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Focussed Review of Modelling-Driven Innovations in Organ-on-a-Chip Platforms using CFD, AI, and AR/VR

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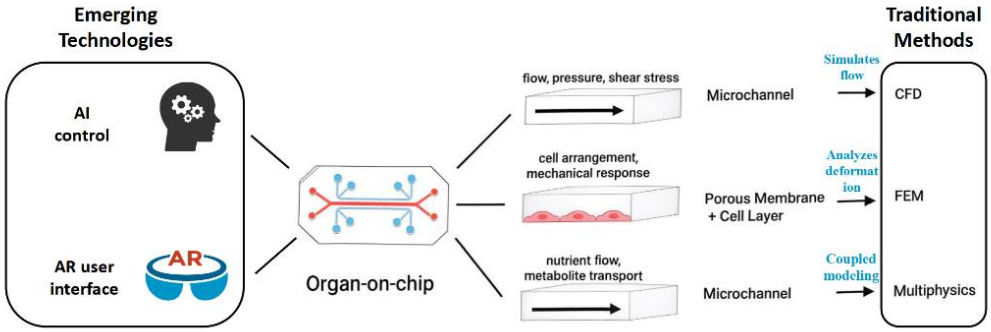
Graphical Abstract

Abstract



Organ-on-a-chip (OOC) is an emerging microfluidic platform that mimics key physiological functions of the human body, offering promising tools for drug screening, disease modeling, and personalized medicine (context). This review highlights recent advances in OOC modeling, with a focus on Computational Fluid Dynamics (CFD), Finite Element Analysis (FEM), multiphysics simulation, artificial intelligence (AI), and augmented/virtual reality (AR/VR) (key advance). We summarize the applications of these approaches in fluid dynamics, mechanical responses, chemical transport, and system visualization, explicitly addressing their roles at different modeling layers relevant to chip performance (scope). Finally, we discuss current challenges, including organ complexity, multi-organ integration, validation, and standardization, and propose that future progress will rely on interdisciplinary collaboration, hybrid modeling strategies, and real-time AI integration to accelerate biomedical translation (outlook).

Keywords: Organ-on-a-Chip, Microfluidics, Artificial Intelligence, Biomedical Applications

1. Introduction

Organ-on-a-Chip (OoC) is a cutting-edge technology that combines biology and microtechnology, capable of simulating key physiological functions of the human body on microfluidic chips[1,2]. It exactly controls trace amounts of fluid through the use of microchannels to supply cells and tissue structures with a close-to-physiological microenvironment[3]. OOC employs chip-based regulated device systems to supply cells and tissue structures with biochemical and physical environments close to in vivo conditions to allow scientists to experiment on these systems in vitro[4]. This allows scientists to more accurately control the microenvironment in which the cells reside and directly view the reaction of the cells and tissues[5].

In comparison to conventional two-dimensional cell culturing, the scale of the channels in microfluidic systems is comparable to that of cells and more effectively replicates the extracellular microenvironment and the three-dimensional tissue structure[6,7]. It is able to perform precise regulation of mechanical stimulation to the cells, delivery of nutrients and chemical gradients. With these technologies, it is possible to create miniature cavities of precise structures and accurately regulate the molecules and the cells within the microfluidic system to accurately duplicate the organs' microenvironment and replicate the physiological and disease conditions in the body[8]. With this technology, it offers a highly bionic and high-throughput new experimental system for drug screening, disease studies and personalized medicine.

But in order to fully tap the potential of OOC, advanced modeling techniques assume key significance[9]. Modeling not only allows for chip design to be optimized, fluid and cell behavior to be predicted, and the trial-and-error experiment to be minimized but also enhances the reproducibility of the system. CFD, FEM as well as multi-physics field simulation provide valuable information on the flow field distribution, the mechanical stress, the nutrient gradient and the response of the cell within the chip. Meanwhile, recent emerging technologies including AI and AR/VR have continuously improved the precision of designs, data analysis functions, and visual interaction to further enhance the accuracy of modeling.

