ML-based enhancement of mechanistic models using omics data

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Intro

Liver cancer is currently the third leading cause of cancer-related deaths worldwide, clinical response rates remain relatively low. One of the key challenges in improving therapeutic outcomes is the ability to predict which patient cohorts will respond favorably to a given treatment. Among the available strategies, patient-derived *in vitro* models have emerged as promising tools for drug screening. However, **translating results from these pre-clinical models to actual patient outcomes is complex** due to biological variability among donors. Mechanistic models have been developed to bridge this gap, simulating pharmacokinetic behavior observed in both *in vitro* and clinical data, but still fail to accurately predict in-human situation. We propose **a hybrid modeling approach integrating high-throughput data with mechanistic modeling** to enhance predictive power. The developed method is implemented as part of a software package called the Virtual Testing Center, which facilitates *in silico* assessment of treatment response and supports translational research.

Virtual Testing Center (VTC)

SCAN ME

MPSlabs offers the world's first **virtual testing center** for microphysiological systems, organ-on-chips, and 3D organoids/spheroids.
The center enables pharmaceutical, crop science, agro, other chemical companies, and chip operators to precisely and accurately predict compounds' distribution in humans – **all without animals.**

DigiLoCs
Interactive, digital liver-chip simulator.

Tox-Classifier
Predictive model for human liver toxicity.

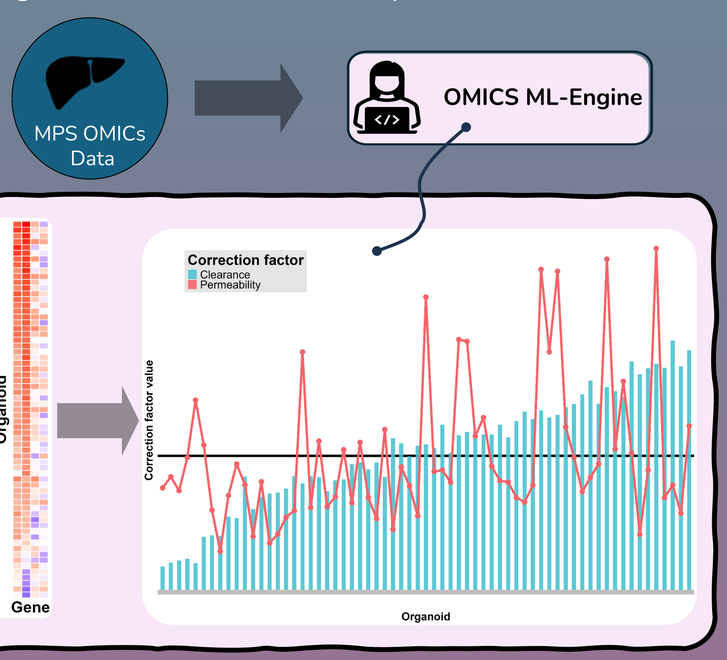
Human Digital Twins
End-to-end simulation of MPS-data and translation to humans.

MIQED
Optimized experimental design - reduced efforts, saves money.

Results

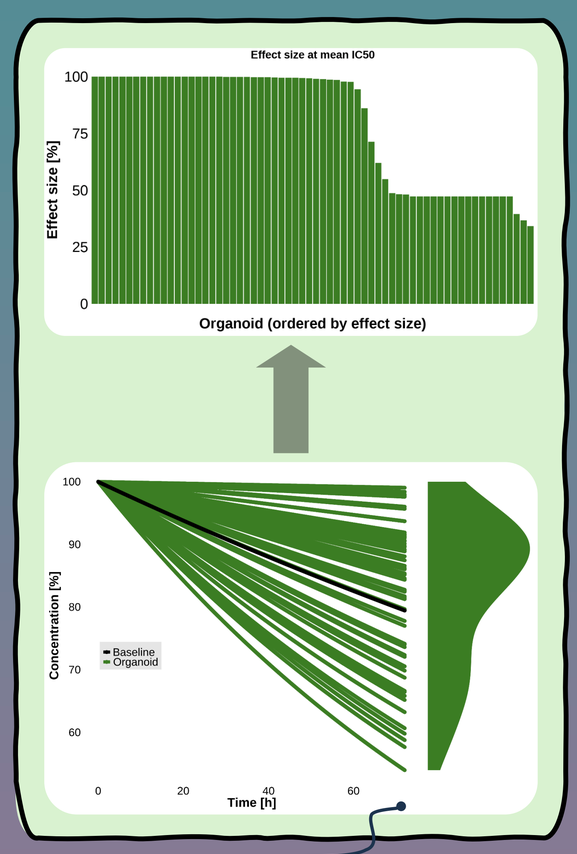
Workflow:

