Towards Predictions of Clinical Trial Outcomes: Combining PBPK and QSP within a Translational Diabetes PB-QSP Disease Platform

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Motivation

Clinical trial simulations are usually conducted at later stages of drug development typically requiring clinical data from Phase I/II/IIb. Common PK/PD approaches do not provide the mechanistic and structural detail at molecular and organ level to drive fundamental research as well as to address specific translational questions in drug development. Our objective is to establish a digital platform for early prediction of clinical (trial) outcomes by leveraging physiological and mechanistic knowledge to translate early in-vitro and preclinical outcomes to the clinic. This is only possible through integration of multi-scale and multi-species data gathered along the R&D process (Figure 1).

Figure 1: Model physiology: Use of a **professional, quality-controlled PBPK/PD modeling & simulation framework** allows integration of multi-scale, multi-source data to build-up and transfer knowledge across all phases of drug research & development within a **single** modeling & simulation **platform.**

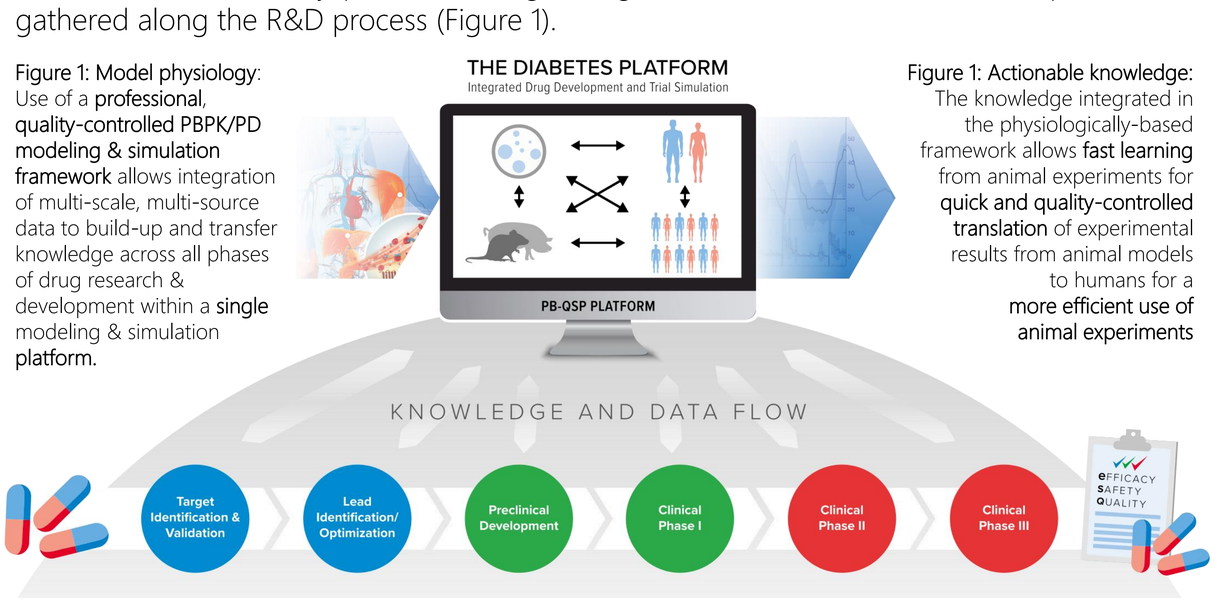


Figure 1: Actionable knowledge: The knowledge integrated in the physiologically-based framework allows **fast learning** from animal experiments for **quick and quality-controlled translation** of experimental results from animal models to humans for a **more efficient use of animal experiments**

Physiologically-based pharmacokinetic modeling (of diabetes)

