Simulation for Designing Clinical Trials

Input-Output Models

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3

1. Clinical Trial Simulation Models

Clinical trial simulation (CTS) depends fundamentally on a set of models to simulate observations that might arise in a clinical trial. Three distinct categories of model have been proposed [1]:

- Covariate distribution

- Input-Output

- Execution

They are presented in this sequence because the first decision that must be made when designing a clinical trial is what kind of subjects will be enrolled. The covariate-distribution model defines the population of subjects in terms of their characteristics such as weight, renal function, sex and so on. Next the input-output model can be developed to predict the observations expected in each subject using that individual's characteristics defined by the covariate distribution model. Finally, deviations from the clinical trial protocol may arise during execution of the trial. These may be attributed to subject withdrawal, incomplete adherence to dosing, lost samples, etc. The execution model will modify the output of the input-output model to simulate these sources of variability in actual trial performance.

This chapter discusses the structure of input-output (IO) models. A single pharmacokinetic model is used to illustrate features of IO models but it should be understood that IO models are quite general and the principles of IO models described below can be applied to any process which might describe the occurrence of an observation in a clinical trial.

2. Simulation and Analysis Models

It is a common aphorism that all models are wrong but some are useful [2]. The usefulness of models for simulating observations that could arise in a clinical trial is directly dependent on the complexity of the model. In general all the levels of the model hierarchy (Section 3.2 *et seq*) should be implemented for the purposes of clinical trial simulation in order to make the predicted observations as realistic as possible.

Analysis of clinical trial observations, however, can be useful with much less complexity. One of the purposes of clinical trial simulation is to evaluate alternative analysis models by applying them to simulated data that may arise from a much more complex but mechanistically plausible model. The following description of input-output models is oriented towards the development of models for simulation. Similar models could be used for analysis of actual data or simulated data but this is usually not required to satisfy the objectives of many clinical trial simulation experiments e.g. an analysis of variance may be all that is required to evaluate a simulated data set.

3. Input-Output Model

The input-output (IO) model is responsible for predicting the observations in each subject. The simplest IO models are non-stochastic, i.e., they do not include any random effects such as residual unexplained variability or between subject variability. More complex IO models may include one or both of these random effect components.

3.1.   IO Model Anatomy

Equation 1 is a model for predicting the time course of concentration, C(t), using a one-compartment first-order elimination model with bolus input. The left hand side of the equation, C(t), is the *dependent variable*. The symbol t is usually the *independent variable* in the right hand side of the equation. The symbols V (volume of distribution) and CL (clearance) are constants that reflect drug disposition in an individual. The symbol dose is also a model constant. In contrast to V and CL, the value of dose is under experimental control and is part of the design of a clinical trial. It is helpful to refer to such controllable experimental factors as *properties* to distinguish them from uncontrollable factors such as V and CL that are usually understood as the *parameters* of the model. In a more general sense all constants of the model are parameters.

$$C(t) = \frac{Dose}{V} \bullet \exp\left(-\frac{CL}{V} \bullet t\right)$$ Equation 1

3.2.   IO Model Hierarchy

IO models can be ordered in a hierarchy that make predictions about populations, groups, individuals and observations. Each level of model is dependent on its predecessor. The simplest IO model is at the population level and the most complex is at the level of an observation. It is the observation IO model prediction that is the foundation of clinical trial simulation.

3.3. *Population IO Model*

The predictions of IO models that do not account for either systematic or apparently random differences between individuals are referred to here as population IO models[1].

3.3.1. Population Parameter Model

Population models are based on parameter values that represent the population. They may have been estimated without consideration of covariates such as weight, etc. and simply reflect the characteristics of the observed population. These parameters can be considered naive population parameters (e.g. Vpop, CLpop).

