

Interactive evaluation of dosing regimens for a novel anti-diabetic agent: a case-study in the application of RxODE

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Introduction and Motivation

Pharmacometric simulation is a valuable tool in drug development, but several factors limit greater utilization:

- Static graphics can't answer "what if" questions that inevitably arise.
- Not feasible to perform and present all simulation scenarios of interest a priori, and iterating to reach desired set of simulations introduces lag time → extra meetings, loss of momentum, and lost opportunities for making quantitatively driven decisions.
- Most currently available simulation tools are cumbersome, tedious, and time-consuming, requiring extensive custom programming and moving between one software to perform simulations and another to visualize results.
- "Black box" problem – particular to more complex models, team's lack of understanding and confidence in model behavior can be a barrier.

Thus, there is a great need for more efficient simulation processes that facilitate interactive, real-time, transparent evaluation and iteration on simulation scenarios.

RxODE

RxODE is a custom R package that facilitates quick and efficient simulations of ordinary differential equation (ODE) models.

- provides elegant, efficient, and versatile way to specify dosing scenarios, including multiple routes of administrations within a single regimen, sampling schedules, etc.
- facilitates simulations with between-patient variability.
- minimizes the amount of custom coding required for pharmacometric simulations.
- Provides extremely fast run times, because RxODE model is automatically translated into C, compiled into machine code, and then loaded into the running R program.
- designed with pharmacometric models in mind, but can be applied more generally to any ODE-based model.
- Allows users to take advantage of the R ecosystem for plotting and analyzing results.
- provides a function for directly generating R shiny applications for interactively probing the model.
- is an open source application available in all computer platforms on which R runs.

