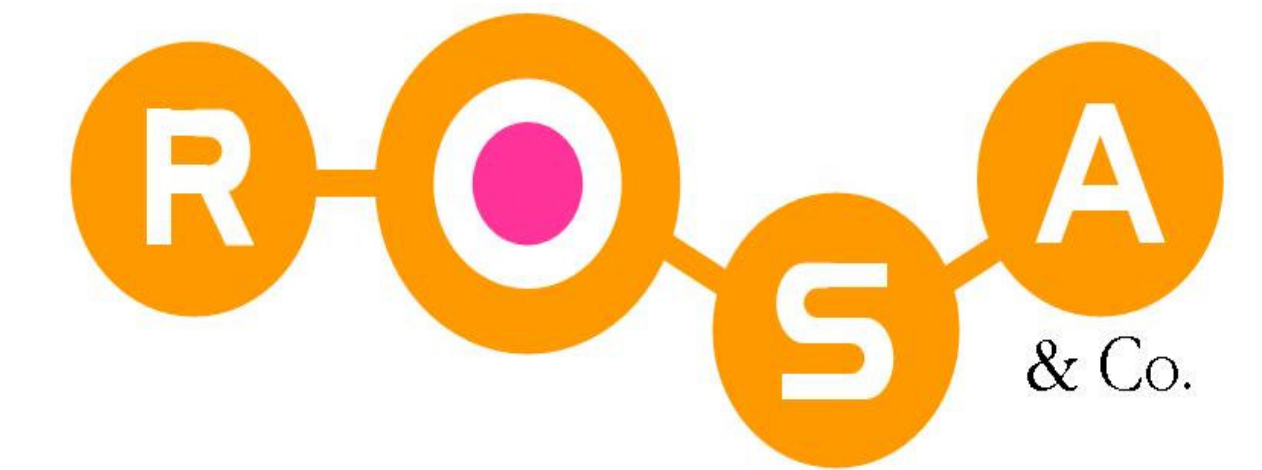


A Simple Method for Approximating Population Pharmacokinetic Parameters

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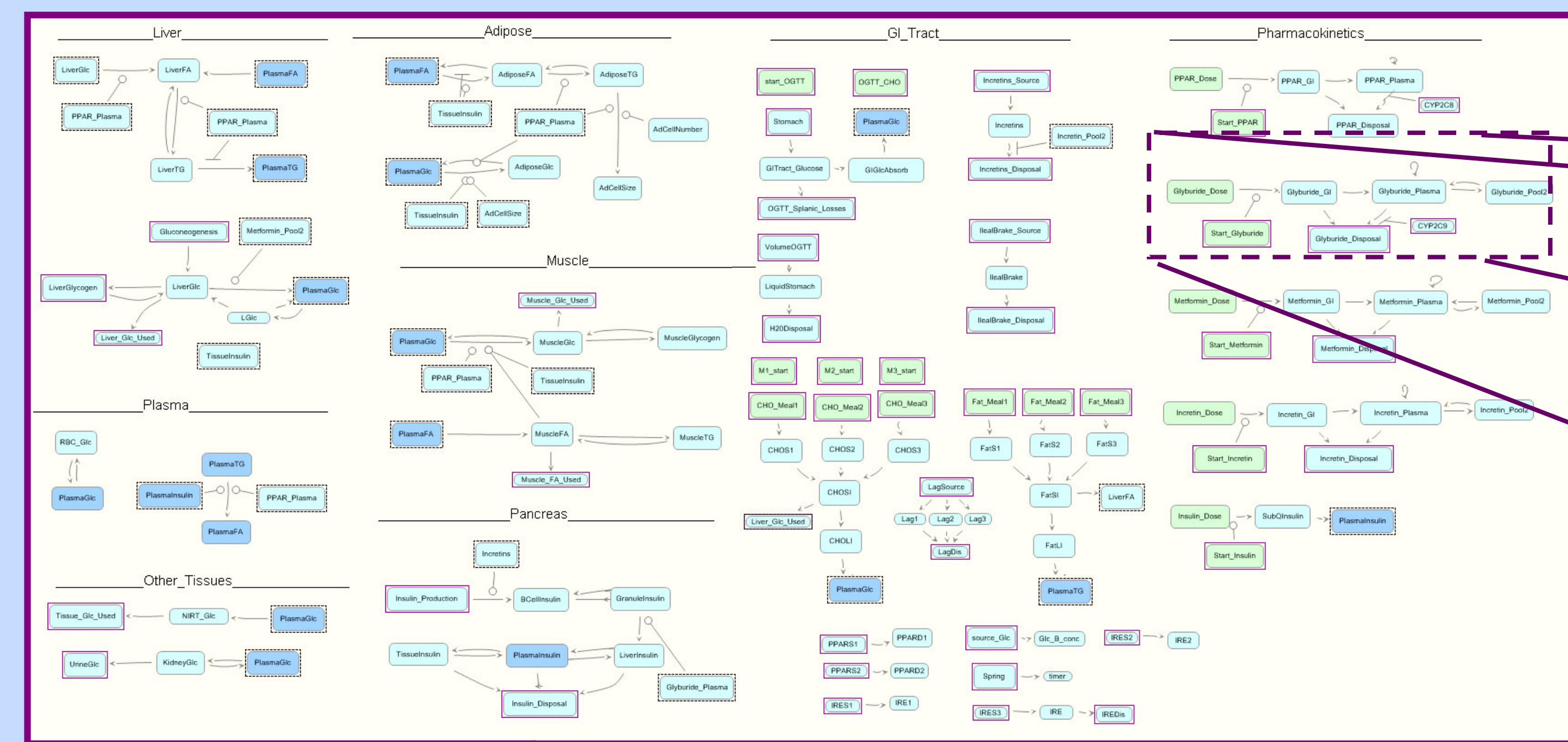