For the purposes of comparing population parameters obtained from different studies population parameters need to be standardized to a common set of covariates [3], e.g., male, weight 70 kg, age 40 years, creatinine clearance 6 L/h. Standardized population parameter values can be estimated using group IO models (see below) and should be distinguished from naive population parameters. All examples shown below refer to standardized parameters e.g. Vstd, CLstd in Equation 2.

3.3.2. Population IO Model Simulation

Equation 2 illustrates the use of population standardized parameters for population IO model simulation. A population IO model simulation based on this equation is shown in Figure 1.

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[1] Others may use this term to encompass a model including what are defined below as group IO, individual IO and observation IO models. However, it seems clearer to define the model based on the source of its parameters.

Equation 2

$$Cpop(t) = \frac{Dose}{Vstd} \bullet \exp\left(-\frac{CLstd}{Vstd} \bullet t\right)$$

3.4. *Group IO Model*

The group IO model is used to simulate non-stochastic variation in the model predictions. Statisticians refer to a model for this kind of variation as a fixed effects model. Note that "effects" has nothing to do with pharmacological drug effects. It is a statistical term referring to a source of variability. The group IO model uses the same functional form as the population IO model but, instead of population parameters, group parameters are used.

3.4.1. Group Parameter Model

If the covariate distribution model includes values that distinguish individuals, e.g., weight, then the model parameters can be predicted from that particular combination of covariate values. Equation 3 to Equation 8 illustrate models that could be used to predict values of V and CL with a particular weight or age. These predicted parameters are typical of individuals with that weight or age and are sometimes known as the typical value parameters but are more clearly identified as group parameters, Vgrp and CLgrp, because they are representative of a group with similar covariates. The group parameter model includes the population parameter and usually a constant that standardizes the population parameter (Wtstd, Agestd). These normalizing constants may reflect a central

tendency for the covariate in the population, e.g. the median weight, or a standard value[3] e.g. 70 kg. Other parameters in the typical parameter model relating age to Vgrp and CLgrp may be theoretical constants such as the exponents in allometric models (Equation 3, Equation 4), or may be empirical parameters, such as $Fage_V$, $Fage_{CL}$, of a linear model (Equation 5, Equation 6). An exponential model may be a more robust empirical model than the linear model for many models because the prediction is always positive (Equation 7, Equation 8). $Kage_V$ and $Kage_{CL}$ are parameters of the exponential model that are approximately the fractional change in the parameter per unit change in the covariate value.

$$Vgrp = Vstd \bullet \left(\frac{Wt}{Wtstd} \right)^1 \qquad \text{Equation 3}$$

$$CLgrp = CLstd \bullet \left(\frac{Wt}{Wtstd} \right)^{3/4} \qquad \text{Equation 4}$$

$$Vgrp = Vstd \bullet \left(1 + Fage_V \bullet \left(Age - Agestd\right)\right) \qquad \text{Equation 5}$$

$$CLgrp = CLstd \bullet \left(1 + Fage_{CL} \bullet \left(Age - Agestd\right)\right) \qquad \text{Equation 6}$$

$$Vgrp = Vstd \bullet \exp\left(Kage_V \bullet \left(Age - Agestd\right)\right) \qquad \text{Equation 7}$$

$$CLgrp = CLstd \bullet \exp\left(Kage_{CL} \bullet \left(Age - Agestd\right)\right) \qquad \text{Equation 8}$$

3.4.1.3. Additive and Proportional Fixed Effects Models for Group Parameters

When there is more than one covariate influencing the value of a group parameter the effects may be combined in a variety of ways. If there is no mechanistic guidance for

how to combine the covariate effects (the usual case) there are 2 empirical approaches that are widely used.