Figure 1: Workflow for performing a simulation with RxODE

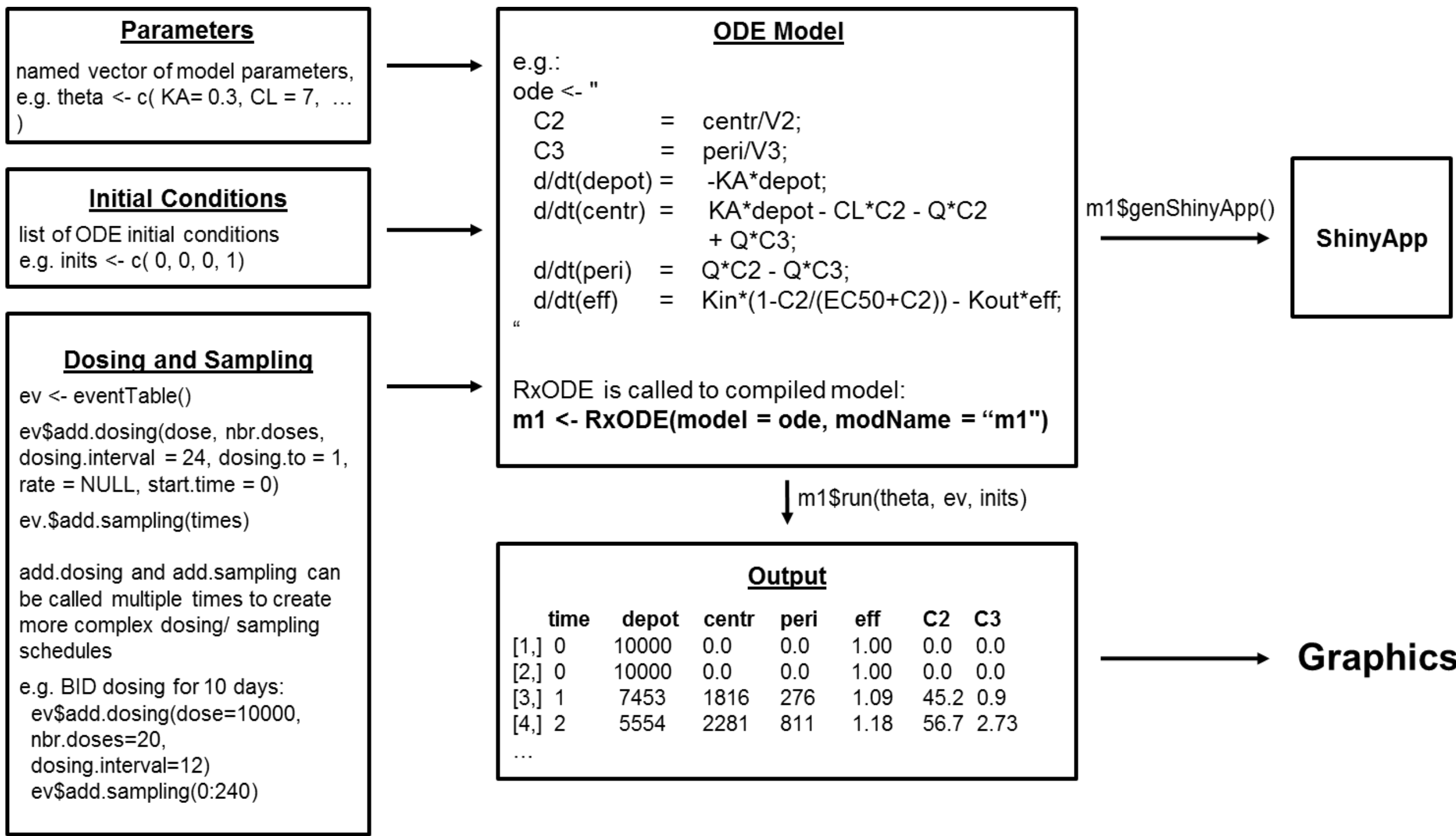
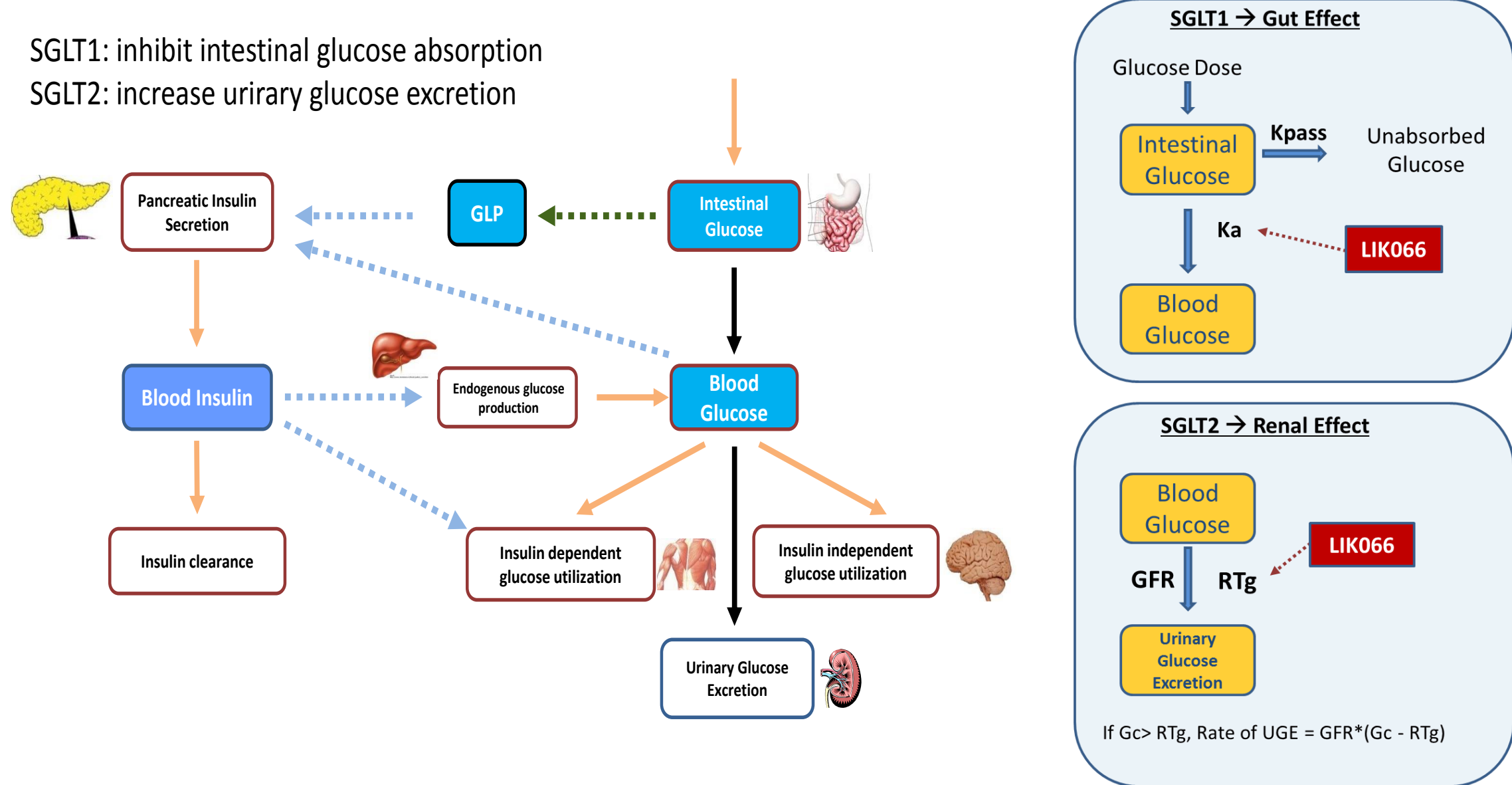


