Virtual Patient Strategies for Quantitative Systems Pharmacology Research

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Introduction

- Application of quantitative systems pharmacology (QSP) models can be challenging due to biological uncertainty and variability
- Used appropriately, QSP models can provide insights regarding the potential impact of uncertainty and variability on clinical outcome
- Virtual Patients (VPs) are alternative versions of a model in which specific pathways or parameters are deliberately varied to explore the systemic effects of those differences
- In effect, a VP represents a precise hypothesis regarding an uncertainty, or a specific instantiation of a variable process or outcome

Objectives

- Propose VP strategies to explore the impact of biological uncertainty and variability
- Show concrete examples from actual projects
- Illustrate the utility of this approach to de-risk efficient development of compounds and treatments

Methods

PhysioPD™ Research Platforms are mechanistic, quantitative models that elucidate the connection between mechanisms and outcomes.

- Rosa's PhysioPD™ Platforms are graphical, mathematical models of biology, a type of QSP
- PhysioPD Platforms combine engineering approaches and scientific data analysis to clarify complex physiology and drug interactions
- PhysioPD Platforms are qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1)

Figure 1. Rosa's Model Qualification Method[1]

VPs can be used to explore the impact of biological uncertainty and variability on response to therapies.

- Clinical variability is a well-recognized challenge of drug development, which results from both PK and PD
- VPs are often used to match and predict the clinical distribution of response, but they have many other uses
- Conceptually, we distinguish between
  - **Variability**: Value of a parameter is known to have a certain range or distribution
  - **Uncertainty**: Interaction or parameter value/distribution is unknown
- PD variability and uncertainty can be present at multiple scales (Figure 2), from target expression and function, to the target role in disease, to the clinical characteristics of the study population

Figure 2. Hierarchy of hypotheses, which informs investigations of uncertainty and variability

- VPs can build on sensitivity analysis to support a more accurate and quantitative evaluation of the impact of biology uncertainty and variability

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Syst Pharmacol 5, 43-53. [PMID 26933515]
2. Giugliano, D., et al. (2011) *Int J Clin Pract* 65(5), 602-611 [PMID 21489084]

Research Strategies

1. When comparing models to data, include VPs whose observable characteristics are similar to the trial subjects.

- Patients may differ in their disease severity or other clinical characteristics (Level 1, Figure 2)
- Patient variability often impacts response to therapy
- Matching VPs to the clinical population (in baseline characteristics and response to diagnostic tests) helps ensure appropriate comparisons
- **Example: Qualifying a Type 2 Diabetes (T2D) Platform**
  - A model of glucose homeostasis should include both healthy and various T2D VPs (Figure 3)

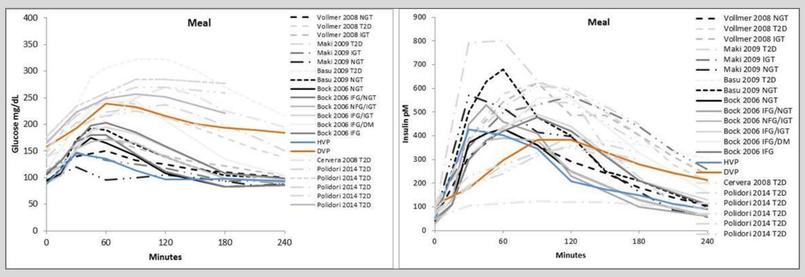

Figure 3. Variability of reported glucose (Left) and insulin (Right) response to a mixed meal tolerance test.

- Comparisons to literature data should consider **baseline disease status**
- E.g., magnitude of HbA1c reduction (a measure of diabetes severity) with treatment is tightly correlated with baseline HbA1c[2]

2. Use VPs to explore the impact of pathway-level variabilities on observed clinical outcomes.

- It is helpful to distinguish between two kinds of variability
  - **Outcome**: variability in observed clinical measurements (Level 1, Figure 2)
  - **Pathway**: known inter-patient variability that occurs at the mechanistic pathway level (Levels 2 and 3, Figure 2)
- Known pathway variability (and drug-specific variability) gives rise to outcome variability
- VPs can help explore the impact of pathway variability on observed clinical outcomes
- This may inform inclusion criteria and support patient stratification
- **Example: Using a model of T2D to anticipate possible outcome variability and aid competitive differentiation**
  - Client was interested in how patient variability may impact response to new vs. existing diabetes drugs
  - Rosa developed a T2D PhysioPD Platform (including glucose, insulin, and lipid metabolism) as well as the client and competitor drug PK and MOA
  - Rosa developed a cohort of VPs (Table 1) to explore the impact of **disease severity** and **variable pathophysiological mechanisms**

