The Sydney Journal of Interdisciplinary Engineering
SJIE 1(4) X–X (2025) https://doi.org/XXXX/XXXX

A Focused Review of Modelling and Technological Advances in Organ-on-a-Chip Systems

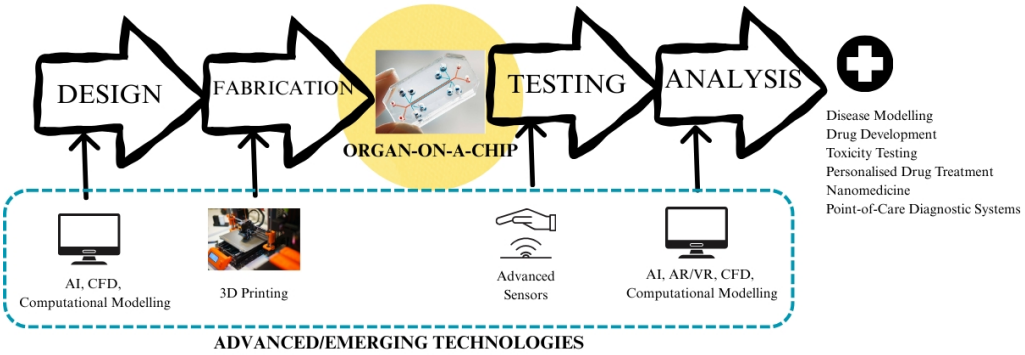
Isabel Iris Claro[1], Gobinath Pillai Rajarathnam[1], Aoni Xu[1]

[1] School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, Australia

E-mail: icla8773@uni.sydney.edu.au

Received xxxxxx
Accepted for publication xxxxxx
Published xxxxxx

Graphical Abstract



Abstract

Organ-on-a-Chip (OoC) technology offers a promising alternative to traditional *in vitro* and animal models by replicating key physiological features of human organs within microfluidic platforms. These systems are increasingly used in drug development, toxicity testing, and disease modelling. However, widespread adoption is limited by challenges such as complex design requirements, scalability issues, data interpretation difficulties, and the integration of diverse technologies. This review explores the role of advanced modelling approaches, such as computational fluid dynamics (CFD), finite element analysis (FEA), pharmacokinetic/pharmacodynamic (PK/PD) models, and artificial intelligence (AI), in addressing these barriers. These tools enable precise simulation, optimization, and data analysis of OoC systems, supporting their design and predictive capabilities. Key challenges identified include limited data quality, computational complexity, organ scaling, and system integration. Modelling solutions, including explainable AI and multiscale simulation, offer pathways to overcome these issues. The integration of emerging technologies like 3D printing, real-time sensing, and automation is also discussed. The review concludes with recommendations for refining existing modelling techniques, improving transparency in AI applications, and supporting interdisciplinary collaboration to drive standardization and regulatory acceptance. These efforts are essential for realizing the full potential of OoCs in biomedical research and preclinical drug development.

Keywords: organ-on-a-chip, OoC, microfluidic, artificial intelligence, AI, machine learning, 3D printing, simulation, computational fluid dynamics, CFD.

1. Introduction

The development of sophisticated *in vitro* models has become increasingly important in life science and industry, particularly for applications in medicine, biology, and chemistry.[1] Traditional two-dimensional (2D) cell cultures and animal models struggle to replicate human physiology, hindering data translation and contributing to high drug failure rates.[2-5] This has spurred the evolution of new technologies aimed at creating more biologically relevant systems.[5,6]

Notably selected as one of the "Top Ten Emerging Technologies" by the World Economic Forum[7], The development of organ-on-a-chip (OoC) technology is driven by these limitations of traditional preclinical models.[4,8] OoCs address these limitations by combining advances in microfabrication, tissue engineering, biomaterials, and stem cell engineering to reconstruct key structural, functional, and physiological aspects of human tissues and organs on a chip.[7,9-11] Miniature tissues, cells, or organoids are cultured within the channels and compartments of a microfluidic device.[3,7,11-13] This device, often made of materials like polydimethylsiloxane (PDMS), is engineered with structures such as tiny channels, chambers, and sometimes porous membranes to recreate the organ's microarchitecture.[3,4,7,11,14] The cells may also be embedded within an extracellular matrix analogue or hydrogel inside these compartments. OoC platforms hold promise for various applications, including enhancing our understanding of tissue and organ physiology, modelling diseases (such as cancer), developing and screening drugs, evaluating drug toxicity and efficacy, and facilitating personalized medicine by using patient-derived cells.[3,4,8-11,15,16]

