QUANTITATIVE SYSTEMS PHARMACOLOGY: APPLICATIONS IN PHARMACEUTICAL R & D

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What is Quantitative Systems Pharmacology (QSP)?

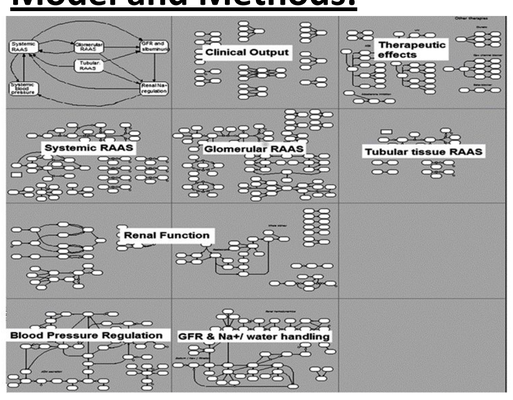
According to the NIH white paper on QSP[1] , the goal of QSP is "to understand, in a precise, predictive manner, how drugs modulate cellular networks in space and time and how they impact human pathophysiology. It aims to develop formal mathematical and computational models that incorporate data at several temporal and spatial scales; these models will focus on interactions among multiple elements (biomolecules, cells, tissues etc.) as a means to understand and predict therapeutic and toxic effects of drugs".

QSP as a Tool for Knowledge Integration and Decision Making

Case Study of Hypertension model developed by Entelos Inc.* (adapted from Hallow et al, 2014[3])

Objective: To develop a model of long term regulation of hypertension which can be used to answer questions related to (1) effectiveness of different therapeutic regimens, (2) effect of therapy on different subpopulations of patients (3) compare new therapeutic agents to existing ones.

Model and Methods:



The Guyton Coleman model of circulation[2] was used as a starting point and several modifications were carried out to result in a model that focusses on the long term regulation of blood pressure based on the Renin Angiotensin Aldosterone System (RAAS).

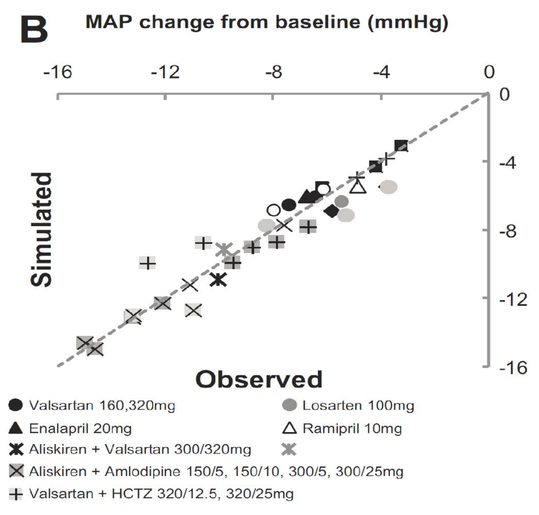
Results:

Fig 1: Simulated values of key model parameters as compared to the physiological range in the literature.

Variable	Units	Data Min	Data Max	Simulation Value
Mean Arterial Pressure (MAP)	mmHg	80	135	83
Glomerular Filtration Rate (GFR)	ml/min	60	170	99
Urinary Sodium Excretion	mEq/min	0.06	0.15	0.126
Extracellular Fluid Volume (ECF)	L	13	18	15
Daily Urine Flow	L/day	1.5	3.2	2.1
Sodium Concentration	mEq/L	140	145	143.3
Cardiac Output (CO)	L / min	4	7	5.15
Renal Blood Flow (RBF)	L/min	0.6	1.15	0.9
Renal Vascular Resistance	mmHg*min/L	70	172	86
Filtration Fraction	ratio	0.15	0.28	0.19
Total Peripheral Resistance (TPR)	mmHg*min /L	12	30	17
Aldosterone Concentration	pg/ml	30	200	100
Plasma Renin Activity (PRA)	fmol/ml/hr	290	3700	350

A 'normal' virtual patient was created whose characteristics fall within allowable ranges for several clinical readouts. Using sensitivity analysis results as a guide, a virtual population of hypertensive patients was also created.

Fig 2: Simulation with the final calibrated model shows that it fits Mean Arterial Pressure (MAP) response to a range of antihypertensive motherapies.

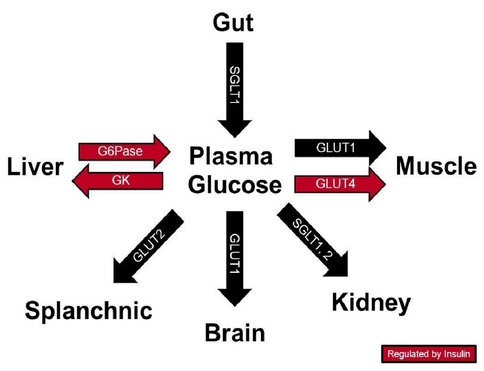


The calibrated model accurately predicts the effect of combination therapies on the MAP.

