addressed. Aspects such as mechanical properties, surface topography, porosity and pore distribution are difficult to control in synthetic biomaterials but essential for interacting at a cellular level and for the success of extracellular matrices for cell-culture, as they are key issues linked to cell dynamics and evolution and also necessary for the proper access to nutrients and elimination of waste.

Therefore, related geometries are especially complex to design and manufacture, and there are still several interconnected parameters of influence needing adequate assessment. In addition, even if cell growth is obtained in 3D scaffolds, final tissue viability requires adequate vascularization, as diffusion can only provide transport of nutrients within a few hundred microns. However, vascularization induction within artificial tissues is an unresolved challenge, laying at the centre of bone regeneration research strategies, demanding even more complexity to the geometries of scaffolds and implants linked to tissue regeneration, so as to promote biomimetic responses.

Clearly, it is interesting to note that biomimetic approaches are marking trends and opening new horizons in fields such as energy, transport and information and communication technologies, but are not still impacting health-related sectors as would be expected, possibly due to the aforementioned intrinsic complexity of biological materials. Fortunately, recent advances in computer-aided engineering, materials science and technology, micro and nanomanufacturing resources, and surface functionalization approaches (Yao et al. 2013), are helping to control the three-dimensional geometries and the surface properties of multiple materials and biodevices, with a remarkable degree of precision and with the possibility of defining desired properties from design stage for interacting at a cellular and sometimes even molecular level.

Nevertheless, such advances have not yet been applied cooperatively and in a systematic way for the resolution of current challenges in tissue engineering and cell biology, hence being their potential beneficial synergies unexploited. Among main current tissue regeneration challenges, it is important to cite the urgent need for synthetic extracellular niches (or advanced scaffolds) capable of adequately mimicking the complex geometries and mechanical performances of the different tissues and organs of interest. The incorporation of defined surface topographies and chemistries to such extracellular matrices for improved biochemical response and the generation of different types of tissues upon a single tissue regeneration biodevices, by correctly combining cells, growth factors, drugs and extracellular matrices (Yao et al. 2013), are also important requirements. Such a cooperative and methodic application of technological breakthroughs will promote our capability of interacting with cells and understanding their behavior, which is indeed relevant for the success of several novel diagnostic and therapeutic strategies.

Researchers in the field should confront the relevant and yet unsolved challenges mentioned in the previous paragraph and manage them by methodically combining complex geometries, design processes, manufacturing technologies, materials, growth factors and drugs, on the basis of biomimetic approaches, whose application in the biomedical field will be reinvented. The shift from more traditional trial and error combinations, between materials and technologies to provide very specific solutions, to a more systematic integral and novel combination of advanced materials, structures, design, manufacturing, biofunctionalization and assessment technologies, will be a key aspect to support a knowledge-based future of tissue regeneration, cell biology and medicine in general.

To systematically develop and assess novel biomimetic strategies in tissue regeneration based on the advancement and integration of advanced bioinspired geometries, materials, technologies and processes for multi-scale, multi-material, multi-phase, time-responsive cell culture platforms and scaffolds (in fact advanced biofunctional niches), will allow us to improve the knowledge about cells and about tissues. To employ the knowledge generated with the help of biomedical microsystems and to apply the integral tissue regeneration strategies to the development of biomimetic diagnostic and therapeutic devices in the fields of tissue