Building upon the foundation of microfluidics, the OoC system has emerged as a biomimetic system.[17] Microfluidics, refers to technologies that manipulate small fluid volumes (mL, nL, pL) within fabricated channels.[1,18] Microfluidic approaches allow for constant miniaturization, automation, and parallelization of processes[1], offering advantages such as low dose requirements, improved sensitivity, efficient processing, great spatial accuracy, good integration, and straightforward control for biological studies.[19] These microfluidic systems can perform several functions, including sample pretreatment, separation, dilution, mixing, chemical reaction, detection, and product extraction, all potentially on a single chip.[18] The precise control offered by microfluidics allows for the emulation of dynamic conditions, such as blood flow, mechanical forces, and concentration gradients, which are crucial for maintaining tissue-specific functions and mimicking the cellular microenvironment.[8,10,11,16]

OoCs are essentially microfluidic cell culture systems designed to precisely replicate the structure and function of a living organ or functional unit *in vitro*.[5,20,21] They can stimulate the tissue or cell microenvironment and regulate crucial parameters like concentration gradients, shear stress, flow

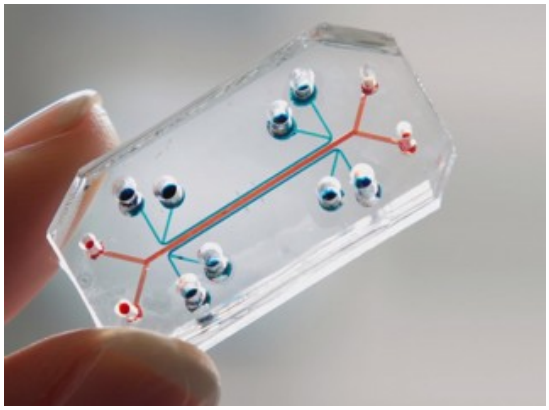


Figure 1. A lung-on-a-chip. Image by 허동은교수, *licensed under CC BY -SA 4.0. Source: Link*

[5,17] These platforms integrate microfluidic networks with three-dimensional (3D) tissue-engineered models to recapitulate physiological conditions.[5]

The applications of organ-on-a-chip platforms are diverse and rapidly expanding. They are used as models for studying development and diseases, such as Alzheimer's and schizophrenia, particularly through brain-on-chip models. OoCs play a significant role in drug development, including drug screening and assessing drug release.[2,5,6,18,22,23] They are particularly valuable for toxicity testing, such as evaluating hepatotoxicity, and nephrotoxicity.[5,18] Furthermore, OoCs contribute to personalized medicine by offering functional testing for precision medicine and personalized drug development. They are also explored in the context of nanomedicine for validating the performance and biotoxicity of nanomaterials.[5] Beyond these, OoCs are used to study vascularization of organoids, drug delivery systems, host-microbial interactions, inflammatory processes, and cancer growth and metastasis.[6,23] The technology is even being applied to create point-of-care (POC) diagnostic systems.[18]

The significance of organ-on-a-chip platforms lies in their potential to serve as robust alternatives to animal models, addressing many challenges associated with *in vivo* studies.[2,5] By providing a controlled and realistic environment that mimics human physiology and pathology, OoCs can help reduce the discrepancies observed between preclinical findings and clinical outcomes.[5,18,21] This capability positions them as a fast track for the use of engineered human tissues in drug development and can potentially revolutionize disease modelling and drug testing towards more accurate and personalized healthcare approaches.[18]

Despite the significant progress, the translation of these advanced microfluidic platforms into widespread use, particularly in preclinical validation for clinical applications, still faces limitations and challenges.[5] A critical challenge is the successful integration of biosensor modules into OoCs for automated, continual, and long-term monitoring of various physicochemical and biochemical parameters.[5,18] For complex

applications like pharmacology studies, the development of multiorgan or body-on-a-chip systems is necessary to replicate the interconnections and communication between different organs. However, achieving accurate body scaling and maintaining functional activity across multiple integrated organs is extremely complex.[5] Other challenges include optimizing the design of suitable biomodels, overcoming fabrication complexities associated with microfluidic devices and integrating components like valves and pumps[19], managing potential contamination issues[5], establishing physiologically relevant conditions like oxygen gradients, and bridging the gap between academic research and industrial adoption. Overcoming these challenges is key to unlocking the potential of OoC technology.