Background

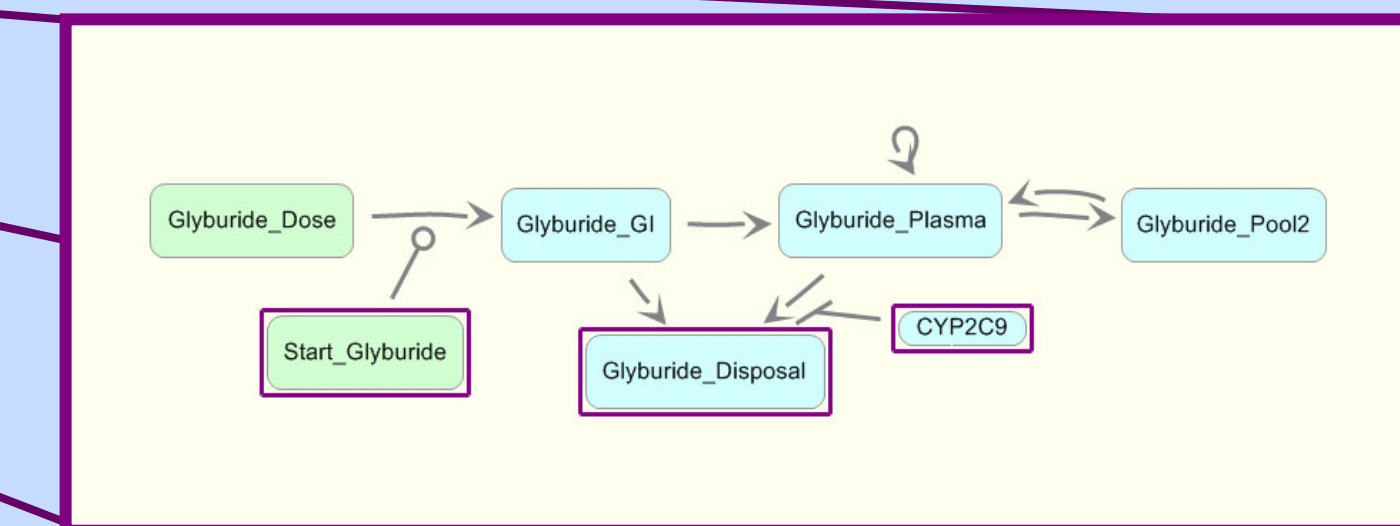
Population pharmacokinetic (PK) models are useful for describing time-concentration data, but often there is little time and no budget to engage corporate or external experts to analyze data and determine these values. The analysis often involves rather specialized software such as Nonmem, SAS NL MIXED, or the nlme package in R/S.

In several recent engagements, we needed to test our models with "reasonable" drug time-concentration profiles to facilitate trial simulation methods development, and wanted to see if a simple method could be used to approximate population PK model without having to teach scientists, not specializing in PK, a new programming language. This effort is necessary because often physiologically-based pharmacodynamic (PhysioPD™) modeling occurs simultaneously or prior to the development of rigorous PK models. The PK information is needed to build and test the physiological model and clinical trial design may be necessary before data from concurrent clinical trials is available. While there are programs available to estimate individual and population PK, we needed a program that could be used by scientists, without specialized training, and at limited cost.

We describe a simple method to generate approximate central tendencies and measures of distribution for PK/PD model parameters. A mean and covariance description of parameters allows easy resampling for Monte Carlo type simulation. The average and distribution of the PK time-concentration curves generated using this approximate method are close to those observed experimentally. We have used the technique to allow the preliminary evaluation of our PhysioPD model structure, parameters, and outcomes using model-generated time-concentration profiles that are similar to those from actual subjects. This method does not account for parametric covariance, and problems in those predictions are known (1-3). However, the model parameters generated by the Rosa Excel macro were very useful for testing of the complex PhysioPD models.

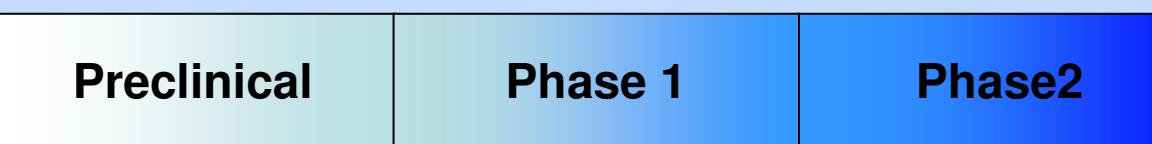
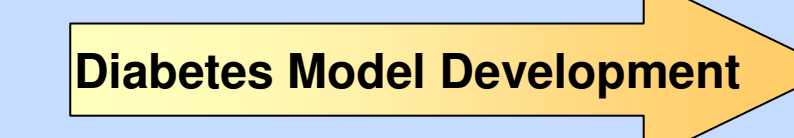


Drug information – nonproprietary and proprietary – was incorporated into the PhysioPD model.