3.4.1.2.Additive

The additive model requires a parameter, Swt_V, to scale the weight function predictions and a second parameter, $Sage_V$, similar in function to the parameter, $Fage_V$ (Equation 5), but scaled in the units of V rather than as a dimensionless fraction. Equation 9 illustrates the additive model using weight and age fixed effect models.

$$Vgrp = Swt_V \bullet \left(\frac{Wt}{Wtstd}\right)^1 + Sage_V \bullet (Age - Agestd) \qquad \text{Equation 9}$$

3.4.1.3.Multiplicative

The multiplicative model combines Equation 3 and Equation 5 so that Vstd retains a meaning similar to that in the population model (Equation 2) i.e. the group value of volume of distribution when weight equals Wtstd and age equals Agestd will be the same as the population standard value and similar to the naïve population value (Vpop) obtained when weight and age are not explicitly considered. It is usually more convenient to use the multiplicative form of the model because it can be readily extended when new covariates are introduced without having to change the other components of the model or their parameter values. Equation 10 illustrates the multiplicative model using weight and age fixed effect models.

$$Vgrp = Vstd \bullet \left(\frac{Wt}{Wtstd}\right)^1 \bullet (1 + Fage_V \bullet (Age - Agestd)) \qquad \text{Equation 10}$$

3.4.2. Group IO Model Simulation

Examples of group IO model simulations with systematic changes in both weight and age are shown in Figure 2. The group model (Equation 11) applies Equation 10 for Vgrp and a similar expression for CLgrp (based on Equation 4 and Equation 8).

$$Cgrp(t) = \frac{Dose}{Vgrp} \bullet \exp\left(-\frac{CLgrp}{Vgrp} \bullet t\right)$$

Equation 11

3.5.   Individual IO Model

3.5.1. Individual Parameter Model

Individual parameter values are simulated using a fixed effects model for the group parameter and a random effects model to account for stochastic variation in the group values. The random effects model samples a value η_i (where the subscript "i" refers to an in individual) typically from a normal distribution with mean 0 and variability PPV (population parameter variability) (Equation 12).

$$\eta_i \sim N(0, PPV)$$

Equation 12

η_i is then combined with the group parameter model to predict an individual value of the parameter, Cl_i (Equation 13).

$$CL_i = CLgrp + \eta_i$$

Equation 13

11

The η_i can come from a univariate or multivariate distribution. Multivariate distributions recognize the covariance between parameters and the importance of this is discussed in Section 5.2.

3.5.1.3.Fixed Effect Models for Random Individual Parameters

There are two main sources of random variation in individual parameter values. The first is between subject variability (BSV) and the second is within subject variability (WSV)[4, 5]. Within subject variability of an individual parameter may be estimated using a model involving an occasion variable as a covariate. The variability from occasion to occasion in a parameter is known as between occasion variability (BOV). BOV is an identifiable component of WSV that relies on observing an individual on different occasions during which the parameter of interest can be estimated. Variability within an occasion e.g. a dosing interval, is much harder to characterise so from a practical viewpoint WSV is simulated using BOV. Other covariates may be used to distinguish fixed effect differences e.g. WSV may be larger in the elderly compared with younger adults.

The total variability from both these sources may be predicted by adding the η values from each source (Equation 22). Representative values of BSV and WSV for clearance are 0.3 and 0.25, respectively [6].

$$\eta BSV_i \sim N(0, BSV) \hspace{3cm} \text{Equation 14}$$

$$\eta WSV_i \sim N(0, WSV)$$ Equation 15

$$\eta PPV_i = \eta BSV_i + \eta WSV_i$$ Equation 16

3.5.1.3. Additive and Proportional Random Effects Models for Individual

Parameters

Both additive (Equation 13) and proportional (Equation 17) models may be used with η_i. The proportional model is used more commonly because PPV approximates the coefficient of variation of the distribution of η. Because estimates of PPV are difficult to obtain precisely it is often convenient to use a value based on an approximate coefficient of variation e.g. a representative PPV might be 0.5 for clearance (approximately 50% CV).

$$CL_i = CLgrp \bullet \exp(\eta_i)$$ Equation 17

3.5.2. Individual IO Model Simulation

An example of individual IO model simulation is shown in Figure 3 based on Equation 18. The figure illustrates the changes in concentration profile that might be expected using random variability from a covariate distribution model for weight and age (PPV=0.3) and a parameter distribution model for V and CL (PPV=0.5) (Table 1).

$$C_i(t) = \frac{Dose}{V_i} \bullet \exp\left(-\frac{CL_i}{V_i} \bullet t\right)$$ Equation 18

3.6.   *Observation IO Model*

The final level of the IO model hierarchy is used to predict observations. Observation values are simulated using individual IO model predictions and a random effects model to account for stochastic variation in the observation values.