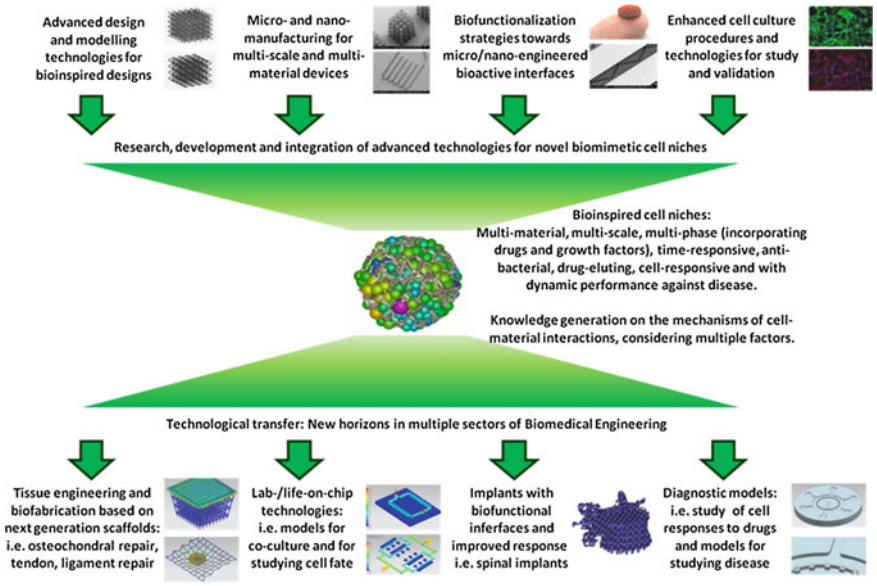


**Fig. 3.1** Schematic representation of the potential of systematically applying recent technological advances to the development of biomedical micro-devices for the promotion of interactions at a cellular level

engineering, biofabrication, biomedical microsystems, implantable devices and in vitro models for drug screening, will allow us to go beyond tissue regeneration and reach the most general concept of integral disease management and personalized knowledge-based medicine. Figure 3.1 schematically represents the potential of systematically and cooperatively applying recent technological advances to the development of biomedical micro-devices for interacting at a cellular level.

Next sections introduce the different types of biomedical microsystems, aimed at interacting at a cellular level, which will benefit from these approaches. The whole Handbook is devoted to explaining and providing cases of study linked to the development of such microsystems. The following research trends are also present along the whole Handbook and drive our efforts:

1. The generation of resources (libraries of designs and properties) for an adequate biomimetic multi-scale modeling of the 3D structures and the surface topographies of biomaterials and structures.
2. The incorporation of advanced lattice structures based on the use of mechanical metamaterials and non-Euclidean (fractal) geometries for promoting novel ways of controlling the properties and performance of synthetic biomaterials for the biomedical field.
3. The systematic combination of several advanced micro and nanomanufacturing technologies with surface modification resources towards multi-scale, multi-

material, biomechanically and biochemically improved cell culture platforms and scaffolds.
4. The generation of new procedures for the suitable incorporation of growth factors and drugs upon the surfaces and into the structures of multi-phase cell culture platforms and scaffolds.
5. The assessment of the combined impact of materials, structures, surfaces, growth factors, microorganisms and supporting drugs on cell behaviour and fate and selection of the most-adequate combinations for the promotion of different tissue formation.
6. The objective and systematic comparative study of cell culture platforms and tissue engineering scaffolds (advanced biofunctional niches) by means of cell culture experiments.
7. The comparative evaluation of microsystem and implant surface structures with data base entries on existing successes and failures.
8. The development of the tissue engineering scaffold of the future, which will be based on functional gradients of properties, on the use of composite materials, on the incorporation of adequately distributed growth factors and drugs for delivery strategies and on special anchorages for promoting cell motility, proliferation and differentiation. Such next generation 4D scaffolds will not only promote adequate three-dimensional cell adhesion and proliferation, but will take into account that the process of musculoskeletal tissue regeneration needs the expression of different phenotypes in a dynamic environment, which must adapt to the requirements of the cells along the regeneration process and include dynamic response to disease.
9. The search for novel applications of the generated knowledge in bioengineering areas including biofabrication (beyond tissue regeneration), biomedical microfluidics "lab-on-chips", "organs-on-chips" and "life-on-chips", other biomimetic implantable devices and diagnostic models for drug screening and disease modeling.
10. The performance assessment, by means of cell culture experiments, of the different applications proposed and developed.

But first it is necessary to introduce the different areas of application and the types of biomedical microsystems aimed at interacting with cells for improving our understanding about the basic units of life.