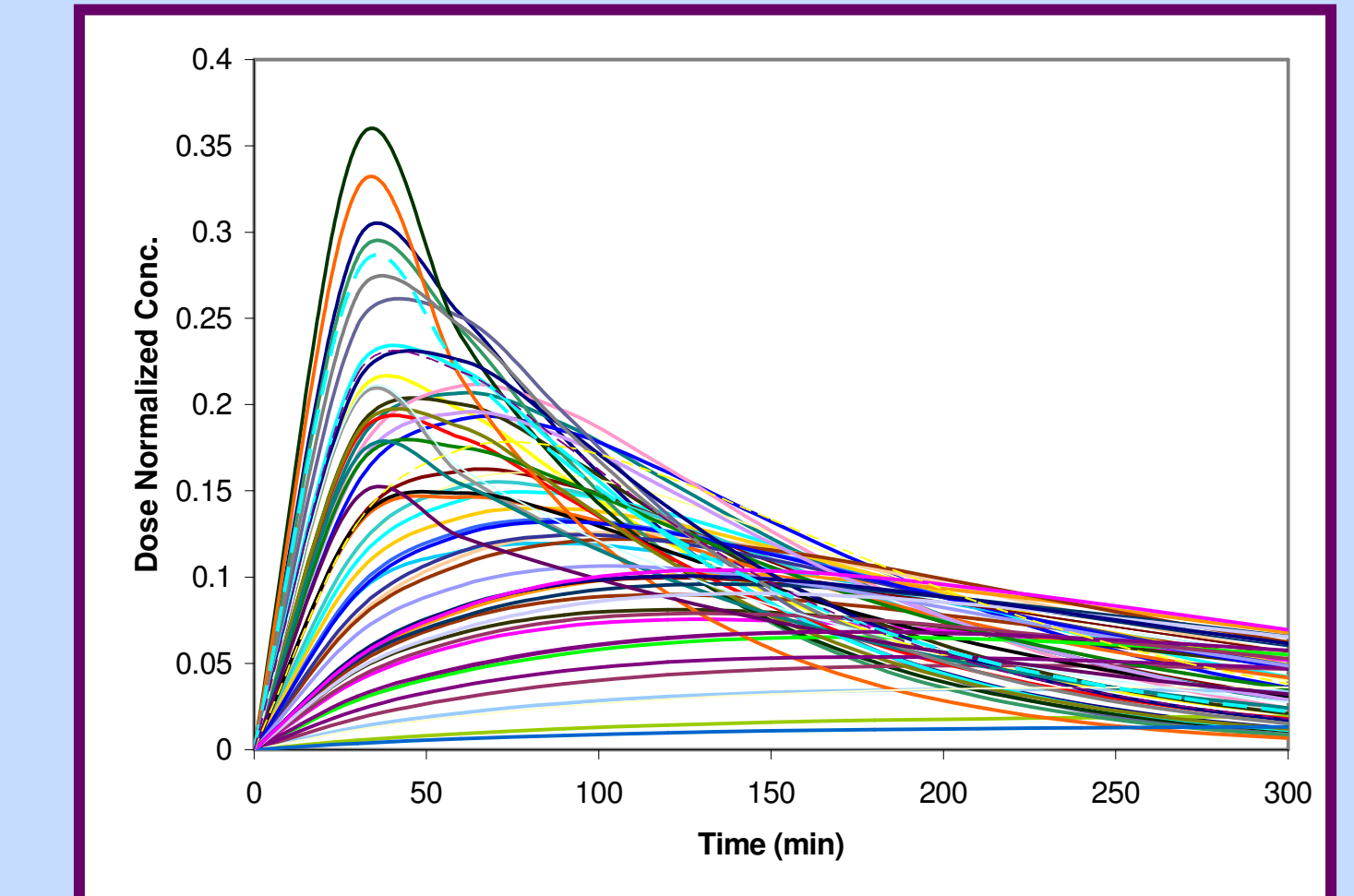


Individual and popPK models were needed to incorporate this data into the PhysioPD model.

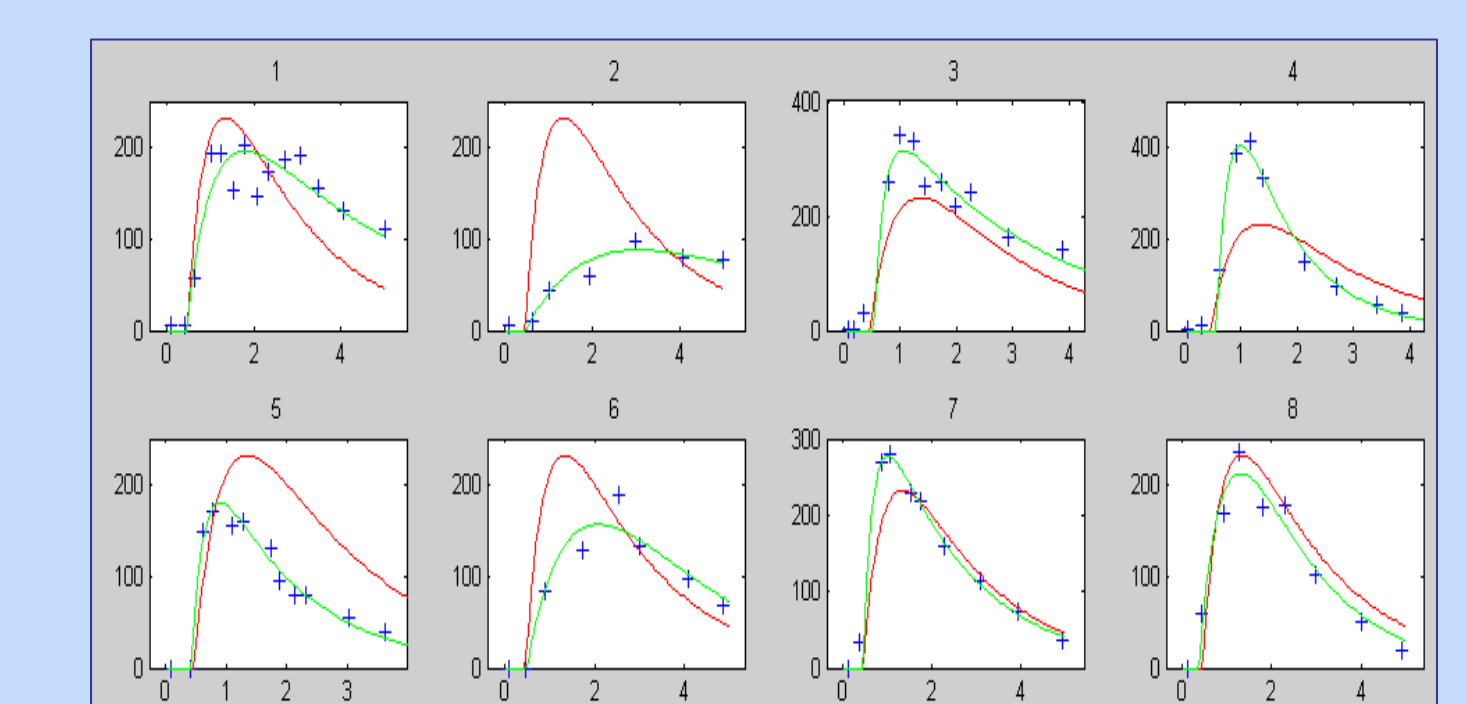
Development of PhysioPD models often occurs before clinical data is available



Stage of Drug Development



Testing the model and trial simulator with approximate popPK parameters: "Spaghetti plot" of predicted time-concentration values



Use rigorous popPK for final trial simulation: Individual pk generated by Monolix. In general, approximate and rigorous time-concentration curves matched well, parameters less so.