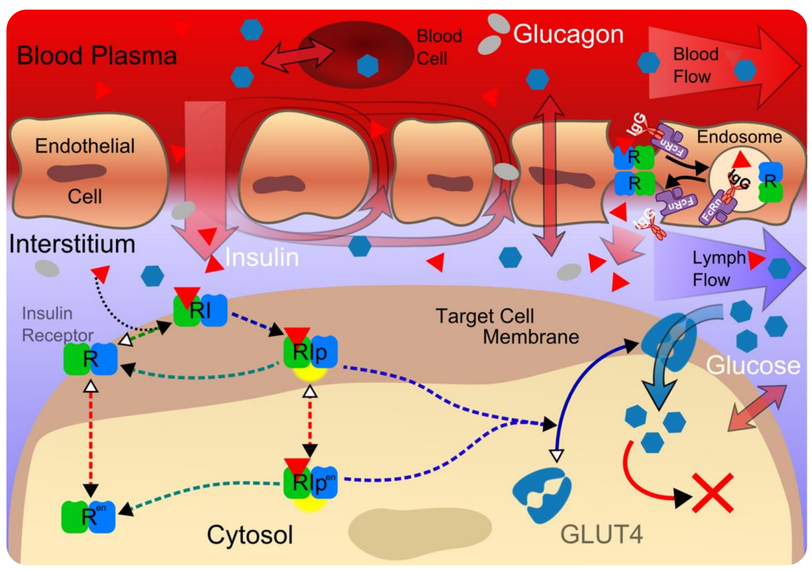
PBPK models describe the mechanisms underlying the absorption, distribution, metabolism and excretion (ADME) of a substance within the body at an in-depth level of detail.

PBPK models are **based to a large extend on prior information** regarding an organism's anatomy and physiology. Most model parameters are either taken from **collections of anatomical and physiological data** or are calculated from **drug-dependent properties**. Based on such basic physicochemical parameters of a substance, generic PK prediction models are automatically parameterized. These models can then be used to **simulate drug concentration profiles in various organs and tissue substructures** (Figure 2) [1-2].

An existing **physiologically based quantitative systems pharmacology (PB-QSP) model of the glucose-insulin metabolism** for healthy individuals and type 1 diabetes patients (Figure 2) [3-5] was translated to animal species most commonly used in preclinical diabetes research (rat, minipig and cynomolgus monkey) to allow seamless integration of data along the drug research and development process (Figure 1). Animal physiology such as organ volumes, organ composition, blood and lymph flows was informed by the PBPK database of **PK-Sim®** as part of the **Open Systems Pharmacology** Suite (OSPS), version 7.2 [6].

Animal PBPK/PD model of the glucose-insulin metabolism

Figure 2: Sub organ level- and molecular details: Organs are divided into five sub-compartments. All compartments are interconnected via passive convection and diffusion flows and facilitative transports. Both insulin distribution and its glucoregulatory PD effects are influenced or mediated at the molecular level. Bound to insulin receptors (IR), insulin is both, transported from the plasma by trans-endothelial transport and eliminated from the interstitial space triggering molecular signaling in target tissues, inherently coupling its PK and PD. Organ volumes & (blood) flow rates, but also Insulin receptor internalization rates (i.e. insulin clearance) and organ glucose metabolism differ significantly between species (Figure 3 & 4).



Animal whole-body energy- and **organ-specific glucose uptake** and metabolism as well as properties of **mechanisms underlying pharmacokinetics** (Figure 2) **and pharmacodynamics** (PK/PD) of insulin and glucagon were informed by extensive literature search (non-exhaustive: [7-10]). This included basal concentrations for glucose, insulin and glucagon and **secretion and turnover rates of insulin and glucagon**. Missing experimental values for glucose metabolization in some organs and species was calculated using allometric principles based on information from other species (Figure 3).