## 3.2 Microsystems for Disease Management

The integrated study of biomechanical and biochemical issues in disease is usually carried out with the essential support of fluidic microdevices and microfluidic diagnostic platforms, as fluids enable the transport of nutrients, debris, gases,

pathogens and drugs to and from cells, help to control the movement of microorganisms in vitro and make the application of controlled stresses in culture systems possible. In fact the field of microfluidic systems for diagnosis has experienced an explosive growth in the last two decades, promoted by the convergence of clinical diagnostic techniques and mature microfabrication technologies capable of producing submillimeter-size fluidic channels and reservoirs in several materials (Jenkins and Mansfield 2013).

These advances have led to the development of versatile and self-sufficient lab-on-chip microfluidic devices or "labs-on-chips", aimed at integrating the complex operations and procedures typical from biochemical and biological laboratories in just a few $cm^2$, by taking advantage of microfluidic operation, which promotes reaction speed, sustainability due to the use of low fluid and sample volumes, and repeatability, thanks to multiplexing and automation. At present, most lab-on-chip devices are in fact "chip-on-lab" systems, as these complex microfluidic platforms still require from several support actuation and characterization technologies for a correct operation (Jenkins and Mansfield 2013). Even if further research in the field will promote additional miniaturization and integration of capabilities, lab-on-chip devices incorporating cells or tissue samples are already very interesting for studying and modeling disease.

Chapter 11 covers the applications for disease management based on the more conventional microfluidic devices and "labs-on-chips", while the development of biomedical microdevices for studying cell behavior and cell-to-cell interactions is detailed in Chaps. 12–14 and 21. Further on, the development of biomimetic cell culture scaffolds (see also Sect. 3.3), which can be also applied to the study of diseases and the testing of new drugs, is explained in Chaps. 15–20. Finally the more recent (and complex) organ-on-chip and life-on-chip approaches are discussed in Chaps. 20 and 22 and the potential of biofabrication is introduced in Chap. 23.

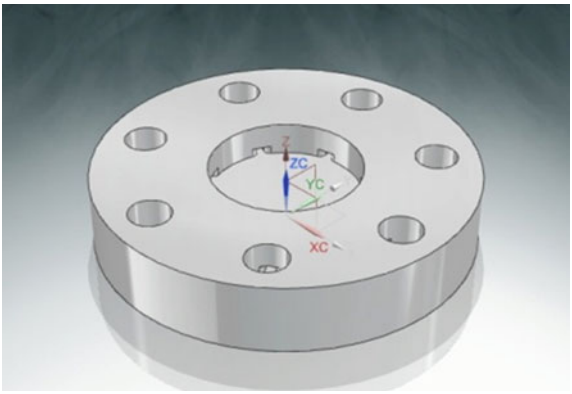


**Fig. 3.2** Example of a diagnostic lab-on-chip actuated by capillary action

Figure 3.2 shows an example of a lab-on-a-chip for illustrating the concept and providing an idea of the typical geometries and components involved in these systems.

## 3.3 Microsystems for Understanding Cell Behavior

The use of conventional cell culture upon Petri dishes is not able to emulate the complex biochemical and biomechanical interactions present in living organisms that drive cell dynamics, differentiation and eventual tissue formation and are, therefore, inadequate for precisely studying and modeling disease, as well as for evaluating the actual potential of novel drugs and therapies. Cell performance is linked to their microenvironment, including the surrounding extra cellular matrix, other cells and soluble factors, such as growth factors and cytokines. Cells respond to biomechanical stimuli and parameters, such as topography of the surrounding material, stiffness of the substrate or environment, effects of vibrations, among others; but also interact biochemically according to the surrounding materials' compositions, to the presence of other cell signals and to gradients of nutrients, drugs and pathogens (Yao et al. 2013). In consequence, more complex devices are needed to assess, model and understand cell behavior.

Microfluidic systems combined with or integrating advanced scaffolds and platforms for cell culture, are ideally suited for an optimized control of cell growth, interactions and motion, by means of adequately producing biomechanical and biochemical phenomena. Cell movement can be mechanically oriented, using channels, walls, holes, bridges, textures and patterns. The fluids in motion can be used to apply the desired shear stresses needed to promote certain cellular differentiations into relevant tissues. Including additional inlets and outlets to a microfluidic disease model can help to introduce nutrients, disease initiators and drugs for therapy. The use of support chambers can facilitate the establishment of chemical gradients to induce cell motility. Producing mechanical and chemical modifications of certain zones of a biodevice, by changing surface topography or stiffness, by patterning surfaces with ligands…, can affect and help to control cell shape, cell size, cell-material adhesion, differentiation and other events necessary for a more complete understanding of cells and their behavior.

