JOURNAL OF MULTIDISCIPLINARY SCIENCES AND INNOVATIONS

VOLUME 5, ISSUE 02
MOPNTHLY JOURNALS

ISSN NUMBER: 2751-4390
IMPACT FACTOR: 9,08

DIGITAL TWINS OF ONCOLOGY PATIENTS: SIMULATION OF TOXICITY AND EFFECTIVENESS OF TARGETED THERAPY IN REAL TIME.

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Abstract: The traditional approach to developing cancer drugs is facing a crisis of effectiveness due to high biological heterogeneity. This requires a transition to quantitative, prognostic methods. An overview of the use of mathematical modeling to create digital twins of patients in oncology to predict the effectiveness and toxicity of targeted therapy in real time.The paper analyzes the principles of Model-Informed Drug Development (MIDD) and the triad of models: systems biology, quantitative systems pharmacology (QSP), and quantitative systems toxicology (QST). It describes methodologies for constructing virtual populations (using Latin Hypercube Sampling) and their individualization into digital twins. Organ-specific QST platforms (CiPA, DILIsym, Chaste, RENAsym) for predicting cardiotoxicity, hepatotoxicity, gastrointestinal toxicity, and nephrotoxicity are considered.It is shown that system modeling serves as a link between drug development stages (Transition Points), allowing data to be extrapolated, risks to be minimized, and clinical trial designs to be optimized. The mathematical superiority of simultaneous combination therapy over sequential therapy for overcoming resistance is justified.The integration of quantitative modeling into clinical practice opens a new era of personalized oncology. Digital twins, based on physiological principles and real-time data, are becoming a powerful tool for supporting medical decisions, improving patient safety, and increasing treatment effectiveness.

Keywords

- Digital Patient Twins
- Quantitative Systems Pharmacology (QSP)
- Quantitative Systems Toxicology (QST)
- Physiologically Based Kinetics/PK-TK modeling
- Oncology
- Targeted Therapy
- Virtual Populations
- Model-Informed Drug Development (MIDD)
- Toxicity
- Personalized Medicine

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Biology is rapidly transforming from a descriptive discipline into a precise engineering science. As a specialist in systems pharmacology, I emphasize that qualitative characteristics are no longer sufficient for modern doctors and biologists. We have entered the era of MIDD (Model-Informed Drug Development), where drugs are developed based on quantitative modeling, and mathematical tools serve not merely as a supplement but as the primary instrument for decision-making.

1. Introduction: Why are words not enough for biology?

The traditional approach to drug development is experiencing a "crisis of effectiveness." According to an analysis of clinical trials (Wong et al.), the overall probability of a drug successfully transitioning from phase I to approval is a mere 3.4% in oncology. The reason for this lies in the enormous biological heterogeneity: we are faced with interindividual, intertissue, and intratumoral heterogeneity that cannot be grasped intuitively.

The mathematical equation in biomedicine is the "predictive engine." To manage the complexity of biological systems, the concept of Transition Points has been introduced:

- TP1 (Discovery): Assessment of target safety and exclusion of off-target effects.
- TP2 (Translation/GLP): Translation of data from preclinical models to humans and justification of doses for phase I.
- TP3 (Clinical/Population): Predicting efficacy in a heterogeneous population and searching for biomarkers.

Modeling is necessary to integrate these stages, minimize testing costs, and manage risks in conditions of uncertainty.

2. The trinity of models: Systems biology, QSP, and QST

The systemic approach is based on the use of **PBK (Physiologically Based Kinetics)**, an umbrella term for physiologically based kinetics, which includes pharmacokinetics (PBPK) and toxicokinetics (PBTK). Three main disciplines are built on this foundation:

Comparison criterion	Systems biology	Quantitative systems pharmacology (QSP)	Quantitative systems toxicology (QST)
Main objective	Understanding the fundamental mechanisms of the system.	Predicting efficacy and selecting optimal dosages.	Predicting safety and mechanisms of organ damage.
Subject of study	Networks of molecular and cellular interactions.	Drug-target interactions in the context of pathology.	ADR (Adverse Drug Reactions) mechanisms and cell survival.
Key question	How does the system work normally?	What is the probability of recovery?	What is the risk of toxic damage?