PhysioPD models are used in a decision process:

- What compounds to develop preclinically and clinically?
- Which compounds should be leads, and which should be backups?
- What is the optimal design for a clinical trial?
- What assets/compounds to in-license/out-license?
- How to prevent/mitigate/manage safety issues and potential adverse events?
- What collaborations/partnerships to undertake?
- What companies/compounds to acquire/divest?

Standard Compartmental PK Modeling

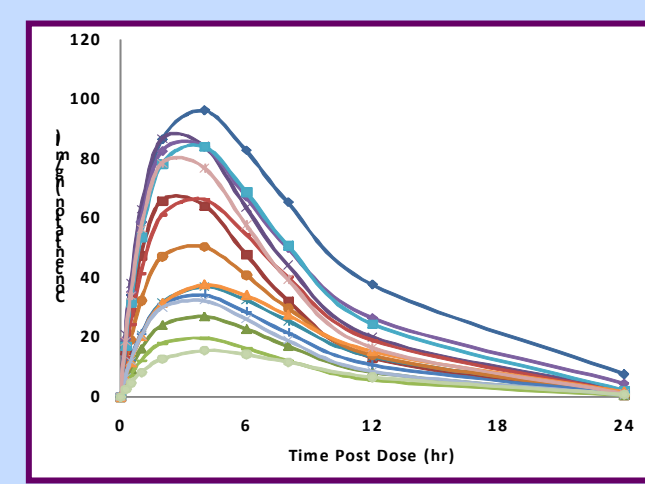
1. Structure
2. Parameters, one set per subject
 - Straightforward (done in WinNonLin)
 - Can choose to resample by selecting different subjects
 - Hard to generate new, physiologically reasonable subjects for simulation

Rosa Excel macro

1. Structure
2. Mean and variance values for parameters
 - Fairly easy
 - Parameters generated are close to "standard"
 - Generates reasonable time-concentration curves
 - Allows testing of PhysioPD models

Population PK Modeling

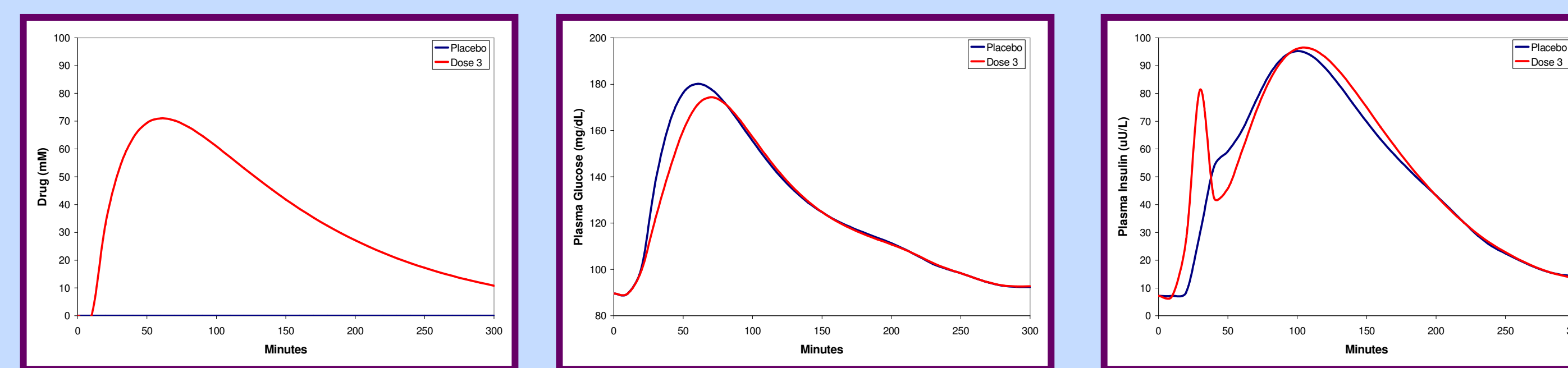
1. Structure
2. Mean and covariance structure of parameters
 - Uses scarce resources
 - Ideal way to generate new subjects for simulation