Details regarding design, manufacturing and testing strategies for the straightforward development of biomedical microdevices for the study and assessment of cell behavior and of cell-to-cell interactions is detailed in Chaps. 12–14.

Figure 3.3 provides a couple of examples, linked to the design of a micro-textured microsystem for studying cell adhesion and motility, for illustrating the typical geometries used in these kind of devices for analyzing cell behavior.

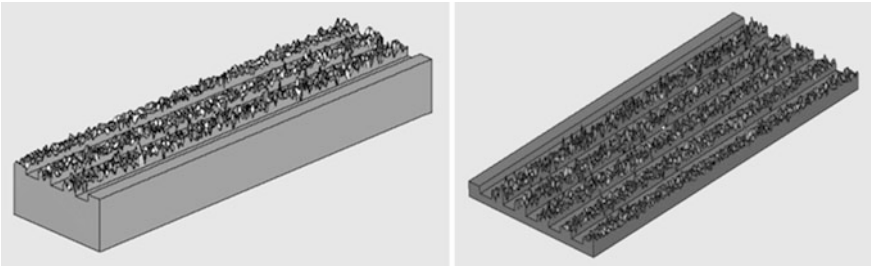

**Fig. 3.3** Microtextured microsystems for studying cell adhesion and motility

## 3.4 Scaffolds and Microsystems for Tissue Engineering

An essential element involved in tissue engineering processes is the extra cellular matrix or scaffold which serves as substrate or framework for cell growth, aggregation and tissue development (Langer and Vacanti 1993). These scaffolds must be porous so as to allow cell migration during the colonization process as well as the transport of nutrients and waste to and from cells, but they have to be also resistant enough to withstand possible mechanical demands, especially if final scaffold (or device) implantation is desired. In many cases biodegradability of the scaffold may be a relevant and desired property, although in many repair strategies the scaffold may act as an optimized, active or "intelligent" implant, seeded with cells from the patient for an improved integration, but remaining within the body of the patient as a bioinert or bioactive element.

Additionally, as cells are able to feel their microenvironment and substrate elasticity and texture upon which they lie by modifying their morphology, their cytoskeleton configuration, and by intra- and extracellular signaling, increasing efforts are continuously being focused on the application of advanced biomimetic design and manufacturing technologies, so as to generate and modify the structures and surfaces of biomaterials. Aspects such as scaffolds' elasticity, porosity, pore size, and surface microtexture promote cell adherence, migration and proliferation within the scaffold, for subsequent differentiation into relevant cell types. Thus, tissue progenitor cells and the scaffold plays a fundamental role in most tissue engineering strategies as its properties can deeply influence the global success of new tissue formation and the controlled fabrication of the scaffold structures is becoming increasingly important for novel approaches within regenerative medicine (Thomas et al. 2010; Chen et al. 2010; Buxboim and Discher 2010).

Several strategies for the design, modeling and manufacture of biomimetic "knowledge-based" tissue engineering scaffolds, together with cases of study linked to the repair and regeneration of hard and soft tissues, will be detailed in Chaps. 15–19. Here we have just provided a brief definition and Fig. 3.4 helps to illustrate the typical morphologies of tissue engineering scaffolds. The use of multi-scale design