Interest in OoC has intensified due to its potential to create more physiologically relevant microenvironments for cell culture, thereby bridging the gap between simplified planar cell cultures and complex human systems.[8,11,16]

Recent breakthroughs and emerging trends are pushing the boundaries of OoC technology, some of which are compared in Table 1 below. A key trend is the move towards integrating multiple individual organ chips into multiorgan-on-a-chip or body-on-a-chip systems, mimicking the physiological coupling and interactions between different organs in the human body.[4,8,16,24] This is particularly beneficial for studying systemic responses, drug metabolism, and complex diseases.[25] Furthermore, there is increasing emphasis on incorporating integrated sensors (mechanical, electrochemical, optical) into OoC platforms for real-time monitoring of cellular behaviors and tissue functions.[8,24,26] Automation and the development of high-throughput systems are also critical for making OoCs more viable for industrial applications like drug screening.[24,26,27] Advances in 3D printing and bioprinting techniques are enabling the rapid fabrication of complex OoC structures and the precise deposition of cells within biomaterial-based scaffolds, creating more realistic three-dimensional tissue architectures.[26] The integration of artificial intelligence (AI), particularly in areas like organoid imaging and data analysis, is enhancing the efficiency and accuracy of OOC-based research, especially for high-throughput drug screening.[9,24] These advancements collectively demonstrate the rapid evolution of OOC technology and its potential to revolutionize biomedical research and drug development.

Table 1. Comparative Table of Different Modelling Approaches Applied to OoCs.

Modelling Approach	Scale	Input	Use	Limitations
Computational Fluid Dynamics (CFD)	Microfluidic channels/ devices[28-30]	Geometry, fluid properties, flow rate, solute and solvent parameters, boundary conditions[29,30]	Simulates fluid flow, shear stress, and concentration gradients[28-31]	Complex multiphysics, time-consuming meshing, sensitivity to surface tension and viscosity[29]
Finite Element Analysis (FEA) / Finite Element Method (FEM)	Microfluidic devices, bioreactors[29,31,32]	Geometry, material properties, physics modules (e.g., CFD), solute parameters[29,32]	Models mechanical stress, strain, gradient formation, and device refinement[29,31,32]	Requires detailed meshing, complex physics coupling, geometric/parameter coherence[29]
Pharmacokinetic/ Pharmacodynamic (PK/PD) & Physiologically-Based Pharmacokinetic (PBPK)	Multi-organ systems (e.g., gut-liver, whole-body)[11,25,28,33-35]	*In vitro*/OoC data (volumes, ADME, flow rates, drug properties)[25,28,33,35]	Predicts drug distribution, toxicity, and human PK/PD profiles; supports *In Vitro-In Vivo* Extrapolation (IVIVE)[11,25,33-35]	Difficult organ scaling, biological/analytical uncertainty, complex model integration[25,33]
Artificial Intelligence (AI) / Machine Learning (ML)	Variable (e.g., single-cell to system-level)[5,9,34,36]	Experimental features (e.g., contractility, solubility, oxygen), labeled/unlabeled data[9,34,36,37]	Classifies cells, predicts outcomes, supports toxicology and experimental design[9,25,34,36,37]	Performance depends on data size/quality, model choice, and validation strategy[9]

This review aims to present the different advanced modelling and analysis techniques that are currently applied and can be applied to OoCs. Section 2 will discuss the current strategies (Section 2.1), and emerging OoC technologies (Section 2.2) with an analysis comparing the technologies (Section 2.3). Section 3 discusses the challenges in OoC

technology (Section 3.1) and how emerging or advanced techniques can help address these challenges (Section 3.2). Finally, Section 3.3 discusses the potential future directions for OoC technology.

2. State-of-the-Art in Advanced Modelling Strategies

2.1. Current Methodologies

Current OoC methodologies are grounded in microfluidic platforms, allowing precise control of microscale fluids to mimic physiological conditions.[16] Device fabrication primarily utilizes soft lithography, often with PDMS, known for its biocompatibility and gas permeability.[38] However, alternatives like thermoplastics and natural materials are gaining prominence to address PDMS limitations such as drug absorption.[12] 3D printing and bioprinting are increasingly used for rapid prototyping and creating complex 3D tissue scaffolds.[11]

A key methodology involves reconstituting functional tissues by culturing cells (primary, cell lines, or induced pluripotent stem cells, iPSCs) within the microfluidic chips, often in 3D structures.[10] This requires maintaining a physiologically relevant cellular microenvironment by controlling factors like fluid shear stress, soluble factor concentrations, and cell-matrix interactions.[39]

To capture systemic complexity, multiorgan-on-a-chip systems are developed by connecting multiple organ models, essential for studying drug Absorption, Distribution, Metabolism, Excretion, and Toxicology (ADME-Tox) and inter-organ communication.[4,11,33] These often incorporate vascular networks to simulate blood flow and interactions.[4]

Sensors are being integrated into platforms for real-time monitoring of tissue function and microenvironmental parameters. This facilitates feedback control systems essential for automating high-throughput drug screening.[4,10,11,24,26,39] This drive towards automation and high-throughput screening is critical for the industrial adoption of OoC technology, particularly in drug development.[11,35]