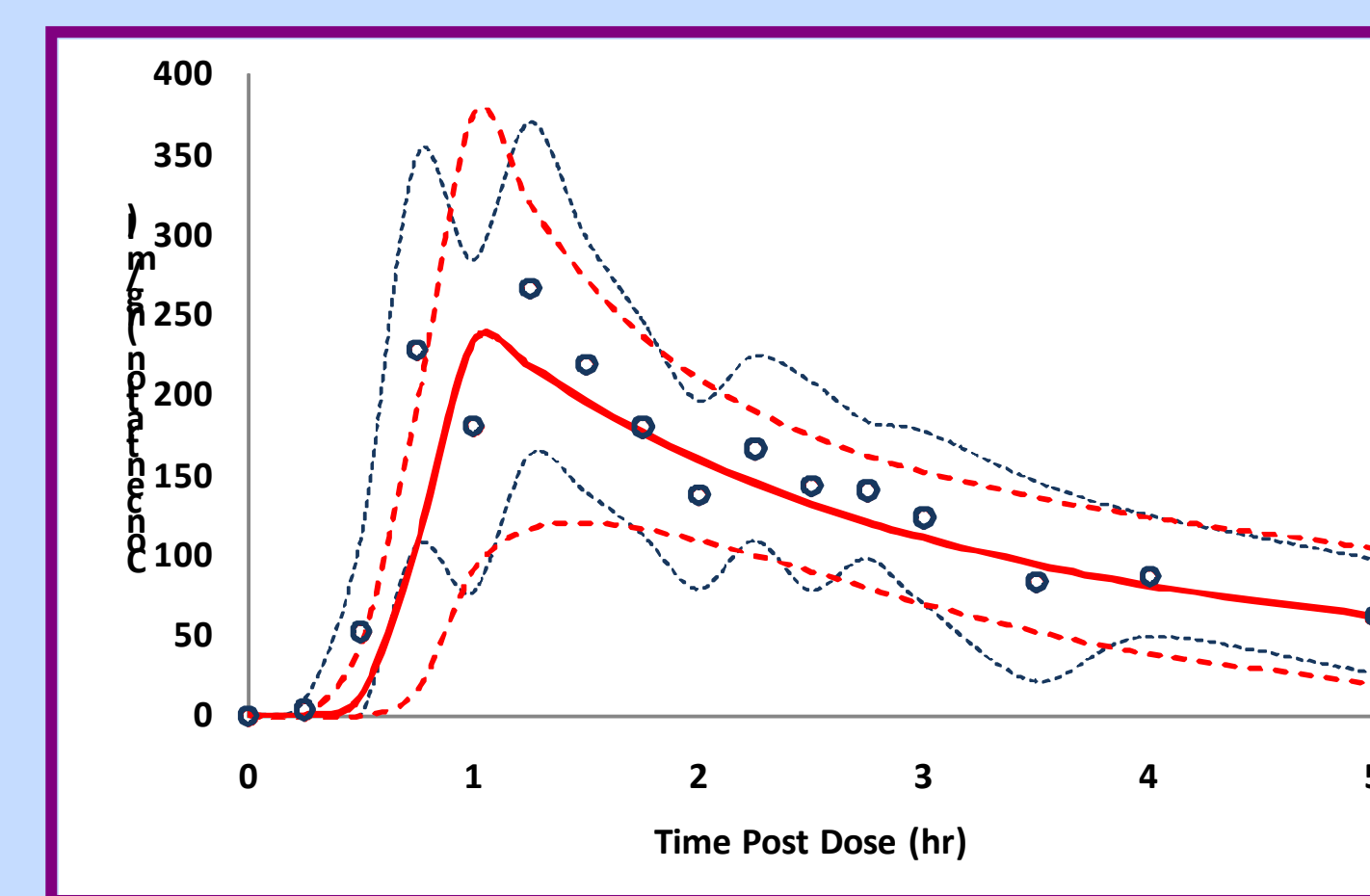
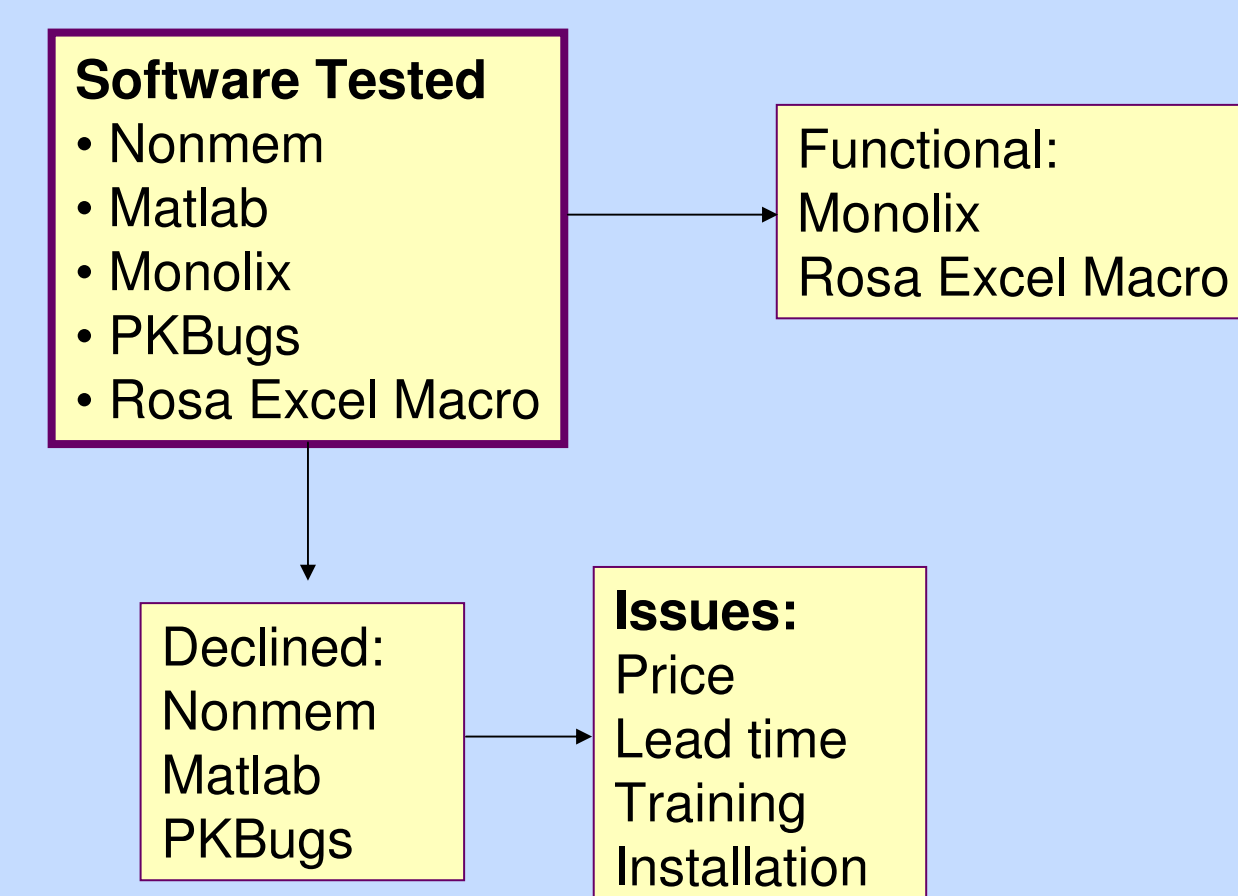
Diabetes PhysioPD model incorporates glucose, lipid metabolism as well as PK.

PhysioPD models use a simulation engine to calculate outputs of interest.