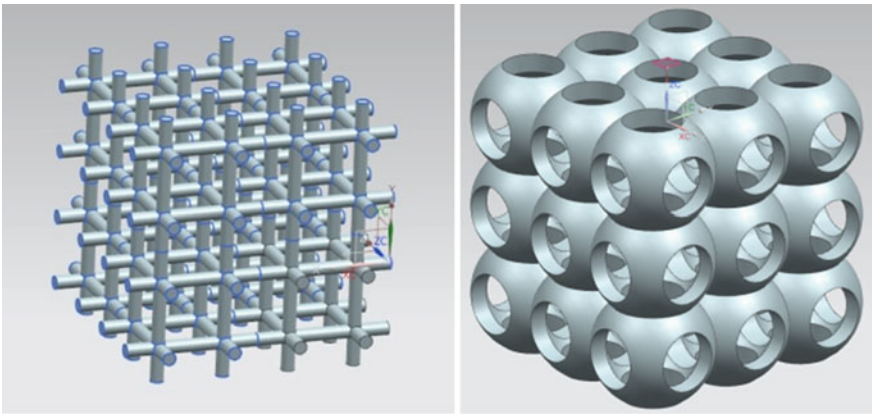

**Fig. 3.4** Examples of typical geometries used as tissue engineering scaffolds

approaches or the employment of functional gradients of porosity and mechanical properties is also common and helps to promote biomimetic approaches, as the biological materials and structures are normally anisotropic.

## 3.5 Cell-Based Sensors and Cell-Based Actuators

Cells and tissues can be seen, from the perspective of Materials Science and Engineering, as "smart materials and structures". In fact, cells and tissues are able to perceive and respond to several environmental stimuli and gradients of them, including the presence of biochemical cues and microorganisms, the mechanical and topographical properties of the extra cellular matrix and surfaces upon which they lie, the application of vibrations and the surrounding electromagnetic fields, to cite just a few, as already detailed in several chapters of the Handbook.

Advances in technologies for manipulating, culturing and monitoring single cells, together with progress in the fields of modeling, simulation, prototyping and testing, have led to a better understanding of how cells respond to several types of stimuli and accurate predictions about the behavior of cells and tissues are already possible. In consequence, cells and tissues can be employed as living transducers for the development of (micro-)sensors and (micro-)actuators, as it is possible to predict and control their responses.

Due to the micro- and nano-geometries of cells and tissues and to the highly specificity and speed of several of their biochemical and biological responses, the sensors and actuators based on them are extremely precise and can provide high throughput, thanks to the possibilities of multi-plexing. Such biohybrid cell-based devices have the potential to outperform most types of already existing sensors and

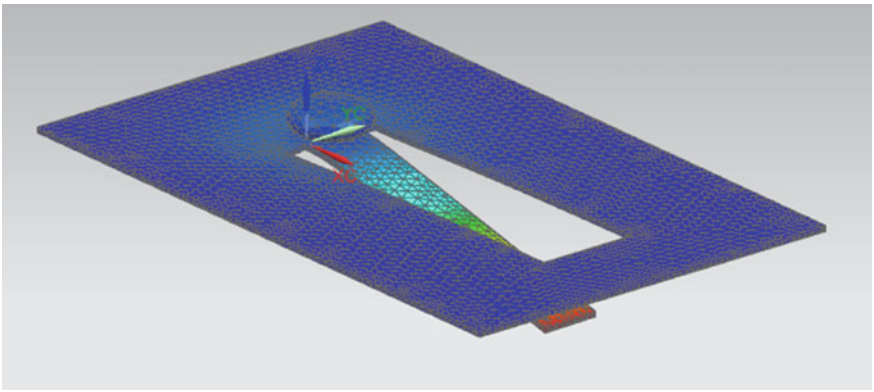

**Fig. 3.5** Schematic simulation of micro-valve actuated by cell expansion

actuators based on inorganic components, although important research in the field is yet necessary.

Chapter 21 provides and introduction to the development of cell-based sensors and actuators and to current main challenges in this novel area. Once such challenges are solved, the frontiers between biological systems, machines and synthetic engineering systems in general will start to fade away. Figure 3.5 provides, as example of these types of solutions, a conceptual design of a micro-valve actuated by means of cell expansion simulated with the help of finite-element modeling.

## 3.6 Microsystems for Modeling Life by Controlling Cells

Counting with simple biomimetic microsystems capable of mimicking the behaviour of complex organs, or at least of some of their significant functionalities, constitutes a realistic and very adequate alternative for disease modeling and management, capable of providing even better results than more conventional animal models. These simplified replicas of human organ functionalities are being developed in the form of advanced lab-on-chip devices generically called "organs-on-chips", and are already providing interesting results (Huh et al. 2011, 2013).