The process begins with high-throughput data processing. Subsequently, the compound-relevant measurements are input into a Bayesian framework to parameterize a custom mathematical model. Parameters are estimated on a per-chip basis to capture genetic background variability. These parameters are subsequently used in simulations to generate drug- and chip-specific kinetic profiles. During training, the simulated profiles are compared to ground truth data to refine parameter estimates.



OMICS ML:

Proteomic data from untreated organoids identify gene products involved in the compound's transport and metabolism. These data are then used to estimate correction factors for the permeability and clearance parameters in the mechanistic model.

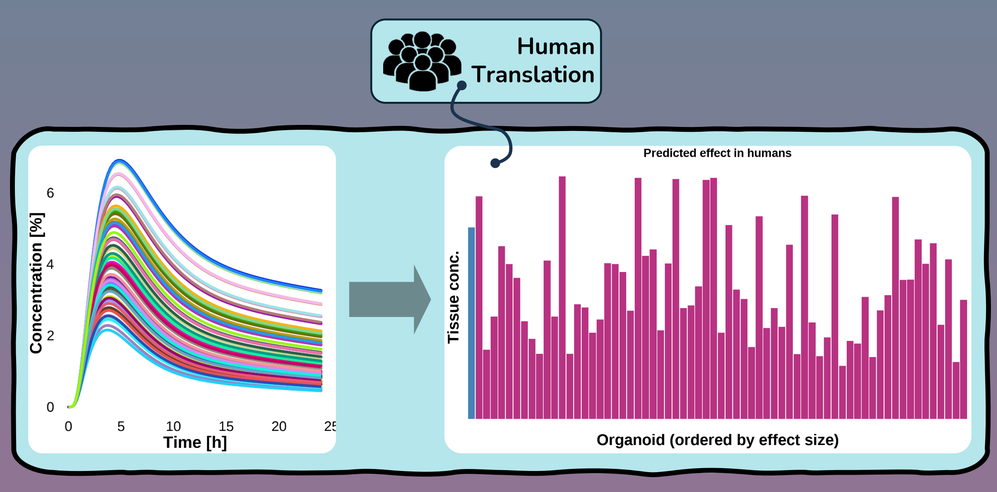


On-ship Simulation:

Permeability and clearance are adjusted using correction factors to generate individual-specific model outputs. When calculating the compound's concentration kinetics, these **individual results** show a significant deviation from the **population-based baseline**.

Results:

- The parameterization effectively captures the relationship between key parameters and the biological entities influencing drug-specific kinetics.
- Unlike traditional approaches that average genetic effects, this method enables the derivation of kinetic profiles at the individual level.
- A virtual population can be generated by sampling from the individual kinetic profiles, allowing for broader population-level analysis.
- Personalized parameterization enhances patient stratification, providing more biologically meaningful subgroupings.



Human Translation:

Permeability and clearance are also used to individualize a PBPK model. These parameters, combined with on-chip PD assessments - such as effect size at a given concentration (left graph) - help determine the dose required to achieve the desired effect in an individual (right graph). The end-to-end pipeline demonstrates that the same dose can lead to different tissue concentrations across individuals (middle graph), necessitating personalized dosing to achieve consistent therapeutic effects.

Conclusion

Our modeling framework enables accurate prediction of:

- individual on-chip drug kinetics,
- individual on-chip drug effect,
- human drug kinetics (and effect of individual differences),
- tumor drug concentration driving EC50

The framework supports **broader and more efficient drug testing** and is implemented within the **Virtual Testing Center**, providing a streamlined platform for *in silico* experimentation and translational decision-making.

References

[1] Ji, S., Feng, L., Fu Z. et al. (2023). Science Translational Medicine 15, 706. doi:10.1126/scitranslmed.adg3358.

Modeling *Scaling* *Coding*

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