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# Incorporating biomechanics as a key evaluation metric for organoids

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# Incorporating biomechanics as a key evaluation metric for organoids

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Organoids have emerged as a revolutionary tool in modern biomedical research, offering an invaluable platform to study disease mechanisms, screen drugs, and explore personalized medicine, all without relying on experimental animals. As three-dimensional structures, they represent the minimum functional units that can replicate key aspects of real organs, thus attracting significant attention from the scientific community[1]. However, despite these promising advances, there remains a substantial gap between the physiological conditions of native organs and how current organoids are engineered. This gap raises questions about the real-world applicability of many organoid-based models, particularly in dynamic biological environments. Current design of organoids primarily focuses on replicating cellular components and the extracellular matrix (ECM) under relatively static conditions, which fails to adequately capture the dynamic interactions that characterize living organs. In physiological environments, human organs are subject to a variety of mechanical stimuli, such as blood flow shear stress, mechanical compression, and tension. These forces are not just incidental—they play crucial roles in tissue differentiation, development, and function, influencing everything from cellular[2] processes to whole-organ performance[3]. The absence of such mechanical factors in most current organoid models significantly undermines their capacity to function as truly representative systems.

Researchers have made remarkable progress in generating diverse types of organoids that aim to model organs such as the liver, intestine, bone, kidney, lung, heart, and even cancer tissues[4]. However, the consideration of mimicking in vivo biomechanics (Figure 1) is missing in most of the cases. For example, liver organoids are promising for replicating hepatic functions[5]. However, the absence of dynamic fluid conditions, similar to in vivo environments, affects essential functions like nutrient transport, cellular signaling pathways, and overall tissue morphology. This not only limits their physiological relevance but also raises concerns about the accuracy of these models for disease research and drug testing. Similarly, intestine organoids are effective at mimicking nutrient absorption processes, but the incorporation of mechanical forces like peristaltic movement could greatly enhance their utility. As demonstrated by Poling et al.[6], the application of compressed nitinol springs to human intestinal organoids improved growth and maturation, emphasizing the necessity of integrating mechanical cues into organoid development. The same challenge persists for other organoid types. Bone organoids, for instance, are useful for understanding bone remodeling under mechanical loads, a process that is significantly influenced by dynamic compressive forces[7]. However, these forces are absent in most current bone organoid models, limiting their utility for studying bone anabolism or simulating in vivo responses. Kidney organoids mimic

glomerular function and provide a unique platform to investigate high-pressure filtration, but most existing models do not account for hydrostatic pressures encountered in vivo[8]. Lung organoids hold great potential for studying alveolar expansion, lung elasticity, and respiratory function, yet many current models do not incorporate cyclic mechanical stretching[9]. Similarly, heart organoids, though capable of spontaneous beating and microvascular formation, lack functional hemodynamics[10]. Most models do not incorporate coronary perfusion or intracardiac flow, both essential for cardiomyocyte maturation. Integrating microfluidic perfusion systems could better replicate physiological conditions. Cancer organoids, while valuable for modeling tumor growth and drug responses, also do not replicate the mechanical stresses present in the tumor microenvironment, which is fundamental in cancer progression[11]. The absence of these mechanical cues could result in inaccurate predictions when it comes to understanding cancer dynamics or testing therapies. Therefore, to make organoids better models for disease research, drug screening, and personalized medicine, biomechanics should be included as a key evaluation metric, especially when organoids are intended to model human organs under physiological conditions.