Case Study of a Diabetes model developed by Eli Lilly and Co. (adapted from joint poster presented in ACoP-6[4])

Objective: To identify optimal PK/PD characteristics for a next generation basal insulin analog that maximizes efficacy and minimizes hypoglycemic risk. The focus of this work was on quantifying the relationship between rate of insulin absorption from subcutaneous space into plasma and clinical outcomes e.g., HbA1c, Fasting Plasma Glucose and rate of hypoglycemia.

Model and Methods:



A systems pharmacology model of plasma glucose regulation was developed by Eli Lilly. After calibration to clinical data on existing therapies, it was used to generate Type 2 Diabetics Virtual Patients (VPs) who were similar to those recruited in Zinman et al [5]. These patients were used to study the effect on glucose and hypoglycemia by different novel theoretical insulins.

Results:

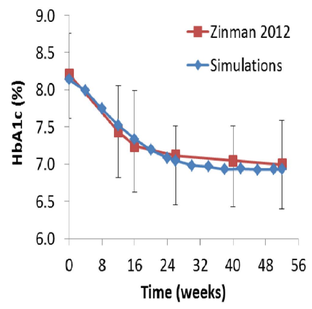


Fig 3: The model output matches the clinical trial data. The figure shows the effect of existing standard-of-care glargine.

Fig 4: PK profiles of the different theoretical insulins after multiple doses

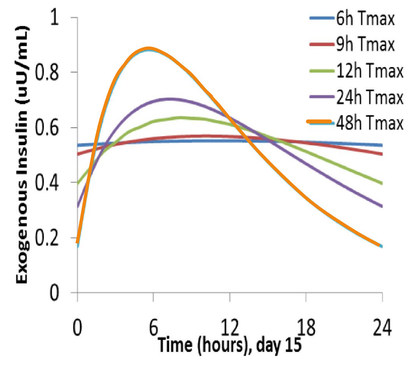
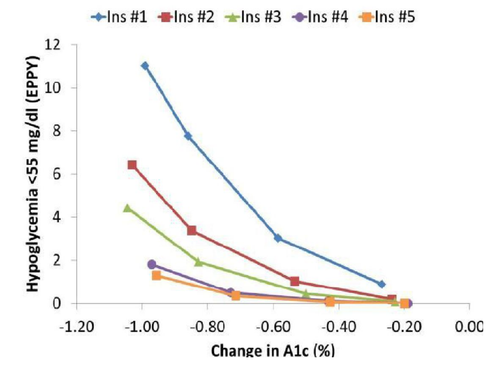


Fig 5: Hypoglycemia increases with increasing dose (and increasing efficiency) for all the insulins.



Five different theoretical insulin PK profiles were studied by adjusting rate of absorption from the injection site. Simulation research showed the relationship between increasing efficacy and safety risk.

Developing a Novel QSP Model for Immuno-Oncology

Objectives: To scope requirements for the development of a QSP model of tumor-immune interactions, that can simulate the effects of novel therapeutics. The model will be used to address questions around effectiveness of different therapies, dosages, etc. The model should also provide a mechanistic understanding of responder versus non-responder phenotypes.

Methods: Detailed survey of available clinical and biological literature and mathematical models.

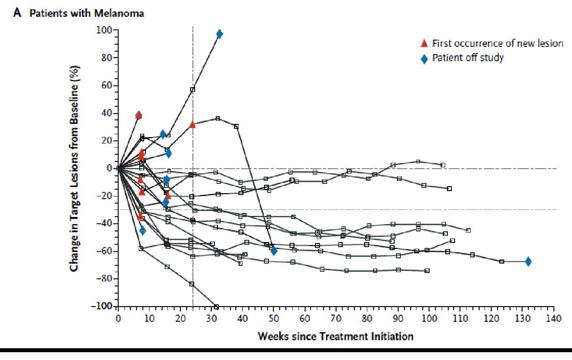


Fig. 6: Activity of anti PD-1 antibody in patients with refractory melanoma. Changes in tumor burden measured by lesion size in response to anti-PD1 antibody. Reproduced from Topalian et al, 2012[6].

Model of the tumor-immune interaction[7]

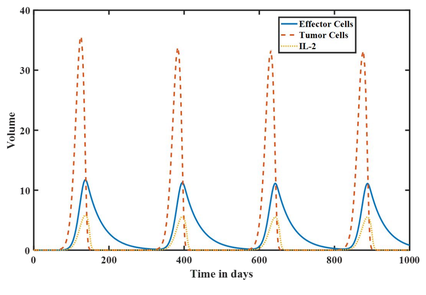


Fig. 7: Time course of effector cells (Solid blue line), tumor Cells (Dashed brown line) and IL-2 (Dotted orange line). The carrying capacity of the tumor is scaled to 10^5. Reproduced from Kirschner and Panetta, 1998[7].

Summary: Examples of QSP models in 3 different disease areas were presented, and their application to relevant therapies were illustrated. A key advantage of such models is the ability to simulate 'what-if' scenarios that allow clinical outcomes to be visualized, thereby improving decision making in the drug development process. The QSP methodology, however, relies on the availability of high quality biological data at multiple scales. At Vantage, we believe that the explosion of biological data along with availability of high powered computing makes QSP a field whose time has come.

References:

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* Entelos: www.entelos.com