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A Brief Introduction to Monte Carlo Simulation

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Abstract

Simulation affects our life every day through our interactions with the automobile, airline and entertainment industries, just to name a few. The use of simulation in drug development is relatively new, but its use is increasing in relation to the speed at which modern computers run. One well known example of simulation in drug development is molecular modelling. Another use of simulation that is being seen recently in drug development is Monte Carlo simulation of clinical trials. Monte Carlo simulation differs from traditional simulation in that the model parameters are treated as stochastic or random variables, rather than as fixed values. The purpose of this paper is to provide a brief introduction to Monte Carlo simulation methods.

Computer simulation in the pharmaceutical industry is used in the discovery of new drugs, in optimising chemical processes, and, most recently, in designing clinical studies. What most people think of as 'simulation' are models that build or design physical 'things'. Examples of this type of simulation include the use of computer-assisted design (CAD) technology in designing a commercial product, such as a car or aeroplane, or the molecular modelling of drug-receptor interactions. Often with this class of simulations, the term 'modelling' is used interchangeably, for example molecular modelling. For our purposes, models will be differentiated from simulations in that models are built on data and look back in time, whereas simulations build on models and look forward in time. Another class of simulations is the so-called 'man in the box' simulation, like a flight simulator. In all cases, the computer, and its ability to do rapid numerical calculations, is essential.

The purpose of this paper is not to review those simulations designed to imitate the real world and build things, but to provide a brief introduction to the class of simulations that use mathematical models of a system, which may include physical processes, events or decision-making processes, which describe the behaviour of the system over extended periods of time and incorporate stochastic or random variability into the model. This class of simulation is used to make decisions, understand complex systems, and to solve problems for which no closed form solution exists.

In 1979, the Society for Computer Simulation[1] presented a framework for computer simulations (fig. 1). Under this framework, a real-world problem is first identified and then converted to a conceptual model, which for our purposes will be defined as an abstraction of a real system containing inputs and outputs of which the model inputs are predictive with the observed outputs. Ideally, the model is defined using a mechanistic basis and validated using observational data, but neither has to necessarily occur. Models have the advantage in that they allow greater understanding of processes and systems, yet allow the user to manipulate the inputs to examine the outputs. Computer simulations use mod-

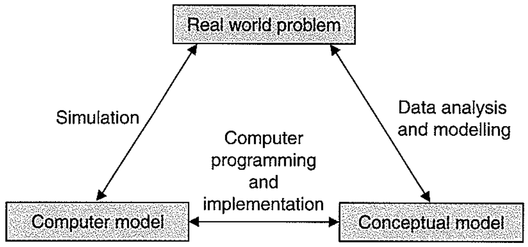
Real world problem
Simulation
Data analysis and modelling
Computer programming and implementation
Computer model
Conceptual model

Fig. 1. Framework for computer simulation (modified from the Society for Computer Simulation Technical Committee on Model Credibility[1]).

els such that for any given set of inputs or model parameters, an outcome, or prediction of some event, is observed. The models in question can be deterministic, in which all the inputs are fixed, or stochastic, in which some or all the model parameters have some degree of random variability associated with them. As pointed out by one of the reviewers, stochastic elements in a model tend to reflect real-world phenomena, whereas models without stochastic properties tend to reflect ignorance of the system and result in simulations for which there is no uncertainty in the outcome. An example of a deterministic simulation is using the mean pharmacokinetic parameters from a single-dose phase I study to predict drug concentrations after multiple doses.

Models, and hence simulations, can be further delineated into discrete event or real-time simulations. Discrete event simulations model a system over time such that the variables change instantaneously at points in time. An example of this is where the triggering of an adverse reaction occurs when plasma concentrations reach a threshold limit. Real-time simulations, which are more often than not what are seen in clinical trial simulation, model systems where the system changes incrementally over time. Of course, some simulations may be a combination of discrete event and real-time.

Monte Carlo simulation is the term applied to stochastic simulations, either discrete, real-time, or some combination thereof, that incorporate random variability into the model. The term 'Monte Carlo' was first coined by Ulam and von Neumann[2] during their work on development of the atomic bomb during World War II and was a reference to the gaming city in Monaco. In order to perform Monte Carlo simulation, the sampling distribution of the model parameters (inputs) must be defined *a priori*, for example a normal distribution with mean μ and variance σ^2. Monte Carlo simulation repeatedly simulates the model, each time drawing a different random set of values (inputs) from the sampling distribution of the model parameters, the result of which is a set of possible outcomes (outputs).

1. Defining the Model

There are a number of considerations in defining any simulation. A very useful document which describes these considerations and 'Best Simulation Practices' related to drug development can be found in Holford et al.[3] For illustration, what will follow will relate to clinical trial simulation (table I).