In the past few years, scientists have constructed various types of organ chips, e.g., the brain[10], heart[11], lung[12] and cancer models[13], and made good performance in various applications. Organ-on-a-chip has become a valuable tool for the academia and industry to study the functions of organs and discover new medicines. For example, the bionic lung chip has effectively duplicated the relationship between human alveoli and capillary structures, offering a new way for drug screening[14].

However, despite the fact that OOC technology is extremely innovative, there are still many challenges[15]. One of the primary challenges is standardization in the process of manufacturing[16]. Up to now, due to the lack of a uniform system of material and techniques, not only does it hinder the reproducibility of experiments but also the mass production and low-cost process. Second, the cooperation and coupling between different chip organs have not yet been effectively integrated, and as a result, it becomes challenging to simulate comprehensive multiple-organ interaction. Likewise, OOC also encounters the problem of medical verification and regulation: how to undergo medical verification and be certified by the US FDA is a primary challenge for the transition of OOC toward application[17].

The aim of this paper is to comprehensively review the modelling approaches for microfluidic platforms in Organ-on-a-Chip (OOC), assess the role of traditional techniques such as Computational Fluid Dynamics (CFD), Finite Element Analysis (FEA), and Multi-Physics Field Simulation (MFSS) in the design and optimisation of OOCs, and explore the innovative breakthroughs brought by the emerging technologies such as Artificial Intelligence (AI), Machine Learning (ML) and Augmented/Virtual Reality (AR/VR). However, existing reviews mostly focus on chip fabrication or biological applications, with less systematic summaries of the synergies of these modelling strategies and their challenges, such as multi-scale coupling, data integration and standardisation issues. By filling this gap, this paper provides ideas and references for the development of OOC in biomedical engineering.

2. Modelling and Intelligent Technologies

With the rapid development of organ-on-a-chip (OOC) technology, advanced modeling methods and intelligent technologies are playing an increasingly important role in it. Modeling tools such as Computational Fluid Dynamics (CFD)[18], Finite Element Analysis (FEM), and multiphysics simulation provide reliable theoretical support for chip design, fluid control, and physiological process prediction. Meanwhile, the introduction of emerging technologies such as artificial intelligence (AI), machine learning, and augmented/virtual reality (AR/VR) has greatly enhanced the efficiency of data analysis, design optimization, and visualization. Figure 1 shows how CFD, FEM, and multiphysics relate to key OOC components.

2.1 Traditional computational modeling methods

2.1.1 CFD

Computational Fluid Dynamics (CFD) is a method based on numerical analysis, which is used to simulate and predict the flow, pressure, velocity, temperature and material transport behavior of fluids (liquids or gases) under different conditions[18].

Hydrodynamic parameters such as shear force, pressure and flow rate can significantly affect the morphology, proliferation, function and survival rate of cells, and thereby

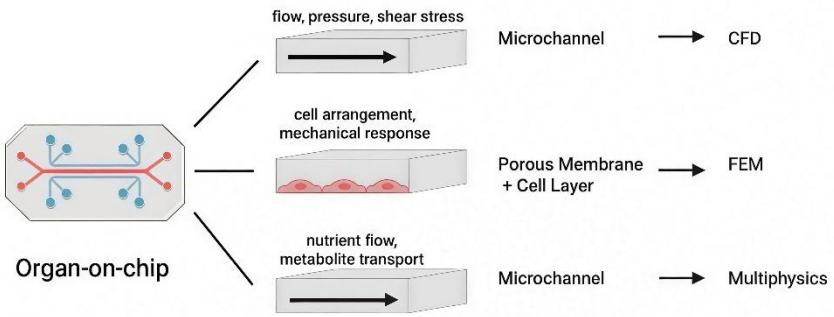


Figure 1. Schematic of Organ-on-a-Chip and modelling methods

play a key role in the overall function and activity of tissues[19]. Microfluidic devices provide a highly promising method for studying these parameters and the fluid behavior in different microchannel structures[20]. Microfluidic devices (MFDS) are made of biocompatible materials and contain tiny channels[21]. Organ-on-a-chip (OOC) utilizes this technology to simulate the microenvironment of specific tissues or organs[22].