Most of the already developed organs-on-chips in fact focus on specific interactions among a couple of cell types cultured together, help to assess the effect of chemicals and drugs on cells cultured upon channel networks resembling the organization of more complex organs, or mimic concrete fluid-cell interfaces.

Among the most remarkable experiences published so far, we would like to highlight studies linked to replicating, to some extent, the behaviour of several human organs and physiological structures including: liver (Ho et al. 2006), heart (Domian et al. 2009), lung (Huh et al. 2011) and blood-brain barrier (Wilhelm et al. 2011), among other interesting proposals. Disease development has been also

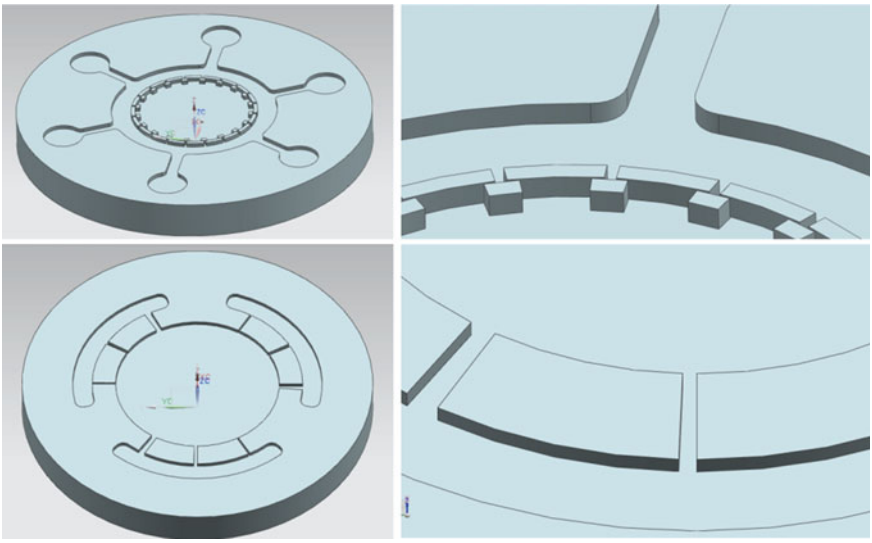

**Fig. 3.6** Examples of versatile platforms for biomimetic cell co-culture

studied and predicted by means of organs-on-chips, as some experiences linked to real-time monitoring of kidney stone formation show (Wei et al. 2012). Main strategies for the design, manufacturing and testing of these biodevices will be provided in Chap. 22; here we have just introduced the concept. Figure 3.6 helps to illustrate it by showing a couple of versatile cell culture platforms with multiple chambers, separated by micropillars or connected by microchannels, for the co-culture of different cell types and the potential modeling of physiological interactions.

## 3.7 Main Conclusions and Future Research

Understanding how cells behave and interact with surrounding cells, tissues, microorganisms and all types of biological, biochemical and biomechanical cues from their environment, constitutes a relevant research challenge and requires the support, not only of advanced manipulation and imaging technologies, but also of specifically designed biomedical microsystems with micrometric and even nanometric details for enabling interactions at a cellular and molecular level.

These types of microsystems, together with the use of advanced design and manufacturing strategies for their efficient development, constitute the core topic of present Handbook. Among the biomedical microsystems, aimed at interacting with and studying the behavior of cells, it is important to consider the following types of devices, according to their area of application and research: microsystems for

disease management, microsystems for understanding cell activities, scaffolds for tissue engineering, cell-based sensors and actuators and microfluidic systems for modeling life by controlling cells.

This chapter has provided an introduction to the different types of biomedical microdevices and to the related basic concepts, to which we will get back in subsequent chapters linked to design, manufacturing, biofunctionalization and testing strategies and to the complete development of different cases of studies linked to the aforementioned families of biomedical microdevices. Main current research trends have been also outlined.

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