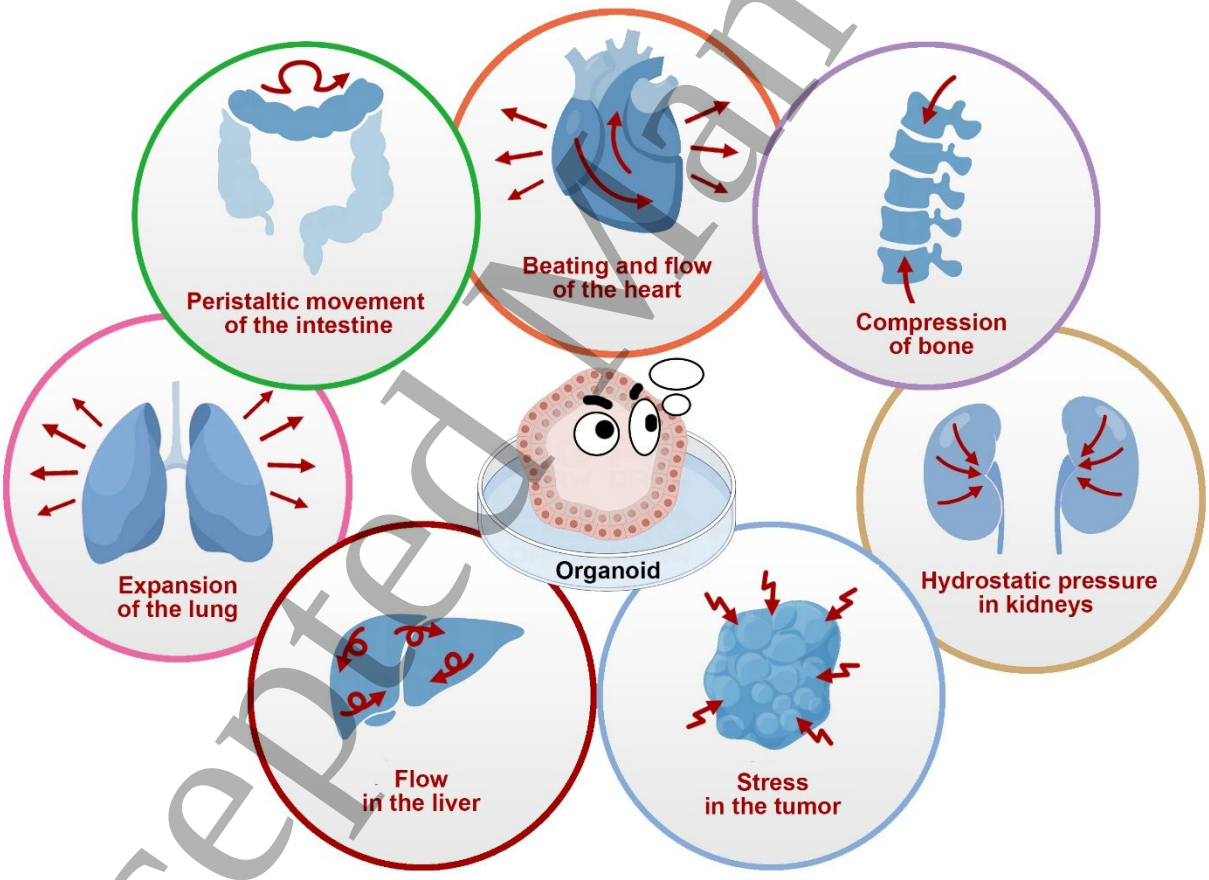


**Figure 1.** Major forms of biomechanics in different organs/tissues.

Biomechanics in organoid research is still in its infancy, and the tools available for evaluating mechanical stimuli in these systems are limited. Traditional methods, such as micro-computed tomography (micro-CT), struggle with imaging soft materials that have low electron absorption.

In contrast, phase contrast CT offers a more promising approach for imaging soft organoid tissues. A major leap forward in this field has been the advent of hierarchical phase-contrast tomography (HiP-CT)[12], which enables imaging of soft tissues at scales ranging from a few centimeters down to entire organs. By combining in situ compression techniques with digital volume correlation (DVC)[13], HiP-CT offers down to nano-scale strain analysis, providing insights into the internal mechanical environment of organoids. These capabilities present significant opportunities for comparing organoid behavior under load to real organ-level conditions. Such comparative studies would yield crucial information on the physiological fidelity of organoids. However, the evaluation of organoids' biomechanics cannot rely solely on imaging technologies. There needs to be a concerted effort to validate these models through functional testing that involves subjecting organoids to cyclic loading, fluid shear stress, and other mechanical conditions that are representative of physiological environments. Without these validation steps, any inferences made from organoid models could lead to oversimplified or incorrect conclusions about tissue function and pathology.