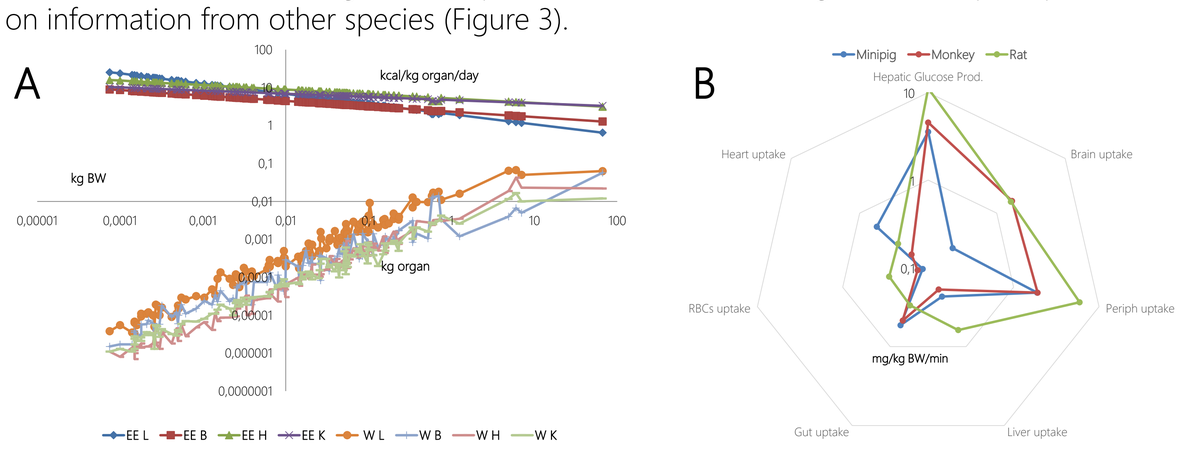


Figure 3: Scaling of organ metabolism: Organ glucose metabolization rates (Panel B) were calculated from multiple sources [7-10] with most values taken from Wang et al. [8] displayed in Panel A (EE = Energy Expenditure, W = Weight, L = Liver, B = Brain, H = Heart, K = Kidney). While specific organ EE scales allometrically with BW, specific organ weight does not so smoothly. This non-smoothness then shows in Panel B, where minipig brain glucose uptake per BW is small due to minipigs relative low brain size.

Model Qualification – Tolerance Tests in Animal Species

For model verification and to inform remaining uncertainties, the PB-QSP diabetes platform was fitted to standard test experiments used in diabetes (Figure 4; oral- and intravenous glucose and intravenous insulin tolerance tests [11–16]). The animal parameterizations (i.e. rat, minipig and cynomolgus parameter sets) of the PB-QSP platform achieved high accuracy in describing the dynamics of animal systems pharmacology for glucose, insulin, and glucagon PK and PD on both, the quantitative and the qualitative level within the same structural (i.e. physiological) model framework.

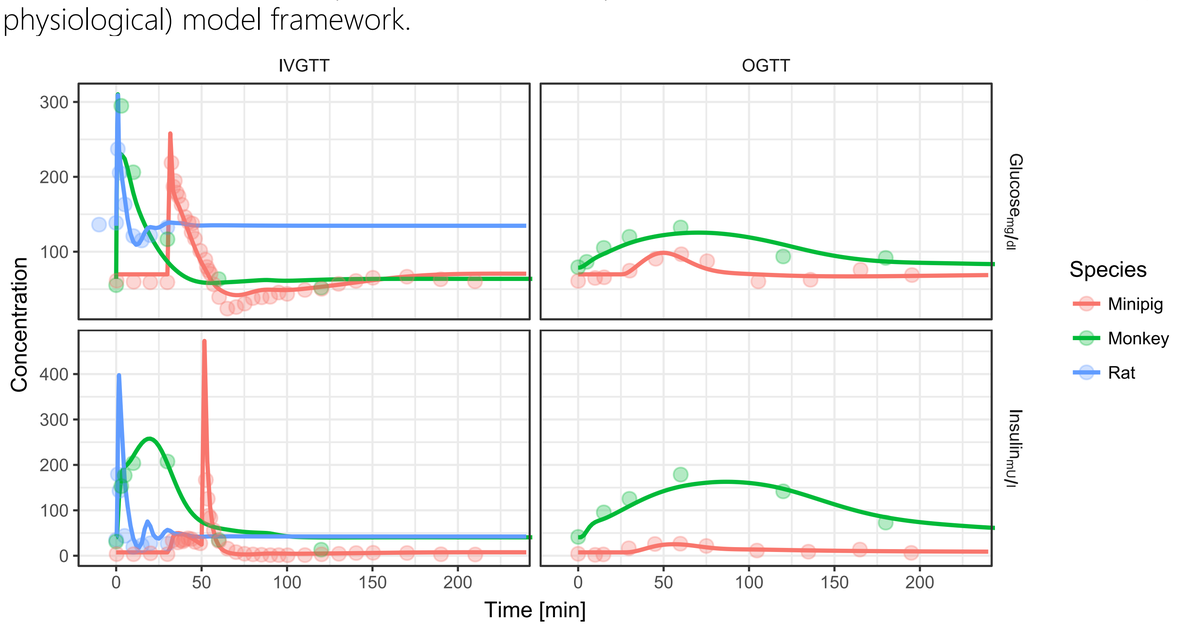


Figure 4: Model : Different tolerance tests (IV glucose (IVGTT), IV Insulin (IVITT) and oral glucose (OGTT), at t = 0) in rat [12], minipig [13, 14] and cynomolgus monkey [16, 17]. Minipig IVGTT (at t = 30 min, red graphics, left column) is combined with an IVITT (at t = 50 min). Simulations were fitted to experimental data to identify parameterizations for insulin secretion and receptor internalization (governing whole-body insulin turnover). Glucose uptake and metabolization was informed a priori on data [7-10].

