Physiologically-Based Pharmacokinetic Modeling
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**Significance.** Pharmaceuticals are one of the most common forms of treatment prescribed by physicians. Drugs may be prescribed as a therapy, as a cure or as a preventative treatment for a wide range of diseases. Knowledge of a drug’s chemical reaction kinetics and transport phenomena is crucial in order to properly dose a patient for the drug to be therapeutically effective without causing adverse side effects.

**Need.** Therapeutic efficacies and possible side effects of novel drugs on targeted organs are currently determined by trial-and-error in extensive pre-clinical animal trials. Classical pharmacokinetic (PK) models merely fit parametric curves to dose-response data obtained from these animal trials while not obeying conservation laws or incorporating biochemical reaction and transport mechanisms. As a result, classical PK models derive very little quantitative information in terms of drug kinetics and biotransport phenomena. Therefore, it is difficult with classical PK models to scale or extrapolate information from one animal to another, from animals to humans or to deal with different compositions and pathologies.

**Proposed Solution.** We propose a rigorous engineering approach based on first principles of mass, momentum and species conservation to overcome shortcomings in classical PK models [1-3]. The methodology enables the determination of a drug’s chemical reaction kinetics and transport phenomena solely from experimental drug dose-response data, see Figure 1 below.

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**Figure 1.** Overview of the pharmacokinetic modeling framework and its components.
The proposed biomathematical modeling framework combines rigorous experimental data analysis with hypothesis testing for pharmacokinetic studies. Large-scale network models for the description of blood flow, organ perfusion and biochemical mechanisms in tissues for entire organisms can be automatically generated for use in the transport and kinetic estimation. Our proposed problem inversion technique yields a complete model of a drug’s fate in the organism based on experimental drug bioavailability data.

**Deliverables.** Our model obeys to conservation balances so it can be extrapolated beyond the scope of the original dose-response curves. These models can be used for intra- and interspecies scaling, and experiment planning in pharmacokinetics and pharmacodynamics. Personalized therapy design can also be achieved by adjusting the total weight, hematocrit fraction, injection regime or the dose for determining the therapeutically effective treatment.

**References**