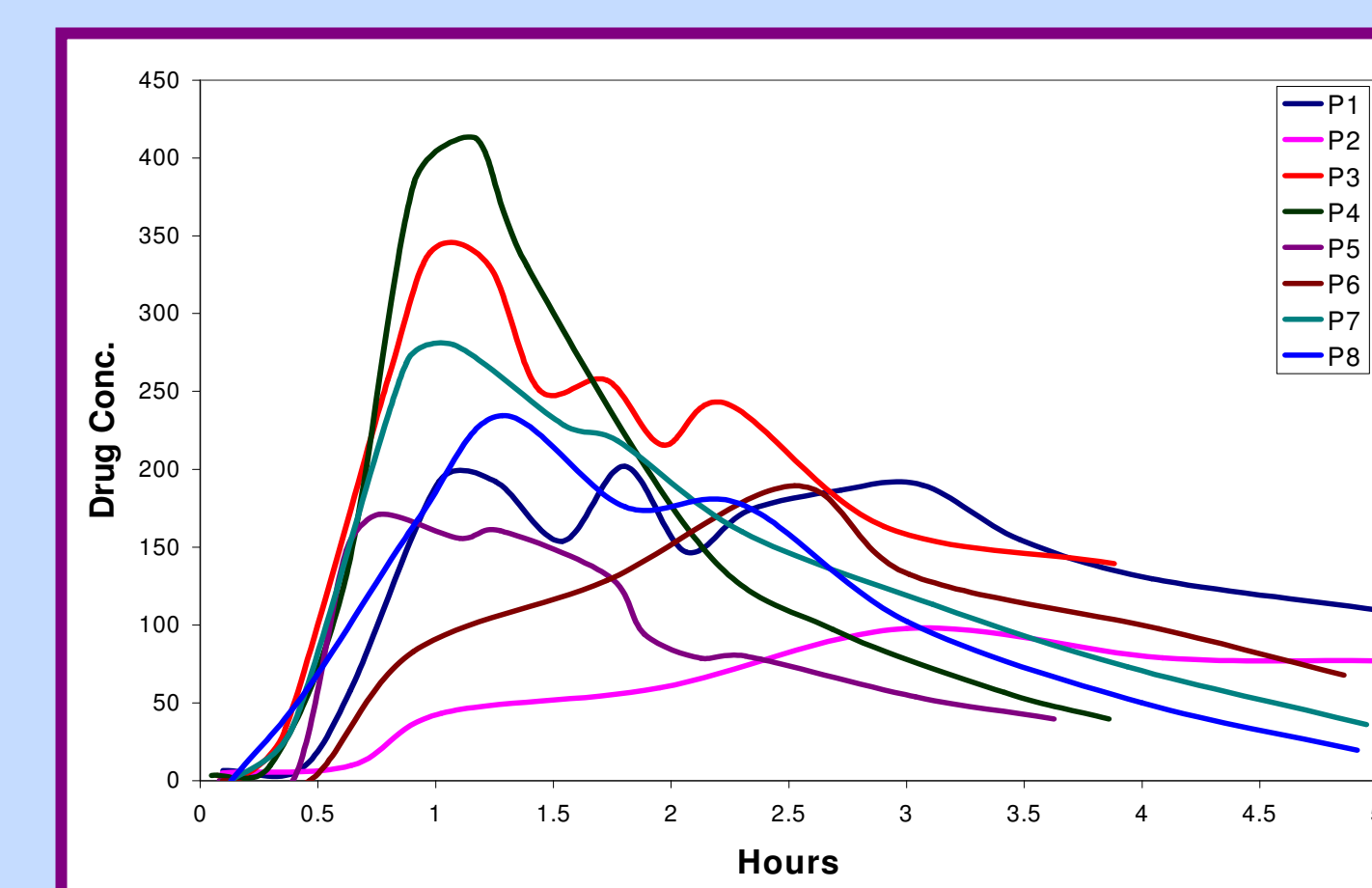
PhysioPD model results when treated with placebo or SUR drug during OGTT



Plasma glucose increased after each meal. The drug effect was a lowering of postprandial glucose.



An Excel macro was designed for ease of use.