Biological scale	Molecular/cellular level.	Organ/Whole organism.	From subcellular to systemic (ADR).

The connecting link: Division of parameters into **systemic** (unchanging biology of a specific species or population) and **drug-specific** (chemical properties of a molecule). This allows for extrapolation of data between species and conditions.

3. Virtual populations and digital twins: A bridge to personalization

Confusion between virtual patients and digital twins is a common mistake. Let's bring some academic clarity.

1. Virtual patients (VP): These are mathematical parameterizations that generate physiologically plausible outputs. To create them, we use the Latin Hypercube Sampling (LHS) method. Unlike simple random sampling, LHS efficiently fills multidimensional parameter space, preventing "clustering" and covering extreme values of the biological norm.
2. Digital twins (DT): Individualized models that require dynamic data updates.

Concept integration: A group of virtual patients serves as a pool of "digital twin candidates." When we receive time series data from a real patient (e.g., tumor size dynamics), we select from the VP population the one whose mathematical profile matches reality. Thus, the VP "advances" to the status of a digital twin.

To select "plausible" patients from random samples, we use Probability of Inclusion (P_i), a function that links the multidimensional probability density of real clinical data (e.g., from iAtlas or TCGA databases) with simulation results.

4. The art of predicting safety: Organ-specific QST models

QST modeling allows us to look into the pathobiology of organs through the prism of equations:

- Cardiovascular system (CiPA): We use modeling of ion channels and the electromechanical functions of cardiomyocytes. This allows us to predict not only QT prolongation, but also the risk of Torsades de Pointes-type arrhythmias using stochastic differential equations.
- Liver (DILIsym platform): Links oxidative stress and bile acid accumulation to hepatocyte death. A striking example is the case of CGRP receptor antagonists. QST modeling explained the toxicity of telcagepant through the inhibition of mitochondrial transport, confirming the safety of its successor, ubrogepant.
- Gastrointestinal tract (agent-based modeling - ABM): ABM models (based on the Chaste framework) are used to predict diarrhea caused by chemotherapy (e.g., 5-fluorouracil). Here, each intestinal epithelial cell, including Lgr5+ stem cells, is represented as a separate agent with its own cycle and interaction mechanics.
- Kidneys (RENAsym platform): Modeling of proximal tubular epithelial cell (PTEC) damage. The models allow the effects of substances such as cisplatin or gentamicin to be linked to the appearance of specific biomarkers in urine even before changes in blood creatinine levels.

5. Mathematical kitchen: How models are built and tested

The development process follows a strict Predict-Learn-Confirm cycle:

1. Data collection: Integration of ADME data, omics technologies (RNA-seq), and clinical biomarkers. The most important standard here is the FAIR (Findable, Accessible, Interoperable, Reusable) principles, which ensure the reproducibility of models.
2. Verification and Validation (V&V):
    - Verification: Checking the program code ("Are we building the model correctly?").
    - Validation: Comparing predictions with independent empirical data ("are we building the right model?").
3. Evolutionary logic of combinations: Mathematics proves that simultaneous combination therapy is superior to sequential therapy. Sequential use of drugs (Line 1, then Line 2) is mathematically doomed to failure due to pre-existing resistance, while simultaneous targeting of different targets radically reduces the likelihood of mutant clones surviving.

6. Conclusion: A new era in medicine

System modeling is not a replacement for biologists, but rather a "cognitive amplifier." The transition to quantitative biomedicine allows us to:

- Implement the 3Rs principle (replacement, reduction, and refinement of animal use in experiments).
- Minimize risks for volunteers in phase I (TP2).
- Move from universal protocols to personalized treatment strategies.

Equations are a way to turn the chaos of biological data into accurate predictions. The future of medicine lies at the intersection of physiology and computation, where every clinical decision is backed by rigorous mathematical logic.

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