Finally, computational modelling, including fluid dynamics and pharmacokinetic and pharmacodynamic (PK/PD) simulations, plays a vital role in optimizing chip design, predicting parameters, and interpreting experimental data.[33,35,39] Computational platforms such as COMSOL Multiphysics and ANSYS Fluent are commonly used for the design and analysis of microfluidic organ-on-a-chip systems. These *in silico* tools allow for simulations of critical fluid dynamics and transport phenomena necessary for device optimization.[29,30,35] AI is being integrated for enhanced data analysis and image processing. These diverse methodologies collectively contribute to creating and analyzing more physiologically relevant *in vitro* models.[37]

2.2. Integration of Emerging Technologies

OoC technology is a rapidly evolving field that is being significantly advanced by the integration of several emerging technologies with established microfluidic and tissue engineering methodologies.[9,10] This convergence aims to enhance the physiological relevance, functionality, and scalability of OoC systems to better recapitulate human biology and meet the demands of applications such as drug discovery and disease modelling.[4,10]

A prominent area of integration is the development of multiorgan-on-a-chip systems, also referred to as body-on-a-chip, which connect multiple individual organ models using vascular networks within a single microfluidic platform.[4,16,24,35] This mimics the physiological coupling and interactions between different organs in the human body.[35] Such integrated systems are particularly valuable for studying systemic responses, such as drug absorption, distribution, metabolism, and excretion (ADME), as well as complex inter-organ disease mechanisms.[4,16]

Another critical integration involves incorporating integrated sensors directly within OoC platforms.[10,24] Integrated sensors (e.g., mechanical, optical, electrochemical) enable real-time, noninvasive monitoring of tissue function and microenvironmental conditions.[10,24] Examples include electrochemical sensors for detecting relevant biological processes and optical oxygen sensors.

To facilitate the widespread adoption of OoC technology, particularly in pharmaceutical research, there is a significant push towards automation and the development of high-throughput systems. Systemized experimental procedures are being developed to minimize user dependency and improve reproducibility, which are crucial for applications like drug screening.[10,16]

Advances in manufacturing techniques are also being integrated. 3D printing and bioprinting are increasingly used for fabricating complex OoC structures and creating more realistic three-dimensional tissue architectures.[26,40] These methods allow for the precise deposition of cells within biomaterial-based scaffolds and the rapid construction of intricate channel geometries.[26] 3D printing techniques are considered potentially more cost-efficient for OoC fabrication.

Furthermore, AI and computational modelling are being integrated to enhance both the design and analysis phases of OoC research.[9,24,32,35] Computational fluid dynamics (CFD) is used to design optimal microfluidic channel geometries and understand fluid flow patterns.[35] PK/PD modelling helps predict drug behavior and optimize experimental design and sampling.[32] AI is particularly beneficial for tasks such as organoid imaging analysis and processing complex datasets, significantly enhancing the efficiency and accuracy of studies, especially in high-throughput drug screening.[24] Numerical simulation is also used to predict parameters like oxygen concentration and distribution within the devices.[35]

These integrations of multiorgan systems, advanced sensors, automation, 3D printing, and computational approaches are collectively driving OoC technology towards becoming more sophisticated, predictive, and applicable tools for biomedical research and drug development.[9,10]

2.3. Comparative Analysis

OoC technologies offer a valuable step towards more physiologically relevant *in vitro* models, providing precise control over the cellular microenvironment and enabling real-time monitoring.[11,41] However, relying solely on traditional experimental methods encounters significant limitations including challenges in achieving industrial scalability, ensuring high reproducibility, accurately replicating complex tissue structures, addressing material compatibility issues, and a lack of widespread standardization.[11,12,42,43] Data acquisition can also be limited by reliance on endpoint assays.[11] The integration of advanced computational modelling and AI is crucial for overcoming these bottlenecks. These *in silico* approaches enable rapid simulation and analysis, providing insights into device design, optimizing parameters for fluid dynamics and transport, and supporting complex analyses like PK/PD modelling.[33,35,38,41] AI and machine learning algorithms further enhance the field by facilitating automated image analysis, cell classification, and predictive modelling based on complex cellular data from OoC systems.[34,44] In the study by Carvalho, et al. [41], a numerical model capable of reproducing the fluid flow behavior within an OoC device was developed and validated. By comparing the model's predictions to experimental results, including qualitative particle paths and quantitative particle velocities, they demonstrated its accuracy and reliability.[41] This synergistic combination of experimental OoC development with advanced computational tools is essential for improving the predictive power and robustness of these platforms.[34]

3. Challenges and Future Perspectives

3.1. Identified Challenges

Applying advanced modelling techniques, such as numerical simulation and mathematical modelling, to OoC platforms presents several key challenges, summarized in Table 2. These challenges arise from the complexity of replicating human physiology in microfluidic devices and the early stage of standardizing the technology.

Table 2. Major Challenges in OoC Systems.