Green et al. investigated the influence of channel geometry on cell adhesion by designing microchannels with sharp turns and curved turns and combining them with fluid dynamics simulations. Their results show that the flow velocity and shear stress distribution in the curved and turning microchannels are more uniform, which helps to improve the cell adhesion effect[23].

Bakuova et al. demonstrated through CFD analysis and experiments based on Huh7 cells that the elliptical cavity liver chip has superior flow and filling characteristics compared to the circular cavity chip, and successfully verified the adhesion and continuous growth of cells[24]

However, CFD mainly focuses on fluid systems and is difficult to directly handle the solid deformation of chips or multi-physics field coupling. Moreover, its mesh division and boundary condition setting are complex, the calculation time is long, and it requires powerful computing resources[25].

2.1.2 Finite Element Analysis (FEM)

Finite element Analysis (FEM) is a numerical tool used to predict the mechanical properties in organ-on-a-chip (OOC), capable of simulating the deformation, stress distribution and fluid-structure coupling effects of chip materials. The application of FEM is conducive to optimizing chip design, improving durability and security. However, its modeling is complex and the parameter setting is cumbersome, and it needs to be combined with experimental verification to ensure the reliability of the simulation. Furthermore, at present, many designs still mainly rely on trial-and-error experiments and have not fully utilized the advantages of FEM[26].

2.1.3 Multi-physics field simulation

Multiphysics simulation is an integrated approach used to simultaneously study the interactions among various physical processes such as fluids, mechanics, chemistry, and heat conduction, and is particularly suitable for complex organ-on-a-chip (OOC) systems. Multiphysics simulation not only helps optimize chip design and enhance the physiological relevance of experiments but also provides a powerful tool for the prediction of complex systems.

Jeon et al. utilized multi-physics field simulation combined with experiments to study the effects of fluid flow in the intestinal-liver microarray on intestinal cells and liver cells, optimized the flow velocity and shear force parameters, and explored the effects of fatty acid transport, liver lipid accumulation, and anti-fatty liver drugs[27].

2.2 The Application of AI in OOC

AI, especially machine learning algorithms, can be used to automate chip design and parameter optimization. By training algorithms, researchers can predict in advance which design is the most suitable for a specific biological application, significantly reducing the cost of trial and error. Machine learning is a common method for achieving artificial intelligence, and deep learning is one of the important algorithms among them.

The research by Li et al. indicates that organ-on-a-chip (OOC) systems based on deep learning have demonstrated great potential at multiple levels[28]. Through algorithms such as convolutional Neural networks (CNN) and recurrent neural networks (RNN), image analysis, cell recognition, dynamic tracking, segmentation and functional prediction in the chip can be efficiently achieved, greatly improving the automation level of data processing. In addition, deep learning has also demonstrated significant value in aspects such as the design optimization of microfluidic chips, fluid dynamics analysis, and cell behaviour prediction. This study points out that by integrating deep learning technology, OOC is expected to achieve higher accuracy and efficiency in drug screening, disease modelling, personalized medicine, and multi-organ

Table 1. Summary of modelling tools, applications, advantages, and challenges in Organ-on-a-Chip research

Tool	Application	Advantage	Challenge	Recent Example
CFD	Simulate fluid flow, shear stress, nutrient transport in microchannels	High accuracy, clear physical principles	Complex setup, high computational cost	Barbosa et al. (2024), thermal and fluid flow modeling in OoC[29].
FEM	Analyze mechanical deformation, stress distribution, fluid–structure interaction	Accurate mechanical predictions, good for membrane deformation	Complex meshing, needs precise material data	de Menezes (2020), finite element approach for OoC design[26].
Multiphysics Simulation	Combine fluid, mechanical, thermal, chemical effects	Comprehensive system analysis	High modeling difficulty, long computation time	Jeon et al. (2021), gut–liver-on-a-chip for hepatic steatosis modeling[27].
AI	Optimize design, predict behavior, analyze images	Fast data processing, automated optimization	Needs large, high-quality datasets; limited interpretability	Isozaki et al. (2020), AI integration in lab-on-a-chip systems[30].
AR/VR	Visualization, training, remote collaboration	Improved visualization and interactivity	Limited integration with physical systems	Broek (2025), visualization tool for OoC fibrotic disease model[31].

system research, bringing new opportunities for in vitro alternative experiments and precision medicine[28].