VP	FPG mg/dL	FPI pM	HbA1c	Peripheral Insulin Resistance	Beta Cell Function	Hepatic Insulin Resistance	GFR mL/min/1.73 m²
DVP1	126-140	50-75	6.5-8	Moderate	Moderate	Moderate	60-90
DVP2	126-140	>75	7-8	High	Good	High	>100
DVP3	140-160	<50	7-8	Moderate	Poor	Moderate	60-90
DVP4	140-160	50-75	7-8	Moderate	Moderate	High	>90
DVP5	140-160	>75	7-9	High	Good	High	60-90
DVP6	>170	<50	8-10	Moderate	Poor	High	<30
DVP7	>170	<50	8-10	Moderate	Poor	High	>90
DVP8	>170	50-75	8-10	High	Poor	High	60-90
DVP9	>170	<50	8-10	High	Poor	High	60-90
DVP10	>170	<50	8-10	High	Poor	High	40-60

Table 1. VP cohort was developed to include variable prototypical subjects with different degrees of disease severity and predominant pathophysiological mechanisms

- VP simulations guided expectations of efficacy, comparison to existing therapies, and which subjects would be most likely to benefit from the novel therapy

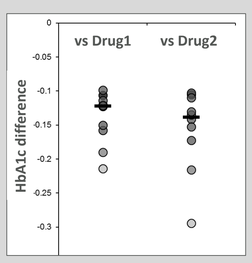

Figure 4. T2D VP responses

3. Use VPs to explore the impact of target-related uncertainties and variabilities.

- Drug target expression and function may be uncertain or variable (Level 3, Figure 2)
- VPs allow one to assess the impact of these uncertainties and variabilities by
  - Formalizing alternative hypotheses
  - Quantifying the impact of these hypotheses
- **Example: Evaluating a Novel Target in Psoriasis**
  - Expression and function of the specific enzyme isoform responsible for the MOA was uncertain
  - Prospective simulations were conducted to evaluate efficacy under a variety of agreed-upon assumptions
  - Systematic **sensitivity analysis** highlighted the key pathways most critical in determining response
  - VPs evaluated the **impact** of these uncertainties by biasing them in favor of, or against, the novel therapy
  - VPs were constrained to be otherwise identical, in terms of other uncertainties, pathway variabilities, and clinical characteristics
  - **Controlled virtual experiments** highlighted those uncertainties which were most critical to de-risking development

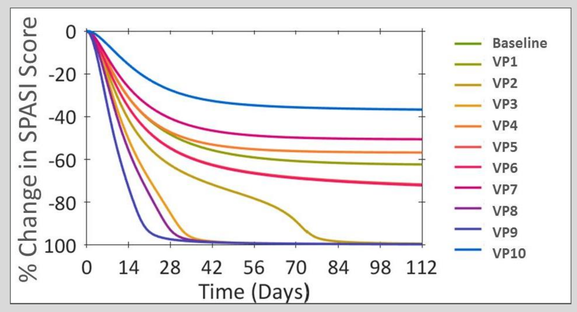

Figure 5. VPs demonstrated the range of possible efficacy and the relative impact of key target-related uncertainties

4. Tailor VP research to the stage of scientific and clinical progress of a given drug program.

- Uncertainty and variability, and therefore drug development risk, are present throughout multiple levels of research (Figure 2)
- Multiple hypotheses related to the target may give rise to a similar physiological state and clinical phenotype
- Sensitivity analysis can help identify pathways with uncertainty or variability that are key for achieving efficacy for a new therapeutic approach
- VPs represent plausible alternative hypotheses of pathophysiology and target involvement
- Qualified VPs can be used to reveal the impact of pathway differences on therapeutic effects, at any stage of development
- This process clarifies how target mechanisms impact outcomes and helps de-risk drug development

Conclusions

- Uncertainty and variability are present throughout the drug development cycle, and at multiple levels of the hierarchy of physiology
- QSP models such as Rosa's PhysioPD Research Platforms enable exploration of the **impact of mechanistic variability and uncertainty**
- Alternative VPs represent **controlled virtual experiments**, the precise statement of a hypothesis or instantiation of a variable process
- VPs can highlight those uncertainties and variabilities which are most critical to program success, and can therefore help **de-risk efficient development** of compounds and treatments

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