Title: Multiscale Simulation Framework for Personalized Pharmacology

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Abstract Text:

Current models for pharmacokinetics (PK) and pharmacodynamics (PD) represent the human body as a simple network of compartments mathematically characterized using simplistic mechanistic modeling approaches (ODEs), commonly referred to as physiologically-based pharmacokinetic (PBPK) modeling. Alone, this approach lacks physiological input, with the exception of cardiac out, organ volumes and organ-specific blood flow rates and neglects barriers to transport. Moreover, these approaches are void of personalized components. PD modeling approaches rely on even more simplistic dose-response correlations (i.e. EC50 or Hill Equation). A multiscale framework is needed to integrate traditional PBPK models, spatially resolved barrier models, and machine learning supported mechanistic modeling approaches.

Our approach in this framework is to combine multiscale mechanistic (MsM) models described by the fundamental laws of physics and biology with machine learning (ML) models to determine model components for which it is difficult to formulate mathematical models or correlations. The unique capability of this novel MsM-ML modeling approach is that the results of MsM simulations, e.g. drug concentration at target, are used as input functions for the ML models to predict outcomes e.g. efficacy, toxicity or disease trajectory. This presentation will demonstrate a *Multiscale Simulation Framework for Personalized Pharmacology*, which combines mechanistic modeling and machine learning-based approaches for various components, with inputs of drug physicochemical properties, human physiology, drug ADME, whole-body PBPK and spatially resolved models of transport barriers (i.e. skin, intestine, airway mucosa, BBB, blood-retinal barrier). We will demonstrate this approach on modeling PK-PD-Effects of the interaction between an opioid agonist and countermeasure antagonist and the dynamic effects on human physiological and cognitive responses [1].

References:

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