Isozaki et al. reviewed the combined application of artificial intelligence (AI) and Lab-on-a-Chip, pointing out that machine learning and deep learning have significantly improved the analytical efficiency and accuracy in aspects such as high-throughput imaging, cell classification, and drug screening[30]. The article also mentioned that algorithms such as Support Vector Machine (SVM) and Convolutional Neural Network (CNN) have been successfully applied in cell cycle analysis and blood cell detection. At the same time, it emphasized future challenges such as model interpretability and data quality.

Lightweight models such as decision trees and embedded machine learning can also be introduced in for real-time control and adaptive tuning[32]. Such methods are faster in computation, consume less power and are more suitable for integration with portable and miniaturised devices.

2.3 The Application of AR/VR in OOC

Augmented Reality (AR) and virtual reality (VR) are visualization and interaction technologies that have developed rapidly in recent years. These two technologies have the advantages of being intuitive, dynamic and highly interactive, which makes them show wide application potential in many scientific research and engineering fields.

Recent works have demonstrated the growing significance of AR and VR in medical applications, including their application in organ-on-a-chip (OOC) studies. For example, VR associated with Computer-aided Modeling (CAM) has been used in tele-surgery to increase the accuracy of operations and collaborative planning[33,34]. In the study of OOC, the use of AR/VR technology can project the Body-on-a-Chip (BOC) system and combine several OOC units to model a whole organism[35,36]. By fusing real-time data and immersive visualization, the use of AR/VR increases the capacity of researchers to track dynamic processes, study drug effects, and tune up experimental protocols without the need for direct physical manipulation. Further, AR/VR also enhances inter-team communications[37].

Although AR/VR has shown great potential in aspects such as visualization, simulation and training, the integration with actual OOC systems still faces some obstacles. Including the limitations of hardware miniaturization and the challenge of real-time data synchronization between virtual and physical systems.

2.4 Comprehensive evaluation

Advanced technologies such as Computational Fluid Dynamics (CFD), Finite Element Analysis (FEM), multiphysics simulation, artificial intelligence (AI), and augmented/virtual reality (AR/VR) are instrumental in the enhanced design and application of organ-on-a-chip (OOC). CFD and FEM offer high accuracy but need complex setup and heavy computing. Multiphysics simulation captures system interactions but is even more demanding. AI brings efficiency and flexibility to design and data analysis but depends on large, quality datasets and often lacks interpretability. AR/VR improves visualization and user

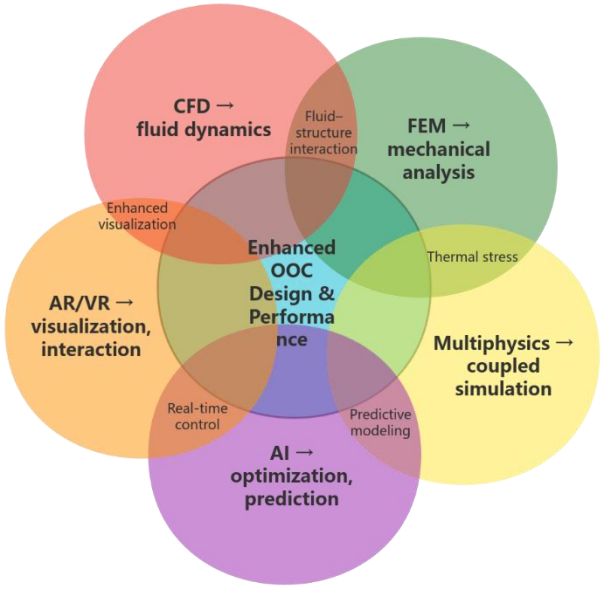


Figure 2. Complementary Modelling Methods in Organ-on-a-Chip

interaction but is still mainly used as a support tool, with limited integration into chip systems.

