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Integrating In Silico Modelling with Organ-on-Chip platforms to enable experimental design, interpretation, and Human translation

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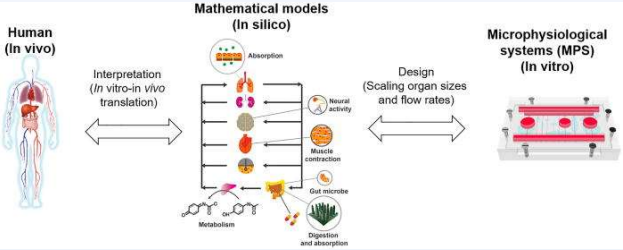
Introduction

New Approach Methodologies (NAMs) including organ-on-chip (OOC) platforms and advanced 3D cell culture systems are gaining rapid adoption as human-relevant alternatives to animal models for drug discovery and safety assessment. OOC datasets are often complex and difficult to scale quantitatively to human physiology.

Using published case studies (terfenadine cardiotoxicity, malaria-on-a-chip efficacy, and DigiLoC hepatic clearance), we illustrate how mechanistic and statistical in silico models enable experimental design, in vitro to in vivo extrapolation (IVIVE), and physiologically based pharmacokinetic (PBPK) based human translation.

This work positions modeling as a translational layer that converts NAM data into decision-ready evidence.



Case study 1: Cardiotoxicity of Terfenadine[1]

A multi-organ human heart–liver OOC system was used to study how terfenadine exposure, hepatic metabolism to fexofenadine (Allegra), and QT prolongation are linked in a physiologically relevant in vitro setting.

Time-resolved measurements of parent drug, metabolite, and cardiac electrophysiology were combined with a mechanistic PK/PD model.

The framework identified temporal hysteresis between exposure and QT prolongation, separated parent drug effects from metabolite-driven cardiotoxicity, and enabled estimation of potency, effect delays, and the contribution of hepatic metabolism to cardiac risk.

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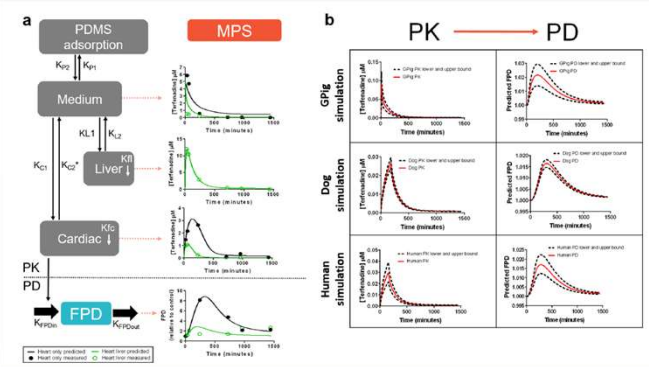
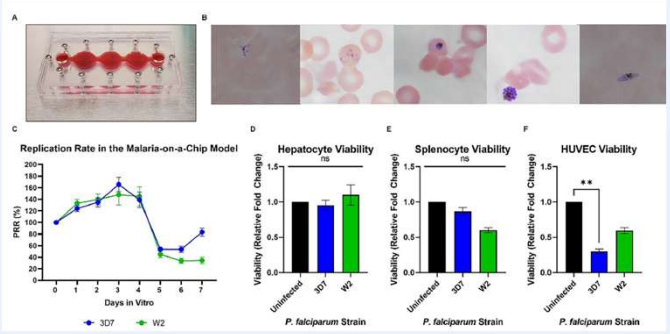


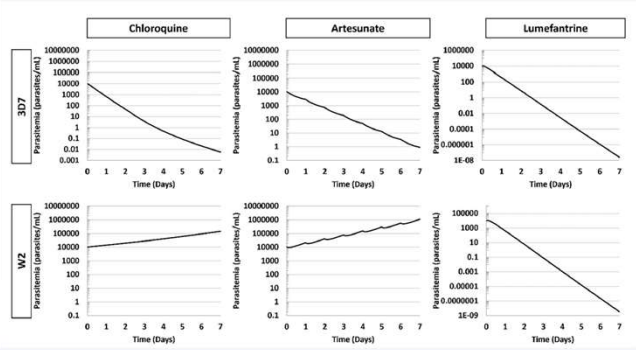
Case study 2: Malaria-on-a-chip[2]

A human-based malaria-on-a-chip system was used to track how parasite levels change over time under controlled antimalarial drug exposure. To interpret these time-resolved responses, we built a PK–PD model that linked on-chip drug concentrations to changes in parasite burden, capturing both parasite growth and drug mediated killing.

The model made it possible to estimate drug potency and killing rates that are relevant to in vivo efficacy, while accounting for experimental variability across runs. By combining these estimates with an IVIVE workflow, phenotypic chip readouts were translated into predicted human dosing regimens and exposure–response relationships

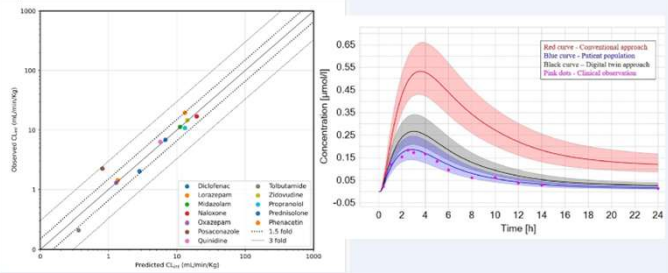


This framework turned descriptive malaria-on-a-chip data into quantitative, decision-ready predictions



Case study 3: DigiLoC (Hepatic Clearance)[3]

A digital twin framework was developed to interpret drug depletion kinetics from liver-on-chip systems. A mechanistic multi-compartment model separated active metabolism from passive permeability and partitioning effects, improving prediction of intrinsic clearance. Integration with PBPK enabled translation of on-chip clearance estimates to human pharmacokinetics.



Conclusion:

Organ-on-chip platforms generate rich, human relevant biological data, but their translational impact depends on quantitative interpretation. Collectively, these examples highlight the need for integrated in silico frameworks capable of unifying PK/PD, IVIVE, PBPK, and systems (mechanism of action) level analyses to support scalable, reproducible, and decision ready interpretation of OOCs.

References:

1. McAleer, C. W. *et al. Sci. Rep.* **9**, 9619 (2019).
2. Rupar, M. J. *et al. Adv. Sci.* **12**, e05206 (2025).
3. Aravindakshan, M. R. *et al. PLOS ONE* **20**, e0314083 (2025).