Table 1. The add.dosing() method of an eventTable object provides an efficient method to specify a variety of dosing schedules

Single Dose	ev\$add.dosing(dose=10000, nbr.doses=1)	
multiple doses	ev\$add.dosing(dose=10000, nbr.doses=5)	
bid for 5 days, followed by qd for 5 days	ev\$add.dosing(dose=10000, nbr.doses=10, dosing.interval=12) ev\$add.dosing(dose=20000, nbr.doses=5, dosing.interval=24, start.time=120)	
infusion for 5 days, followed by oral for 5 days	ev\$add.dosing(dose=10000, nbr.doses=5, dosing.to=2,rate=5000) ev\$add.dosing(dose=10000, nbr.doses=5, start.time=120)	
2wk-on, 1wk-off	for (i in 1:ncyc) { ev\$add.dosing(dose=10000, nbr.doses=14, start.time=(i-1)*21*24) }	

Application of RxODE to a physiologic model of dual SGLT 1 and 2 inhibition in diabetes

Dual SGLT 1/2 inhibitors may provide additional glucose lowering in diabetic patients.



Dose-response for each mechanism estimated by modeling of OGTT data from Phase I studies. But choice of dose, regimen, study design for phase II complex because:

- EC50 for SGLT1 effect several times larger than EC50 for SGLT2.
- Duration of gut effect not fully characterized.
- Impact of dose timing not characterized.
- Impact of patient characteristics (renal function, etc.) not characterized.

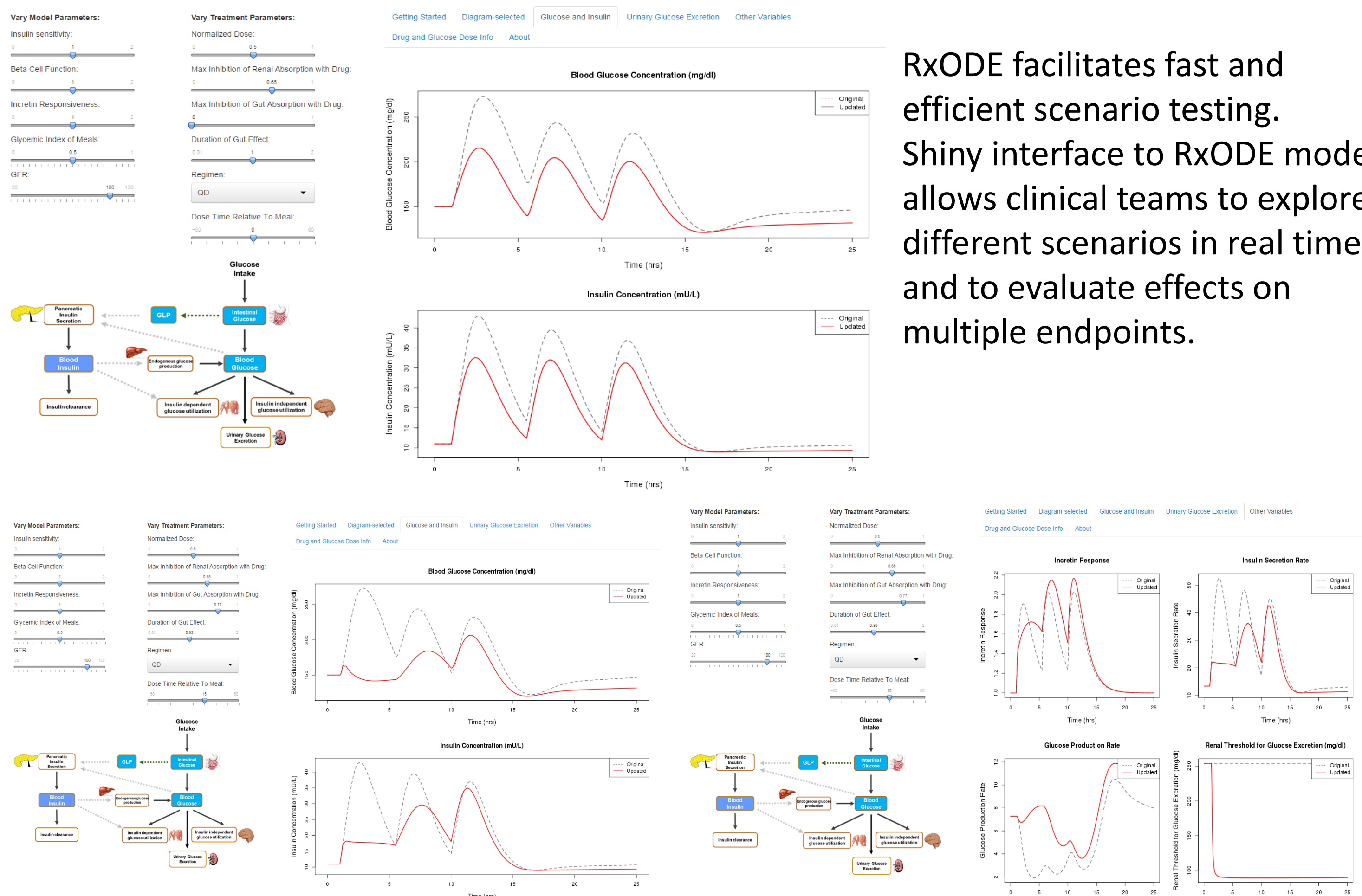
Approach:

Physiology-based model of glucose-insulin dynamics used to estimate K-PD parameters in NONMEM, using Phase I OGTT data

RxODE used to perform simulations and generate Shiny app for real-time scenario exploration

App is hosted on web server, so team can access it from weblink – does not require any software installation by end-users. Generalized webapp can be found at:

<http://qsp.engr.uga.edu:3838/GluIns/GluIns1.d/>



RxODE facilitates fast and efficient scenario testing. Shiny interface to RxODE model allows clinical teams to explore different scenarios in real time, and to evaluate effects on multiple endpoints.

RxODE also facilitates easy and flexible simulation with variability, and direct visualization/analysis of results.

Code for performing simulation with variability

```
#Assuming model, lists of thetas and initial conditions, and dosing/sampling  
event table already loaded/created as described above  
nsub=100  
#Create a matrix of theta values, and add 25% variability on parameter CLGI  
theta.all=matrix(rep(theta,each=nsub), nrow=nsub)  
theta.all[, "CLGI"] = theta$CLGI*exp(rnorm(nsub,0,0.25))  
obs.rec = ev$get.obs.rec()  
nobs = sum(obs.rec)  
cp.all = matrix(NA, nobs, nsub)
```

```
#Perform simulation for each row of parameter values in the theta matrix  
for (i in 1:nsub) {  
  x <- gluinsmod$run(theta.all[i,], ev, inits=inits)  
  cp.all[, i] = x[obs.rec, "Glucose_concentration"]  
}  
#It is now easy to directly plot or perform statistical calculations on simulation  
results  
matplot(cp.all, type="l", xlab="Time (hrs)", ylab = "Glucose Concentration  
(mg/dl)")  
#Calculate quantiles and plot  
cp.q = matrix(NA, nobs, 3)  
for (i in 1:nrow(cp.all)) {  
  cp.q[i, ] = quantile(cp.all[i,], prob=c(.05, .5, .95))  
}  
matplot(cp.q, type="l", lty=c(2,1,2), col=c(2,1,2), xlab="Time (hrs)", ylab =  
"Glucose Concentration (mg/dl)")
```

References

- [1] Jauslin et al. An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. J Clin Pharm 2007; 47(10): 1244-55.
- [2] Wang W, Hallow KM, James DA. A tutorial on RxODE, an R package for simulating from ordinary differential equation pharmacometrics models: case study on adaptive dosing. In preparation.

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