Challenge	Source	Impact	Modelling Solution
Data Availability & Quality	Data often comes from end-point assays; lacks spatio-temporal resolution. Validation is hard due to low robustness and missing standards. Sampling is limited.[9,11,33,42]	Reduces reproducibility and hinders dynamic analysis. [11,42]	Use of AI/big data analytics for interpretation; optimization of sampling; push for standardized reporting[9,11,33]
Computational Complexity	Models are essential but hard to apply; 3D tracking is complex. Analysis must match biology.[9,12,25,41]	Limits predictive accuracy and optimization.[25]	Custom numerical and PK/PD models handle complexity. Tailored analysis improves relevance.[12,25,41]
Scalability Issues	Scaling organs and translating data is difficult. Industrial scale-up is limited.[10-12,15,16,25,43]	Affects *in vivo* relevance and slows commercialization.[25]	Use of PBPK scaling models; development of high-throughput and modular system designs.[16,25]
Integration of Multiple Technologies	Combines microfluidics, biomaterials, and sensors. Multi-organ signals and system miniaturization are complex.[7,9,10,13,15,26,31,45]	Increases system complexity; hinders functional replication and commercial viability.[9,16,26,42]	Modular design frameworks; collaboration-driven system modelling; incorporation of real-time sensor data into simulations.[9,13,26]

In addition to these, other challenges include the need for model validation with existing platforms[11,42], the lack of standardization in design, manufacturing, and operating procedures[11,42,43], the requirement for technical skills and user dependency leading to low reproducibility[10,13], limitations of current biomaterials[3,13,15,24], difficulties with sensor integration and data acquisition[9,11,26,42], and the overall engineering limitations in recreating the full physiological complexity of human organs.[9,11,24,42]

3.2. Role of Modelling in Addressing Challenges

Advanced modelling techniques are critical for overcoming many of the challenges associated with OoC technology.[25,35] Mathematical and computational models are essential tools for

quantitatively analysing OoC systems and predicting their complex responses.[12] They offer significant advantages over purely experimental approaches, providing insights into fluid flow physics with good precision and accuracy in a rapid and cost-effective manner.[30,41] Computational tools can be used alongside theoretical and experimental methods in microfluidics research.[41] Integrating computational models with OoC experiments provides more quantitative, mechanistic, and physiologically relevant insights than experiments alone.[25] Numerical studies and simulations are performed for optimization purposes, helping to expedite the OoC design process by reducing the need for fabricating numerous prototypes and conducting costly laboratory experiments.[30,41]

Examples from past and current studies demonstrate the impact of these strategies. In the study done by Jeong, et al. [30], numerical approach-based simulation models have been developed to accurately predict *in vivo* levels of shear stress in microfluidic Blood-Brain Barrier (BBB)-on-a-chip models. This prediction, which showed a low error rate compared to experimental results, helps to mimic *in vivo* conditions and establish parameters for successful cell culture, such as tight junction formation. The shear stress model was validated by comparing numerical simulation results with experimental data, achieving a <3% error rate, and demonstrating its reliability in mimicking *in vivo* conditions.[30] CFD and Finite Element Analysis (FEA) are important tools for characterizing biological microflows, predicting biofluid dynamics, and even solid biomechanics.[25] In another study done by Zheng, et al. [35], numerical simulations can also assess the feasibility and efficiency of a microfluidic design before fabrication, reducing experimental trial and error and speeding up the development process. Beyond optimizing design and flow, modelling is used to simulate complex biological behaviors in multicellular constructs, providing critical insights for improving reproducibility or guiding the achievement of desired form and function.[35] Multiscale models for multi-organ or human-on-a-chip systems are more suitable for modelling long-term drug transport and PK/PD effects.[12,34,35] Computational modelling can assist in analyzing, optimizing, and revising the design of 3D culture microfluidic chips, significantly reducing cost and time compared to repetitive experimental measurements.[35] For instance, mathematical models have been used to predict tumor angiogenesis by integrating quantitative experimental data in the study done by Phillips, et al. [37] Furthermore, the integration of machine learning algorithms can accelerate data analysis and image classification in OoC systems, enabling real-time monitoring and automated decision-making in cell culture.[11,34,46] This helps to accelerate preclinical drug screening and disease modelling.[34]

