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# Editorial overview: Scaffold-based and scaffold-free approaches for mechanobiology, *in vitro* disease modeling and treatment

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**Angelo Accardo, PhD**, is an Associate Professor at the Department of Precision and Microsystems Engineering of Delft University of Technology, co-founder of the Delft Young Academy, committee member of the Delft Bioengineering Institute, member of the Holland Proton Therapy Center Programraad (Program Board), and Scientific Steering Committee Member of the International Micro and Nanoengineering Conference. By exploiting high-resolution light-assisted 3D additive manufacturing techniques (two-photon polymerization, stereolithography, micro-digital light processing), he creates engineered polymeric/hydrogel microenvironments for fundamental mechanobiology, *in vitro* disease/treatment modeling and tissue engineering applications involving brain (e.g. microglia, iPSCs-derived/primary neurons), cancer (e.g. glioblastoma), or bone (e.g. preosteoblasts) cells. He is author of 60+ publications in peer-reviewed journals and he was awarded several prizes and grants by the Dutch Research Council (NWO).

The realization of biomimetic microenvironments is crucial for the development of tissue engineering and *in vitro* drug screening strategies. Indeed, creating favorable conditions for cell growth, migration and functional interplay with their surroundings involves several approaches in different fields, including biochemistry, neurosciences, physics, nanotechnology, microfluidics, and mechanobiology. In the last two decades, this multidisciplinary activity led to the blooming of numerous strategies aiming at creating architectures that mimic the topological, biochemical and mechanical properties of the natural extracellular matrix present in the tissues of our body. Despite each experimental methodology being unique and original, and scopes differing significantly, the vast majority of the currently available approaches for fabricating biomimetic microenvironments can be generally classified into either (i) scaffold-based or (ii) scaffold-free.

This special issue offers a synthetic yet comprehensive overview of a number of cutting-edge scaffold-based and scaffold-free techniques to address mechanobiological and drug screening fundamental questions.

Leveraging on a beginner-accessible structuring and writing style of their review, Fladung et al. [1] provide an essential guide to microscaffolds characterized by mechanical properties which are typical of metamaterials. In general, both synthetic and native materials offer useful insights into how cells respond to different biomaterials. For example, mechanoregulation of cells using polymeric substrates with different degrees of crosslinking has been well investigated. However, the potential of nonconventional mechanical materials has not been exploited yet. Metamaterials provide previously inaccessible or rare mechanical properties that can now be achieved by rational design and appropriate micro-manufacturing. These properties include viscoelastic behavior under long-lasting mechanical loads, and resistance to shear forces or material characteristics. Indeed, all of them are present *in vivo*, but their impact on cell behavior is yet poorly understood. Therefore, the possibility to realize metamaterials at the microscale offers a significant breakthrough in scaffold-based approaches for basic cell biology. The authors point out the main theoretical and practical aspects that well- and less-experienced researchers should consider when designing experiments and analyzing results with this very peculiar kind of microscaffolds.

It is important to note that scaffold-based environments do not solely refer to static 3D structures. Indeed, significant progress in the understanding

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of several biochemical and mechanobiological behaviors has been made by exploiting dynamic (usually referred to as four-dimensional, 4D) scaffolds, which are capable of modifying their mechanical properties and shape in response to one or more external stimuli. Sonn et al. [2] review the most recent strategies usually adopted to actuate microscaffolds/biomaterials for cell/organoid biology investigations. These include direct indentation/manipulation, and contactless stimulation, which can be performed exploiting specific properties of the materials the scaffolds are made of. In particular, pH and temperature variations as well as electromagnetic external fields and even focused light can be exploited to induce elastic deformations in the structure of 3D microscaffolds. In turn, this can be exploited to study how cell mechanotransduction pathway (de)activation and cell response to drugs change over time. The authors conclude their work with an interesting suggestion: it is restrictive to consider the scaffold as the only active player in cell/structure interactions. Instead, cells themselves may act as actuators of the microenvironments in which they grow and migrate. This let the readers envision a novel role for scaffolds, i.e. not just architectures to support cell functions but functional cell-empowered micromachines.

Scaffold-free approaches may be less frequent in the literature, given the reduced control over spatial distribution of cells. Hydrogels mimicking the extracellular matrix (ECM), in which cells are encapsulated and investigated, have been extensively used to highlight specific cell/ECM interactions, but are typically not able to provide cell lining with a well-defined arrangement into the microenvironment. Yet, scaffold-free solutions may be well integrated within microfluidic platforms, eventually in combination with the scaffolds. This aspect is addressed in the contribution by Coricciati et al. [3], which provide a biological focus on physiopathology of gut and liver in organ-on-chip (OoC) devices. In particular, the authors extensively review state-of-the-art methodologies employed to mimic gut and liver tissues as well as biological outcomes. They also delve into integrated approaches aimed at reproducing the gut–liver axis, i.e. to establish the bi-directional connection between the gut (and its microbiota) and the liver, in a controlled microenvironment. As one of the most significant strengths of OoCs is their physiological relevance, achieved by replicating the microenvironment of native organs, such as cellular arrangement, biochemical gradients, and complex interactions between multiple cell populations, OoCs offer insights that traditional scaffold-based models often miss. Therefore, the development of hybrid scaffold-free/scaffold-based approaches may be envisioned as one of the next frontiers to reach functional biomimetic reliable platforms for understanding mechanobiological patterns and drug response mechanisms.

## References

1. Fladung M, Berkes A, Alletzhäusser T, Chen Y, Munding N, Tanaka M, Wegener M, Bastmeyer M: **What lies beyond—Insights into elastic microscaffolds with meta-material properties for cell studies.** *Curr Opin Biomed Eng* 2025, **33**, 100568. <https://doi.org/10.1016/j.cobme.2024.100568>.
2. Sonn A, Tomba C, Selhuber-Unkel C, Schamberger B: **3D fabrication of artificial cell microenvironments for mechanobiology.** *Curr Opin Biomed Eng* 2025, **33**, 100574. <https://doi.org/10.1016/j.cobme.2024.100574>.
3. Coricciati C, Mello E, De Luca E, Gigli G, Rainer A, Mozetic P: **Gut-on-chip and liver-on-chip platforms for pathophysiological modeling.** *Curr Opin Biomed Eng* 2025, 100601. <https://doi.org/10.1016/j.cobme.2025.100601>.