Another significant hurdle in the integration of mechanical forces into organoid models is the technical complexity of maintaining a bioreactor culture system that provides the required level of mechanical stimulation. Current bioreactors are mostly designed to ensure proper mechanical conditions at cellular level. Very few tools are capable of accurately replicating physiological mechanical conditions at the scale of organoids, which hinders widespread adoption. Integrating biomechanics into organoid models calls for increased interdisciplinary collaboration. Progress in this field will be accelerated by the combined efforts of biologists, engineers, and computational scientists. Collaboration across these fields can lead to innovative solutions, such as designing sophisticated bioreactors that incorporate principles from tissue engineering, fluid dynamics, and biomechanics. By better simulating the mechanical conditions found in real tissues, these bioreactors could substantially improve the physiological relevance of organoid models. Recent developments in bioreactor that mimic specific physiological conditions like blood flow or tissue-specific strain could be adapted for organoid research in the near future[14]. However, mechanical stimulation can also be applied through independent methods, including mechanical stretching devices, microfluidic platforms that generate pulsatile flow, and acoustic/mechanical wave stimulation. These methods can be used separately or integrated into bioreactors. Table 1 summarized techniques that suitable for applying mechanical stimuli on specific types of organoids. In addition to enhancing organoid functionality, the integration of biomechanics could boost the predictive power of organoid models in drug screening applications. Drugs that impact mechanically active tissues—such as those in cardiovascular or musculoskeletal systems—could be tested in environments that better reflect the physiological conditions of those tissues. This could lead to more reliable preclinical results and reduce the risk of inaccurate conclusions during the drug development process.

**Table 1.** Mechanical stimulation methods for organoids.

| Method | Mechanism | Suitable organoids |
|---|---|---|
| Bioreactors | Provides a controlled environment with mechanical stimulation, fluid flow, and biochemical regulation. | Cardiac, bone, lung, kidney, tumor, etc. |
| Mechanical stretching | Applies cyclic stretching to simulate physiological strain and tissue expansion. | Cardiac, skeletal muscle, lung, intestine |
| Microfluidic platforms | Uses micro-scale channels to generate shear stress and control perfusion dynamics. | Liver, kidney, lung, intestine, tumor |
| Acoustic/Mechanical wave | Uses sound waves or mechanical vibrations to apply localized mechanical forces. | Neural, cardiac, bone, muscle |
| Electromagnetic field | Applies electromagnetic fields to influence mechanotransduction and cellular responses. | Neural, muscle, cardiac |
| Hydrostatic pressure | Applies static or cyclic pressure to mimic in vivo physiological loads. | Kidney, brain, lung |
| Centrifugal force | Uses centrifugal force to induce compression and simulate gravitational effects. | Bone, cartilage, cardiovascular |

Computational models, including computational fluid dynamics (CFD) and finite element modeling (FEM), could also play an important role in predicting mechanical behavior and aiding in the design of bioreactors that provide appropriate mechanical cues[15]. CFD simulations allow for the optimization of perfusion systems by modeling shear stress and fluid flow, while FEM can be used to analyze stress and strain within organoid scaffolds and even simulate cell behavior. Nevertheless, more research is needed to standardize these technologies and to validate their efficacy in accurately replicating in vivo conditions. standardization in evaluating the impact of mechanical cues on organoid development is another critical issue. Without standardized protocols, it is challenging to compare results across different studies. Standardization would provide a consistent framework for determining the functional integrity of organoids under various mechanical conditions, allowing for a more comprehensive understanding of how closely organoids can approximate native organ functions.

Despite the promising outlook, there remain several criticisms of current efforts in this area. The limited availability of commercial bioreactors that are optimized for specific tissue types suggests that most laboratories will struggle to reproduce the mechanical environments required for high-fidelity organoid development. Additionally, there is still very little understanding of how various mechanical stimuli interact with each other and with biochemical cues to influence tissue maturation and differentiation. Further research is needed not only to implement these forces but also to understand their synergistic effects. Ignoring these

complexities risks developing models that fail to offer real predictive power or yield mechanistic insights that could otherwise revolutionize fields like regenerative medicine, oncology, and pharmacology.