3.3. Future Directions

Advanced modelling techniques are already critical for the quantitative analysis and prediction capabilities of OoC systems, offering speed and cost advantages over purely experimental methods.[28,33,37] Incremental advancements in these methodologies, particularly through enhanced integration of AI and improved visualization, hold significant potential for further progress. Enhanced AI integration, utilizing algorithms like machine learning and deep learning[34,37,44], can accelerate data analysis and interpretation, such as automated image classification and quantitative assessment of cellular responses[34,37], while also refining predictions in areas like drug efficacy and toxicity by improving the estimation of PK/PD parameters from complex data.[33,35,37] The design and optimization of microfluidic devices and experimental protocols can be streamlined by more tightly coupling simulation techniques (e.g., CFD[4]) with AI, allowing for rapid exploration of design parameters, prediction of optimal configurations, and optimization of aspects like sampling times.[14,33,37] Additionally, making AI models more transparent through explainable AI is important for gaining regulatory trust and improving their use in OoC platforms, especially since some deep learning methods are difficult to interpret and can limit understanding in drug development.[47]

Improved visualization techniques, such as layering simulation data onto experimental images or potentially exploring 3D renderings (with techniques like those used for segmented medical images), can enhance researchers' understanding of complex, dynamic processes within the chip, making data interpretation more intuitive and potentially improving reproducibility.[37,44] Projects like ARinBIO explore Augmented Reality/ Virtual Reality (AR/VR) to improve data visualization and collaboration. This initiative seeks to streamline laboratory workflows, reduce errors, and facilitate personalized medicine by providing real-time data visualization and interaction within augmented environments.[48]

Regulation and standardization are crucial for the wider adoption and implementation of OoC technology, as a lack of regulatory consensus on acceptance criteria currently presents a significant hurdle to their use by end-users.[42] International efforts are underway by regulatory agencies and organizations, including the International Organization for Standardization (ISO), which is developing the ISO/AWI 25693 standard.[49,50] This standard, currently under development, specifies requirements for the development process of OoC used for the evaluation of substances, aiming to ensure fitness for purpose and support broader regulatory acceptance.[49]

4. Conclusion and Recommendations

This review highlights the critical role of advanced modelling techniques, such as computational fluid dynamics, finite element analysis, PK/PD simulations, and artificial intelligence, in enhancing the design, function, and analysis of OoC systems. These tools enable the replication of complex physiological environments, support data interpretation, and improve predictive modelling for drug development. However, key challenges remain, including limited data quality, computational complexity, scaling issues, and the integration of multidisciplinary technologies. Addressing these barriers is essential for advancing OoC adoption in both research and industrial settings.

Future research should focus on the following priorities to advance Organ-on-a-Chip (OoC) technology:

- Refine current modelling techniques to enhance physiological accuracy and predictive power, especially for multiorgan and systemic models.
- Develop explainable AI frameworks to improve model transparency and build trust for regulatory approval and clinical integration.
- Integrate emerging technologies cautiously, including:
    - Real-time sensor data for continuous monitoring
    - 3D bioprinting for replicating complex tissue structures
    - Augmented and virtual reality tools for enhanced visualization and collaboration
- Ensure compatibility and usability of integrated technologies with biological systems to facilitate practical adoption.
- Promote interdisciplinary collaboration among biologists, engineers, data scientists, and regulators to standardize platforms and accelerate their application in personalized medicine and drug development.

Acknowledgements

The author would like to thank her unit coordinators and the University of Sydney for institutional support and access to technical resources through CHNG5603 - Advanced Industrial Modelling and Analysis. The author would also like to thank her friends for their patience and understanding. This study also acknowledges the use of publicly available data and generative AI tools under author supervision to assist in writing this paper.

This research received no external funding.