3.6.1. Observation Parameter Model

The random effects model samples a value ε_j (the subscript "j" is enumerated across all individuals and observations) typically from a normal distribution with mean 0 and variability RUV (random unidentified variability) (Equation 19).

$$\varepsilon_j \sim N(0, RUV) \hspace{3cm} \text{Equation 19}$$

ε_j is combined with the individual IO model to predict the observation. Common models include additive (Equation 20), proportional (Equation 21) and combined (Equation 22). The combined model most closely resembles the usual residual variability when pharmacokinetic models are used to describe concentration measurements.

3.6.1.3.Additive

$$C_{i,j}(t) = C_i(t) + \varepsilon_{i,j} \hspace{3cm} \text{Equation 20}$$

3.6.1.3.Proportional

$$C_{i,j}(t) = C_i(t) \bullet \exp(\varepsilon prop_{i,j}) \hspace{2cm} \text{Equation 21}$$

3.6.1.3.Combined

$$C_{i,j}(t) = C_i(t) \bullet \exp(\varepsilon prop_{i,j}) + \varepsilon add_{i,j}$$

Equation 22

3.6.2. Observation IO Model Simulation

An example of an observation IO model simulation is shown in Figure 4. Random variability in the observations was generated using a mixed additive (RUVsd=0.05 mg/L) and proportional (RUVcv=0.2) residual variability model.

Simulated observations less than the lower limit of quantitation (0.05 mg/L) are shown as open symbols in Figure 4. These observations would not be included in the analysis of this simulation. The removal of observations in this manner is an example of the application of an execution model. The IO model predicts the observation but the execution model reflects local policy for removal of observations that are classified as unquantifiable.

4. Sensitivity Analysis

A clinical trial simulation experiment should include an evaluation of how the conclusions of the simulation experiment vary with assumptions made about the models and their parameters (see Chapter 4.2 for more details). The nature of this sensitivity analysis will depend on the objectives of the simulation. If the objective is to determine the power of a confirming type trial then the sensitivity of the predicted power of a trial

design should be examined. Repeating the simulations with a different model e.g. a linear instead of an Emax pharmacodynamic model may do this. One may also examine the influence of the model parameters e.g. changing the EC50 of an Emax model. The extent to which the power of the trial varies under these different scenarios of models and parameters is a key focus of a sensitivity analysis.

5. Parameters

5.1. Source

There are 3 sources of model parameters for clinical trial simulation.

5.1.1. Theory

Theoretical values are usually not controversial but there is still not widespread acceptance of the allometric exponent values for clearance and volume of distribution that are suggested by the work of West et al. [7, 8].

5.1.2. Estimates from data

The most common source will be estimates from prior analysis of data. Inevitably it will be necessary to assume that parameter estimates obtained in a different population are suitable for the proposed clinical trial that is being simulated (see Chapter 2.4). It is particularly valuable to have standard, rather than naïve, population parameter estimates so that they can be coupled with a covariate distribution model in order to extrapolate to a population that has not yet been studied.

5.1.3. Informed guesses

Informed guesses are always a necessary part of a clinical trial simulation. For example, the size of a treatment effect will have to be assumed and the model performance modified by suitable adjustment of dosing and parameters in order to mimic an outcome of the expected magnitude.