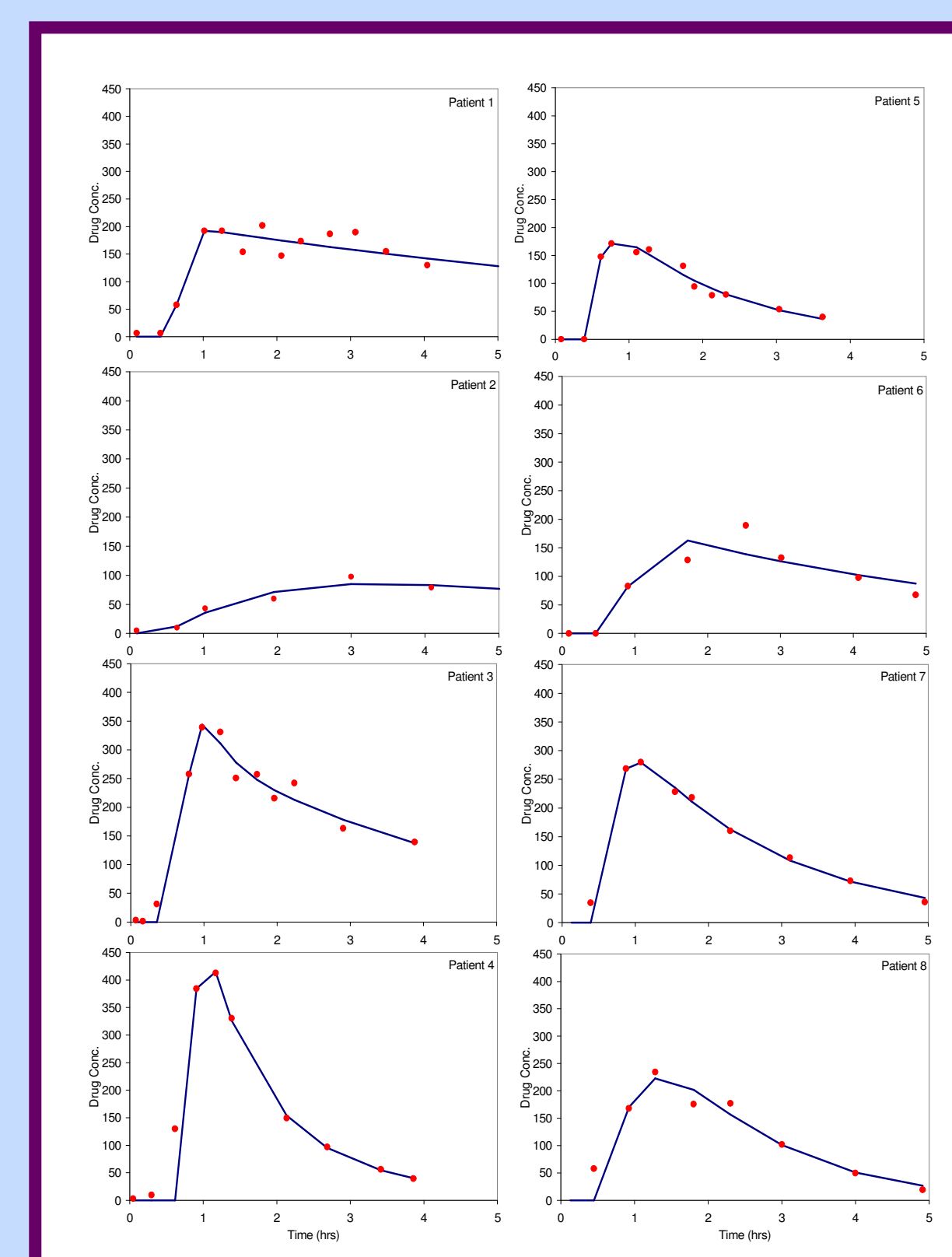


Our goal: approximate PK parameter distributions should give predictions that match data, and should approximate popPK parameters

| PK Param | Mean | SD | Min | Max |
|-------------------|--------|--------|--------|--------|
| CL | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| V | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₁₂ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₂₁ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₁₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₂₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₁₀₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₂₀₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₁₀₀₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |
| K ₂₀₀₀ | 1.0000 | 0.1000 | 0.8000 | 1.2000 |

Parameters – one set per subject

Generate individual PK fit



Methods

This experiment was done as two steps. The first step was to evaluate the available software for use by individuals who were not trained pharmacologists. The second step was to evaluate the results from the software itself.

Published data for glyburide and metformin were selected to use as supply data for comparative examples. We attempted to generate individual PK and pop PK for each data set using a) Monolix, b) PK Bug, and c) Rosa PK Macro. To help us understand how usable each system was for someone not trained in PK, we had scientists download, install and run each program. Each program was rated on ease of acquisition, ease of use, usefulness of the results, and cost. The results from each program were then compared to published or NONMEM generated models.

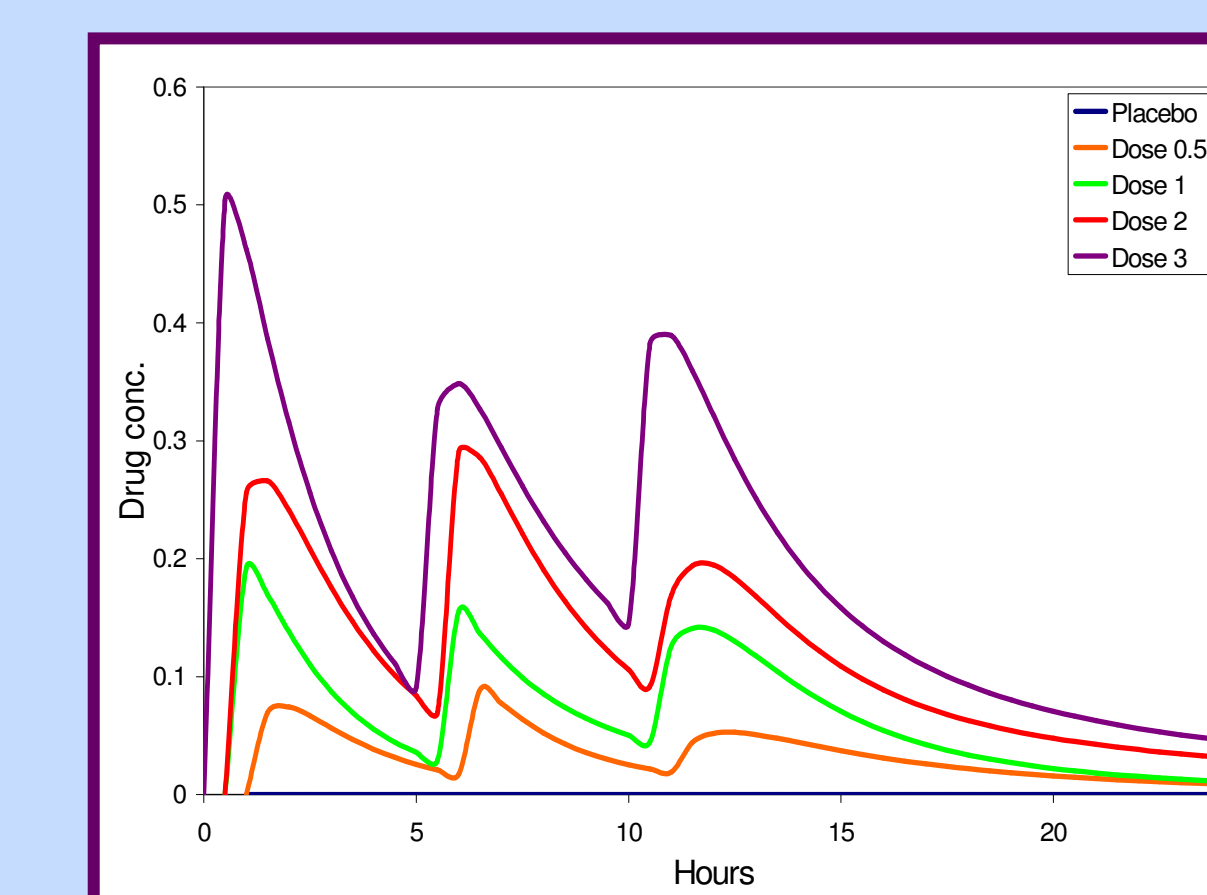
Because MS-Excel is often used to contain and transmit data, we utilized the MS-Excel's Visual Basic macro functions to generate and test model parameters. The first step was to create a system to fit concentration curves and provide a matrix of patient-specific parameters for a PK model. We generated a series of macros utilizing time by concentration data to provide PK model parameters for a standard one or two-compartment model. The fittings were done to optimize the sum of the weighted square errors. These optimizations were done using the Solver feature (based on Generalized Reduced Gradient method) of Microsoft Excel. The system functions with single dose or multiple doses of drug with each dose during the day displaying different kinetics. The individual peaks for each dose were determined by classic "peak stripping" techniques. For the population PK, the individual parameter values with the variance estimates from a small data set were used to generate a large random population. The mean and variance of the random population were then compared to original to determine if the variability from the random population matched the variability from the small dataset. The model parameters that were generated were compared to the literature and those generated using Nonmem.