References

1 Ali, A. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 1-18 (Academic Press, 2024).
2 Amir, S. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 149-174 (Academic Press, 2024).
3 Farhang Doost, N. & Srivastava, S. K. A Comprehensive Review of Organ-on-a-Chip Technology and Its Applications. *Biosensors* **14** (2024).
4 Driver, R. & Mishra, S. Organ-On-A-Chip Technology: An In-depth Review of Recent Advancements and Future of Whole Body-on-chip. *BioChip Journal* **17**, 1-23 (2023). https://doi.org/10.1007/s13206-022-00087-8
5 Rodrigues, R. O. *et al.* Organ-on-a-Chip: A Preclinical Microfluidic Platform for the Progress of Nanomedicine. *Small* **16**, 2003517 (2020). https://doi.org/https://doi.org/10.1002/smll.202003517
6 Grace Raji, R., Anjali, K. & Kumar, V. B. S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 199-213 (Academic Press, 2024).
7 Wu, Q. *et al.* Organ-on-a-chip: recent breakthroughs and future prospects. *BioMedical Engineering OnLine* **19**, 9 (2020). https://doi.org/10.1186/s12938-020-0752-0
8 Ferreira, G. M. *et al.* Numerical simulation, fabrication, and characterization of a heating system for integration into an Organ-on-a-Chip. *Sensors and Actuators A: Physical* **363**, 114699 (2023). https://doi.org/https://doi.org/10.1016/j.sna.2023.114699
9 Koyilot, M. C. *et al.* Breakthroughs and Applications of Organ-on-a-Chip Technology. *Cells* **11** (2022).
10 Cho, S., Lee, S. & Ahn, S. I. Design and engineering of organ-on-a-chip. *Biomedical Engineering Letters* **13**, 97-109 (2023). https://doi.org/10.1007/s13534-022-00258-4
11 Leung, C. M. *et al.* A guide to the organ-on-a-chip. *Nature Reviews Methods Primers* **2**, 33 (2022). https://doi.org/10.1038/s43586-022-00118-6
12 Nahak, B. K., Mishra, A., Preetam, S. & Tiwari, A. Advances in Organ-on-a-Chip Materials and Devices. *ACS Applied Bio Materials* **5**, 3576-3607 (2022). https://doi.org/10.1021/acsabm.2c00041
13 Liu, X. *et al.* Recent Advances of Organ-on-a-Chip in Cancer Modeling Research. *Biosensors* **12** (2022).
14 Grant, J. *et al.* Simulating drug concentrations in PDMS microfluidic organ chips. *Lab on a Chip* **21**, 3509-3519 (2021). https://doi.org/10.1039/D1LC00348H
15 Wang, Y. *et al.* Emerging trends in organ-on-a-chip systems for drug screening. *Acta Pharmaceutica Sinica B* **13**, 2483-2509 (2023). https://doi.org/https://doi.org/10.1016/j.apsb.2023.02.006
16 Azizipour, N., Avazpour, R., Rosenzweig, D. H., Sawan, M. & Ajji, A. Evolution of Biochip Technology: A Review from Lab-on-a-Chip to Organ-on-a-Chip. *Micromachines* **11** (2020).
17 Jacob, S., Kaushik, P. & Parvez, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 309-325 (Academic Press, 2024).
18 Vishwakarma, N. & Singh, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 75-90 (Academic Press, 2024).
19 Shah, M., Prakashan, D. & Gandhi, S. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 91-112 (Academic Press, 2024).
20 Gupta, V. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 233-249 (Academic Press, 2024).

21 Poojary, B. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 251-259 (Academic Press, 2024).

22 Mukherjee, A. G. *et al.* in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 411-424 (Academic Press, 2024).

23 Chowdary, P., Yadav, D. N., Pogu, S. V. & Rengan, A. K. in *Human Organs-on-a-Chip Technology* (ed P. V. Mohanan) 439-457 (Academic Press, 2024).

24 Huang, Y., Liu, T., Huang, Q. & Wang, Y. From Organ-on-a-Chip to Human-on-a-Chip: A Review of Research Progress and Latest Applications. *ACS Sensors* **9**, 3466-3488 (2024). https://doi.org/10.1021/acssensors.4c00004

25 Sung, B. In silico modeling of endocrine organ-on-a-chip systems. *Mathematical Biosciences* **352**, 108900 (2022). https://doi.org/https://doi.org/10.1016/j.mbs.2022.108900

26 Carvalho, V. *et al.* 3D Printing Techniques and Their Applications to Organ-on-a-Chip Platforms: A Systematic Review. *Sensors* **21** (2021).

27 Ma, C., Peng, Y., Li, H. & Chen, W. Organ-on-a-Chip: A New Paradigm for Drug Development. *Trends in Pharmacological Sciences* **42**, 119-133 (2021). https://doi.org/10.1016/j.tips.2020.11.009

28 Prot, J. M. *et al.* First pass intestinal and liver metabolism of paracetamol in a microfluidic platform coupled with a mathematical modeling as a means of evaluating ADME processes in humans. *Biotechnology and Bioengineering* **111**, 2027-2040 (2014). https://doi.org/https://doi.org/10.1002/bit.25232

29 Menezes, P. D., Gadegaard, N., Natal Jorge, R. M. & Pinto, S. I. S. Modelling human liver microphysiology on a chip through a finite element based design approach. *International Journal for Numerical Methods in Biomedical Engineering* **37**, e3445 (2021). https://doi.org/https://doi.org/10.1002/cnm.3445

30 Jeong, S., Seo, J.-H., Garud, K. S., Park, S. W. & Lee, M.-Y. Numerical approach-based simulation to predict cerebrovascular shear stress in a blood-brain barrier organ-on-a-chip. *Biosensors and Bioelectronics* **183**, 113197 (2021). https://doi.org/https://doi.org/10.1016/j.bios.2021.113197

31 Wang, L. *et al.* A new approach of using organ-on-a-chip and fluid–structure interaction modeling to investigate biomechanical characteristics in tissue-engineered blood vessels. *Frontiers in Physiology* **Volume 14 - 2023** (2023).

32 Filipovic, N., Nikolic, M. & Sustersic, T. in *Biomaterials for Organ and Tissue Regeneration* (eds Nihal Engin Vrana, Helena Knopf-Marques, & Julien Barthes) 753-790 (Woodhead Publishing, 2020).