5.2.   Covariance

It is important to retain information about the covariance of individual IO model parameters in order to obtain plausible sets of parameters. While some covariance between parameters may be included in the simulation via the group IO model, e.g. if weight is used to predict Vgrp and CLgrp, there is usually further random covariance which cannot be explained by a model using a covariate such as weight to predict the group parameter value.

The need to include parameter covariance in the model is especially important for simulation. It can often be ignored when models are applied to estimate parameters for descriptive purposes but if it exists and it is not included in a simulation then the simulated observations may have properties very different from the underlying reality. For example, if clearance and volume are highly correlated then the variability of half-life will be much smaller than if the clearance and volume were independent.

The methods for obtaining samples of parameters from multivariate distributions are the same as those used for obtaining covariates (see Chapter 2.2). They may be drawn from

parametric distributions e.g. normal or log normal, or from an empirical distribution if there is sufficiently large prior population with adequate parameter estimates.

5.3. Posterior Distribution of Parameters

It is worth remembering that point estimates of parameters will have some associated uncertainty. It is possible to incorporate this uncertainty by using samples from the posterior distribution of the model parameter estimates rather than the point estimate. For instance, if clearance has been estimated and a standard error of the estimate is known then the population clearance used to predict the group clearance could be sampled from a distribution using the point estimate and its standard error.

5.4. Parameterisation

The choice of parameterisation of a model is often a matter of convenience. A one-compartment disposition model with bolus input may be described using Equation 23 or Equation 24. The predictions of these models, with appropriate parameters, will be identical.

$$C(t) = \frac{Dose}{V} \bullet \exp\left(-\frac{CL}{V} \bullet t\right)$$
<div style="text-align:right">Equation 23</div>

$$C(t) = A \bullet \exp(-\alpha \bullet t)$$
<div style="text-align:right">Equation 24</div>

The apparent simplicity of Equation 24 may be appealing but it hides important features when applied to clinical trial simulation. An explicit value for the dose is not visible and doses are essential for clinical trials of drugs. The rate constant, α, appears to be independent of the parameter A, but when it is understood that both A and α are functions of volume of distribution it is clear that this population level interpretation of independence is mistaken. Finally, because clearance and volume may vary differently as a function of some covariate such as weight (see Equation 3, Equation 4) the value of α will vary differently at the group and individual level from the way that A differs.

If the model parameterisation corresponds as closely as practical to biological structure and function then the interaction between different components of the model is more likely to resemble reality.

6. Conclusion

The input-output model brings together the warp of scientific knowledge and weaves it with weft of scientific ignorance. The art of combining signal with noise is the key to successfully simulating the outcome of a clinical trial and to honestly appreciating that the future cannot be fully predicted.

7. References

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and allometric scaling of organisms. Science 1999;284(5420):1677-9.