Datasets used:

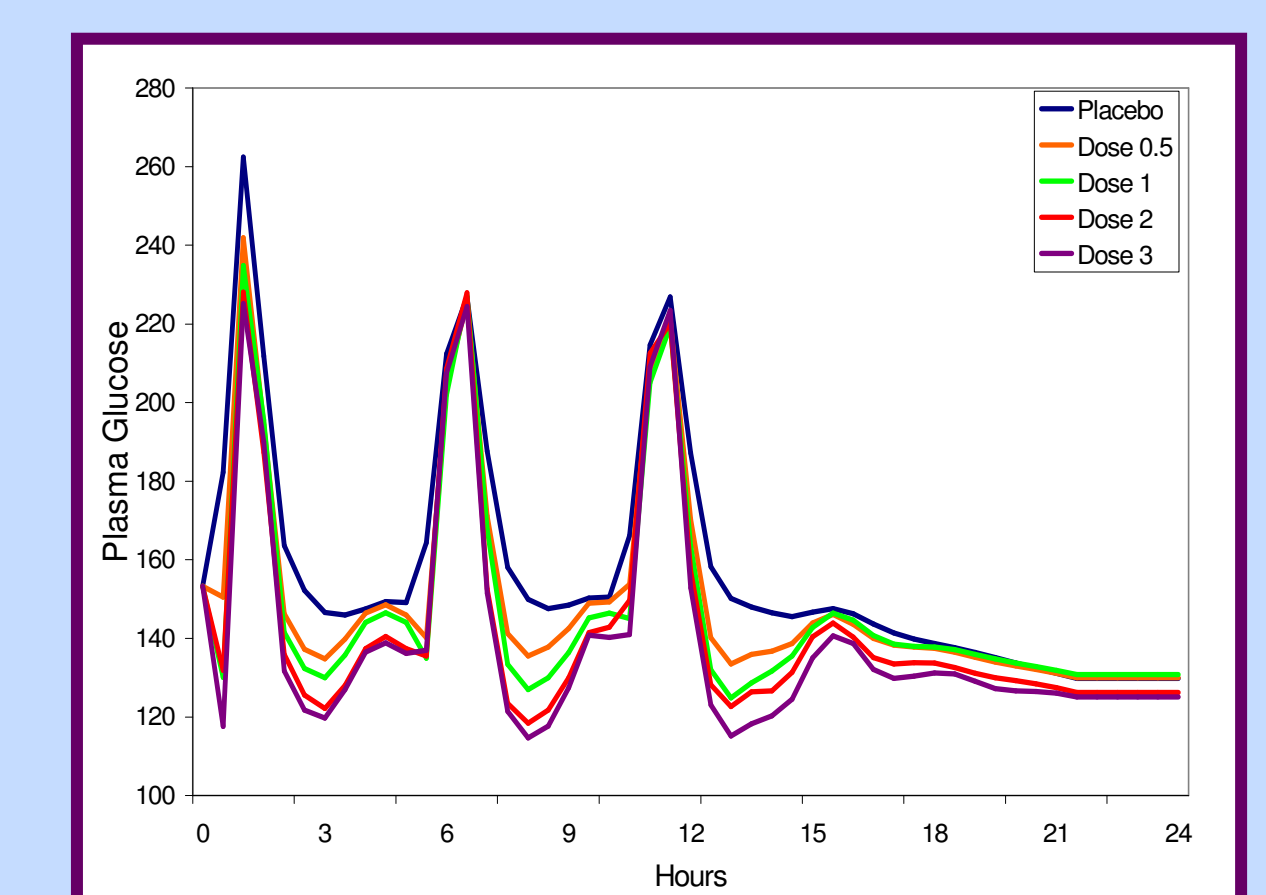
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4. Pearson JG. Pharmacokinetics of glyburide. *Am J Med.* 1985 Sep 20;79(3B):67-71.

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A TID dosing of a new compound with three meals experiment. Results plotted are mean values. PK values differed with each dose.



Conclusions

A system was designed to allow a simple method to fit individual PK model parameters using concentration data and to approximate population PK parameters using widely available software. The system utilized either single dose data or multiple dose data and provided reasonable PK model parameters for each dataset tested. The population PK model parameters generated by the system provided parameters and variance values that were useful in testing Rosa's PhysioPD models. The ease of generating approximate estimates for these parameters for testing the PhysioPD model and trial simulations was useful to our scientists. The method implemented has the advantage of utilizing standard worksheet software for those users who do not have access to and training in specialized software or the time of expert kineticists.

We emphasize that this is an approximation, with some deficiencies that are well known. However, this approximation has been used to test our PhysioPD models prior to the availability of rigorous popPK, and the approximate values were used as initial estimates for the more rigorous analysis. The agreement of the concentration-time profiles was very good, and the approximate parameter values were useful as starting points for the rigorous popPK analysis.

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