33 Milani, N., Parrott, N., Galetin, A., Fowler, S. & Gertz, M. In silico modeling and simulation of organ-on-a-chip systems to support data analysis and a priori experimental design. *CPT: Pharmacometrics & Systems Pharmacology* **13**, 524-543 (2024). https://doi.org/https://doi.org/10.1002/psp4.13110

34 da Silva Pereira, J. D. T. *Machine Learning Algorithms and Organs-on-Chips as New Technologies for the Modeling of Human Cardiac Toxicity and Disease*, Universidade do Minho (Portugal), (2022).

35 Zheng, F., Xiao, Y., Liu, H., Fan, Y. & Dao, M. Patient-Specific Organoid and Organ-on-a-Chip: 3D Cell-Culture Meets 3D Printing and Numerical Simulation. *Adv Biol (Weinh)* **5**, e2000024 (2021). https://doi.org/10.1002/adbi.202000024

36 Ibrahim, M., Chakrabarty, K. & Schlichtmann, U. Synthesis of a Cyberphysical Hybrid Microfluidic Platform for Single-Cell Analysis. *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems* **38**, 1237-1250 (2019). https://doi.org/10.1109/tcad.2018.2846662

37 Phillips, C. M. *et al.* Towards integration of time-resolved confocal microscopy of a 3D in vitro microfluidic platform with a hybrid multiscale model of tumor angiogenesis. *PLoS Computational Biology* **19**, e1009499 (2023).

38 Silva, D. F. C. *et al.* Design of a microfluidic platform for monoclonal antibody extraction using an aqueous two-phase system. *Journal of Chromatography A* **1249**, 1-7 (2012). https://doi.org/https://doi.org/10.1016/j.chroma.2012.05.089

39 Pisapia, F., Balachandran, W. & Rasekh, M. Organ-on-a-Chip: Design and Simulation of Various Microfluidic Channel Geometries for the Influence of Fluid Dynamic Parameters. *Applied Sciences* **12** (2022).

40 Seyed Zolfaghari, S. H., Pourmand, A. & Kiyoumarsioskouei, A. A low-cost 3D-printing based rapid fabrication procedure for modular microfluidic platform. *Journal of Micromechanics and Microengineering* **35**, 045013 (2025). https://doi.org/10.1088/1361-6439/adc313

41 Carvalho, V. *et al.* Numerical evaluation and experimental validation of fluid flow behavior within an organ-on-a-chip model. *Computer Methods and Programs in Biomedicine* **243**, 107883 (2024). https://doi.org/https://doi.org/10.1016/j.cmpb.2023.107883

42 Teixeira, S. G. *et al.* National reflection on organs-on-chip for drug development: New regulatory challenges. *Toxicology Letters* **388**, 1-12 (2023). https://doi.org/https://doi.org/10.1016/j.toxlet.2023.09.011

43 Candarlioglu, P. L. *et al.* Organ-on-a-chip: current gaps and future directions. *Biochemical Society Transactions* **50**, 665-673 (2022). https://doi.org/10.1042/BST20200661

44 Oliver, C. R., Westerhof, T. M., Castro, M. G. & Merajver, S. D. Quantifying the Brain Metastatic Tumor Micro-Environment using an Organ-On-A Chip 3D Model, Machine Learning, and Confocal Tomography. *J Vis Exp* (2020). https://doi.org/10.3791/61654

45 R, N., Aggarwal, A., Sravani, A. B., Mallya, P. & Lewis, S. Organ-On-A-Chip: An Emerging Research Platform. *Organogenesis* **19**, 2278236 (2023). https://doi.org/10.1080/15476278.2023.2278236

46 Movčana, V. *et al.* Organ-On-A-Chip (OOC) Image Dataset for Machine Learning and Tissue Model Evaluation. *Data* **9** (2024).

47 Gangwal, A. & Lavecchia, A. Artificial intelligence in preclinical research: enhancing digital twins and organ-on-chip to reduce animal testing. *Drug Discovery Today* **30**, 104360 (2025). https://doi.org/https://doi.org/10.1016/j.drudis.2025.104360

48 *Augmented Reality Solutions for Organ-on-Chip applications*, <https://www.gobiond.com/2021/05/01/interview-with-emanuele-borasio-ceo-and-founder-wear-srl/> (2021).

49 *ISO/AWI 25693: Biotechnology - Developing process of Organ-on-Chip using for evaluation of substances*, <https://www.iso.org/standard/91185.html> (

50 Centre, J. R. *Setting out a roadmap for standardisation of organ-on-chip technology*, <https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/setting-out-roadmap-standardisation-organ-chip-technology-2025-01-13_en> (2025).