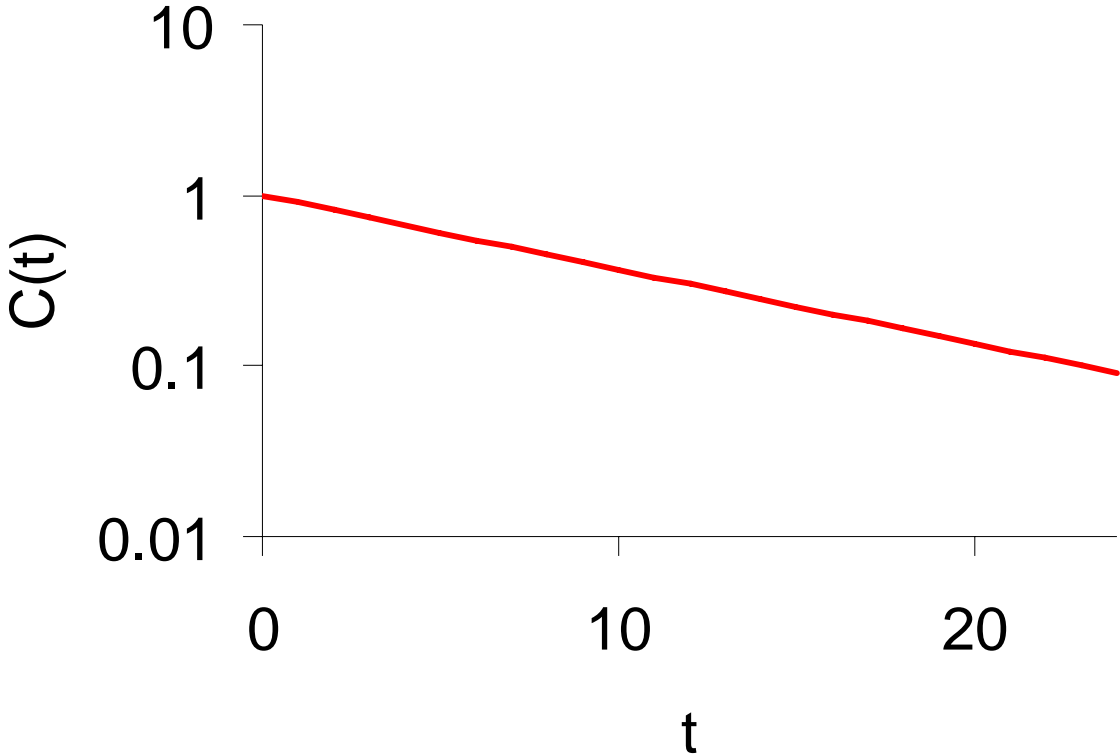**Figure 1 Population IO Simulation: Solid line is population IO model prediction.**