## Declaration of Competing Interest

The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Data availability

Data not available.

## References:

[1] Z. Zhao, X. Chen, A. M. Dowbaj, A. Sljukic, K. Bratlie, L. Lin, E. L. S. Fong, G. M. Balachander, Z. Chen, A. Soragni, M. Huch, Y. A. Zeng, Q. Wang, H. Yu, *Nature Reviews Methods Primers* **2022**, 2, 94.
[2] K. H. Vining, D. J. Mooney, *Nat Rev Mol Cell Biol* **2017**, 18, 728.
[3] W. L. Stoppel, D. L. Kaplan, L. D. Black, 3rd, *Adv Drug Deliv Rev* **2016**, 96, 135.
[4] M. Hofer, M. P. Lutolf, *Nature Reviews Materials* **2021**, 6, 402.
[5] M. Huch, H. Gehart, R. van Boxtel, K. Hamer, F. Blokzijl, M. M. Verstegen, E. Ellis, M. van Wenum, S. A. Fuchs, J. de Ligt, M. van de Wetering, N. Sasaki, S. J. Boers, H. Kemperman, J. de Jonge, J. N. Ijzermans, E. E. Nieuwenhuis, R. Hoekstra, S. Strom, R. R. Vries, L. J. van der Laan, E. Cuppen, H. Clevers, *Cell* **2015**, 160, 299.
[6] H. M. Poling, D. Wu, N. Brown, M. Baker, T. A. Hausfeld, N. Huynh, S. Chaffron, J. C. Y. Dunn, S. P. Hogan, J. M. Wells, M. A. Helmrath, M. M. Mahe, *Nat Biomed Eng* **2018**, 2, 429.
[7] E. Ozcivici, Y. K. Luu, B. Adler, Y. X. Qin, J. Rubin, S. Judex, C. T. Rubin, *Nature Reviews Rheumatology* **2010**, 6, 50.
[8] Z. Zeng, B. Huang, R. K. Parvez, Y. Li, J. Chen, A. C. Vonk, M. E. Thornton, T. Patel, E. A. Rutledge, A. D. Kim, J. Yu, B. H. Grubbs, J. A. McMahon, N. M. Pastor-Soler, K. R. Hallows, A. P. McMahon, Z. Li, *Nature Communications* **2021**, 12, 3641.
[9] Y. Yamamoto, S. Gotoh, Y. Korogi, M. Seki, S. Konishi, S. Ikeo, N. Sone, T. Nagasaki, H. Matsumoto, S. Muro, I. Ito, T. Hirai, T. Kohno, Y. Suzuki, M. Mishima, *Nature Methods* **2017**, 14, 1097.

[10] Y. R. Lewis-Israeli, A. H. Wasserman, M. A. Gabalski, B. D. Volmert, Y. Ming, K. A. Ball, W. Yang, J. Zou, G. Ni, N. Pajares, X. Chatzistavrou, W. Li, C. Zhou, A. Aguirre, *Nature Communications* **2021**, 12, 5142.
[11] D. T. Butcher, T. Alliston, V. M. Weaver, *Nat Rev Cancer* **2009**, 9, 108.
[12] C. L. Walsh, P. Tafforeau, W. L. Wagner, D. J. Jafree, A. Bellier, C. Werlein, M. P. Kuhnel, E. Boller, S. Walker-Samuel, J. L. Robertus, D. A. Long, J. Jacob, S. Marussi, E. Brown, N. Holroyd, D. D. Jonigk, M. Ackermann, P. D. Lee, *Nat Methods* **2021**, 18, 1532.
[13] K. Madi, K. A. Staines, B. K. Bay, B. Javaheri, H. Geng, A. J. Bodey, S. Cartmell, A. A. Pitsillides, P. D. Lee, *Nat Biomed Eng* **2020**, 4, 343.
[14] N. Sarkar, S. Bhumiratana, L. Geris, I. Papantoniou, W. L. Grayson, *Nature Reviews Bioengineering* **2023**, 1, 361.
[15] W. Zhang, J. Li, J. Zhou, A. Rastogi, S. Ma, *Trends Biotechnol* **2022**, 40, 1121.