Table 1 summarizes the main tools, their typical applications in organ-on-chip systems, as well as their respective main advantages and challenges.

To illustrate the complementarity and integration of various modelling approaches in Organ-on-a-Chip systems, Figure 2 presents a schematic Venn diagram highlighting the overlaps and shared roles of CFD, FEM, multiphysics simulation, AI, and AR/VR technologies.

Overall, each technology has its own focus and complementary advantages in OOC. In the future, it is necessary to promote cross-disciplinary integration, combining the rigor of traditional modeling with the predictive ability of AI and the intuitiveness of AR/VR, to achieve a more efficient, intelligent and reliable OOC system, opening up broader prospects for biomedical research and precision medicine.

2.5 Validation

Verification is a key step to ensure that the modeling results accurately reflect the biological performance in the OOC system. For instance, the fluid flow and shear force obtained from CFD simulation can be verified through microparticle imaging velocity measurement (μPIV) or tracer dye experiments[38]. The results predicted by FEM can be compared by observation with a high-resolution microscope or traction microscopy[39]. The prediction of cell behavior or drug response by AI needs to be verified through means such as time series imaging, molecular analysis or histological analysis[40]. Effective verification can not only enhance the credibility of the model, but also identify the deficiencies that need improvement in the model.

Meinicke et al. combined μPIV measurement and CFD simulation to study the single-phase fluid dynamics in porous SiO_2 glass foam. In the study, μPIV was used to observe the flow of DMSO in porous structures, and the experimental data were compared with the CFD model reconstructed by X-rays. The research shows that the experimental results are highly consistent with the numerical results, effectively verifying the CFD prediction[41].

3 Challenges and Future Perspectives

Although organ-on-a-chip (OOC) technology has made many advancements, it still faces many challenges in practical applications. How to accurately restore the complex structures of human organs and biological interfaces remains difficult[42].

Although traditional modeling methods (such as CFD, FEM, and multiphysics simulation) are accurate in calculation, they are complex in operation and time-consuming. AI offers new approaches to design optimization and data analysis, but it relies on a large amount of high-quality data and has limited model interpretability. AR/VR has improved visualization and interaction, but the deep integration with OOC is still insufficient.

Furthermore, OOC lacks a unified platform and standards, resulting in the difficulty of repeating experiments and integrating and analyzing data. The stable supply of human cells and the development of multi-organ shared culture media are also key bottlenecks for promotion.

Interdisciplinary cooperation among biology, engineering and computational science needs to be strengthened in the future. By integrating modeling, AI and AR/VR, drive OOC to achieve more intelligent and efficient applications. And accelerate its clinical transformation in drug screening, disease research and precision medicine.

4 Conclusion and Recommendations

As the core technology of organ-on-a-chip (OOC), the microfluidic platform provides a solid foundation for its application in biomedical engineering. The combination of traditional modelling methods, artificial intelligence (AI), and augmented/virtual reality (AR/VR) has jointly promoted the design optimization, data analysis, and functional expansion of OOC, opening new avenues for fields such as drug screening, disease research, and personalized medicine.

In the future, the development of organ-on-a-chip (OOC) will increasingly rely on close collaboration in the fields of engineering, computing and biology. Hybrid digital twins are expected to combine sensors and AI to achieve real-time monitoring and regulation of OOC for personalized drug screening and disease prediction. Through the real-time feedback system embedded in machine learning (embedded

ML), researchers can adjust the fluid parameters, drug concentrations, etc. of the chip based on real-time data in the experiment, improving the flexibility and physiological relevance of the experiment. These advancements are expected to shorten the transition from the laboratory to clinical practice and promote the wide application of OOC in drug development and personalized medicine.

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