The available datasets (mean) used for fitting were not consistent regarding basal insulin levels when compared to available basal concentration data from large datasets. The animal models were thus fitted to the most prevalent of the reported basal concentration levels (see Figure 5 for an exemplary distribution of basal insulin levels in cynomolgus monkeys).

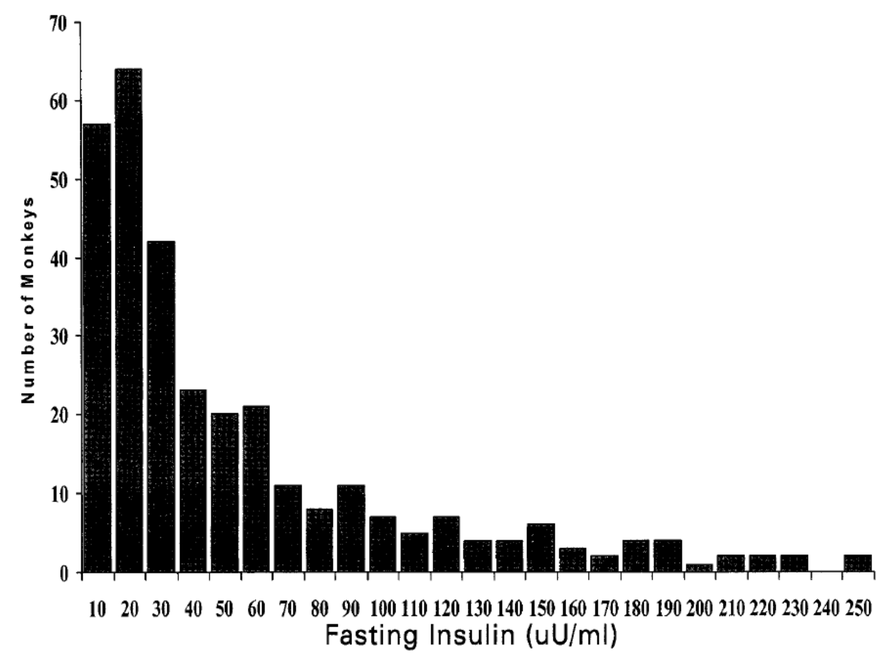


Figure 5: Distribution of basal insulin levels in a population of cynomolgus monkey (taken from [18]) to illustrate the challenge of inter-individual variability in preclinical experiments. Current endeavors focus on elucidating co-factors of differences in mechanisms underlying the metabolism of insulin (i.e. differences in the insulin receptor system) and glucose metabolism in animal species.

Conclusions

Structural and mechanism-based characterization of both the animal and human glucose metabolism is of great value when new treatments need to be analyzed and translated during transition from research to development. The captured structural and mechanistic knowledge allows for an informed extrapolation and thus accurate prediction of the treatment PK, the mode of action concept and the effect on whole-body glucose metabolism (e.g. effects on fasting plasma glucose, post-prandial glucose or HbA1c) when translating PK and PD from animals to humans. Leveraging its PBPK and QSP framework and a population of characterized in-silico diabetes patients, the platform allows population-level in-silico first-in-man and proof-of-concept evaluations for conceptualized treatments of diabetes. This can be done by translation of either pre-clinical outcome data or in-vitro compound properties at the drug discovery or lead-optimization stage. Another aspect that has proven invaluable is that even hypothetical compound properties can be translated into an estimate for efficacy in humans for an in-silico evaluation of ideas for novel treatment modalities prior to initializing costly in-vitro experiments and preclinical studies. However, variability in animals remains a challenge for translational approaches, thus our current endeavors focus on elucidating co-factors of differences in mechanisms underlying the variability in animal species.

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