Figure 2 Group IO Simulation: SystematicVariability in Two Covariates (Weight,Age) . Solid line is population IO model prediction. Dashed lines are group IO model predictions
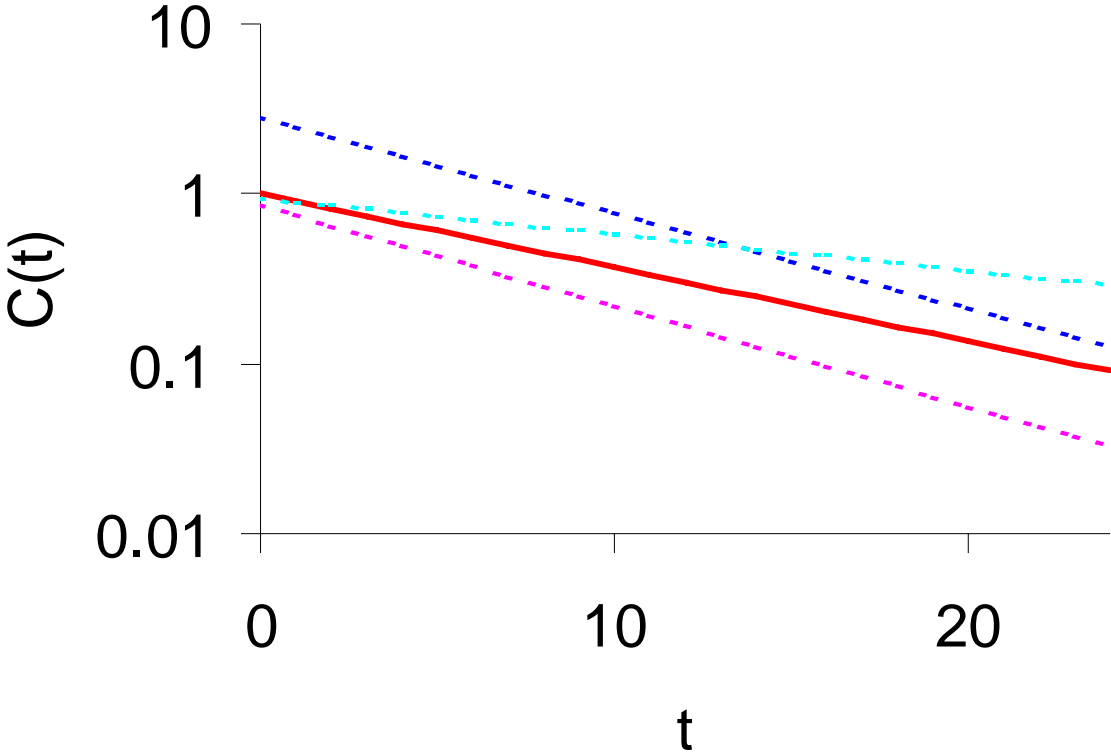
Figure 3 Individual IO Simulation: RandomVariability in Covariates (Weight, Age) and Group Parameters (V,CL) . Solid line is population IO model prediction. Dashed lines are individual IO model predictions
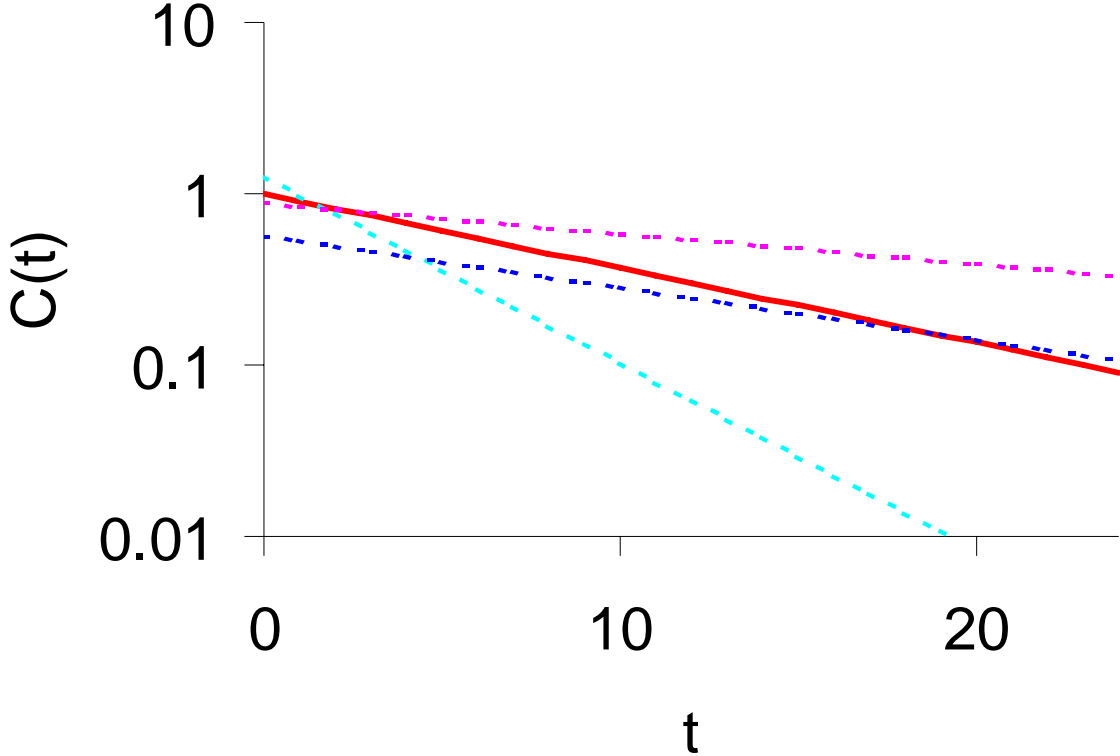
Figure 4 Observation IO Simulation: RandomVariability in Covariates (Weight, Age), Group Parameters (V,CL), and Residual Unexplained Variability (Additive,Proportional) . Solid line is population IO model prediction. Dotted line is individual IO model prediction. Symbols are observation IO model predictions. Filled symbols are execution model predictions which will be used for data analysis.
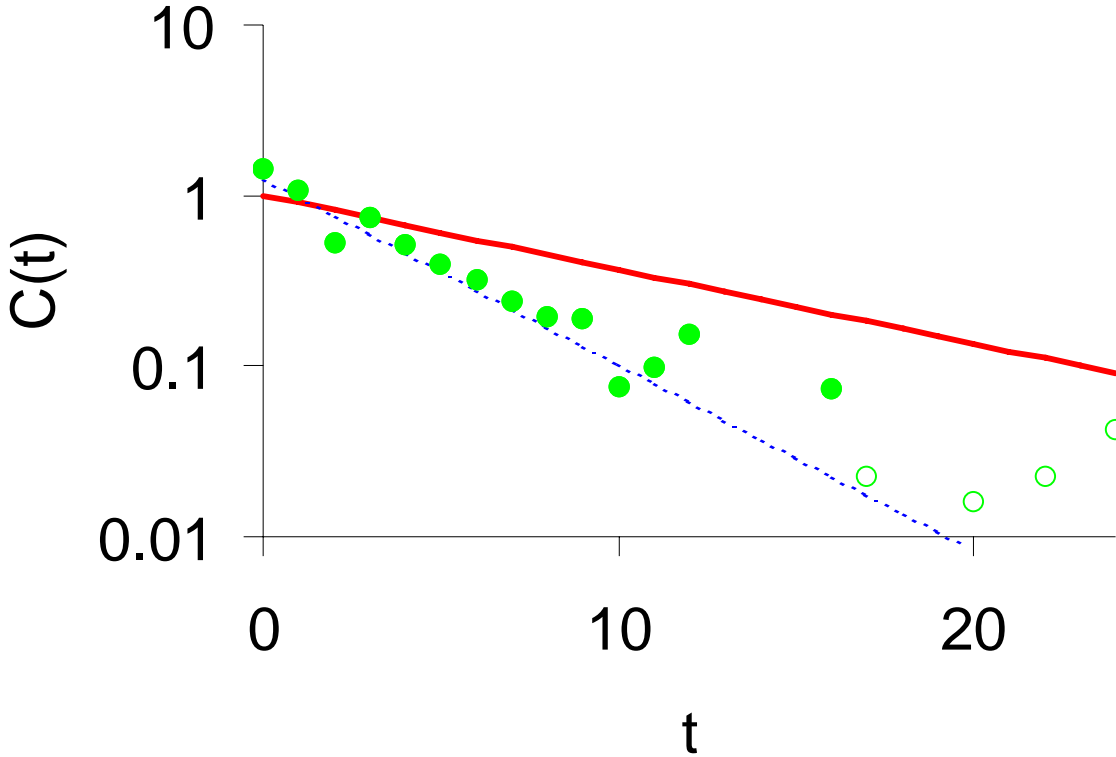
Model	Level	Name	Value	Units	Description
Covariate Distribution	Population	WTstd	70	kg	Standard weight
		AGEstd	40	y	Standard age
	Individual	PPVwt	0.3		Population parameter variability for Weight
		PPVage	0.3		Population parameter variability for Age
Input Output	Population	Dose	100	mg	Dose
		Vstd	100	L	Volume of distribution
		CLstd	10	L/h	Clearance
	Group	Kagev	0.01	h^{-1}	Age and volume of distribution factor
		Kagecl	-0.01	h^{-1}	Age and clearance factor
	Individual	PPVv	0.5		Population parameter variability for Volume
		PPVcl	0.5		Population parameter variability for Clearance
	Observation	RUVsd	0.05	mg/L	Residual unexplained variability Additive
		RUVcv	0.2		Residual unexplained variability Proportional
Execution	Observation	LLQ	0.05	mg/L	Lower Limit of Quantitation

Table 1 Simulation Model Parameters[2]

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[2] Simulations illustrated in this chapter were performed using Microsoft Excel. A workbook file is available

http://www.phm.auckland.ac.nz/Courses/PHARMCOL.716/pgio.xls.