First, the underlying structural pharmacokinetic model must be defined, for example, a 2-compartment open model with first order absorption, along with the distribution and covariance between the pharmacokinetic parameters in the model, for example clearance is log-normal with mean 75 L/h and a coefficient of variation of 15%. The usual source for this information is the result of a population pharmacokinetic analysis where an underlying structural pharmacokinetic model has been established and an assessment of the distribution

Table I. Some of the components to be defined in a clinical trial simulation

Structural pharmacokinetic model
Dose administration model
Compliance model
Distribution and covariance of pharmacokinetic parameters
Link between pharmacokinetics and pharmacodynamics
Pharmacodynamic model
Distribution and covariance of pharmacodynamic parameters
Disease progression model
Relationship between pharmacodynamic effect and outcome
Measurement error model for pharmacokinetics, pharmacodynamics, and/or outcome
Survival model

and inter- and intra-individual variability of a set of pharmacokinetic parameters has been defined.

Next a dose administration model and a compliance model must be defined, for example 95% of the patients take their dose of 10mg as scheduled, once daily in the evening; 3% of the patients skip a dose, of which 50% take 2 doses (20mg) the next time. Dose administration is typically fixed or changes according to some decision rule defined in the study protocol. Compliance models are far more difficult to develop, since the reason why people are noncompliant is largely unknown and, more often than not, they are random events with no apparent underlying structure. As such, there are few published mathematical models of drug compliance.[4,5] For some simulations, however, especially those that are interested solely in pharmacokinetic outcomes, these conditions may be sufficient to define the simulation in its entirety.

If a pharmacokinetic-pharmacodynamic link can be established, then simulations of greater complexity can be developed. For example, it may be of interest to determine what percentage of individuals for a given dosage regimen will show more than 80% ion channel inhibition based on *in vitro* pharmacodynamic models. In such a case, a model for the link between pharmacokinetics and pharmacodynamics must be developed, i.e. effect compartment, indirect response model, etc. Then the pharmacodynamic model itself, along with its pharmacodynamic parameters, must be defined. Simulations of even greater complexity can be developed using underlying disease progression models[6] or models that relate pharmacodynamic biomarkers to outcomes.

Knowing the system, its input parameters, and their distributional properties is crucial in any simulation. Defining the distribution of the system inputs is probably the most challenging step in a simulation because of the lack of knowledge. Obviously, specifying the distribution of a random variable in the absence of prior knowledge may represent a weak link in any simulation. Sometimes, scientists use their or others' 'expert' knowledge to generate distributions and what they consider to be typical variability for a random variable. Good simulation practices dictate that in the absence of knowledge those variables that are defined in the absence of actual data should be identified in any report or technical document. However, simply because the distributional properties of a random variable, which are unknown, are created from expert knowledge, and used in a simulation, does not necessarily invalidate the simulation results because some variables are more important than others and the random variate in question may have little impact on the overall outcome. This may be confirmed by a sensitivity analysis where the results are compared with alternative distributions for the random variable of unknown distribution.

2. Running the Simulation

Once the conceptual model is defined, the model needs to be translated to computer code. Often, early simulations were written using a generic programming language, such as BASIC or FORTRAN. Later, simulations were written using higher level programming languages, such as MATLAB or GAUSS, which vectorise the operations for the programmer, thereby simplifying the programming task. Recently, software programs designed specifically for simulation with graphical user interfaces, such as MATLAB Simulink or the Pharsight Trial Designer, became available, further simplifying the programming task. Once the model is translated to computer code, it is imperative that verification be done on the code to ensure accuracy in the translation. When verification is poorly done or not done at all, the results may be dramatic. Who will forget that the Mars Probe launched by the National Aeronautics and Space Administration crashed into Mars in 1999 because the scientists did not convert from English to metric measurements in their computer code?

Once the model is translated to computer code and verified for accuracy, the simulation needs to be run. There are really only 3 issues related to the running of a Monte Carlo simulation on a computer. First, the number of replications of the simulation must be defined. Should 50 replications or

50 000 replications be used? If the goal of the analysis is to generate estimates of the mean output, then a small number, usually less than 100, is sufficient. If, however, the goal is to observe the variability of an outcome, then many simulations, usually in the thousands, must be performed since rare events happen rarely and in order to quantify a sufficient number of such events, a large number of observations must be collected.

Second, and this issue is intimately tied to the first issue, is the actual time it takes for the simulation to run and the demands the simulations place on the CPU of the computer. The greater the number of replications, the longer the run-time of the simulation and the greater the demand on the processor in terms of memory and speed. Indeed, some simulations may require a dedicated computer or supercomputer.

The last issue in regard to running a simulation relates to the random number generator (RNG), and this is considered in more detail in section 3.

3. Random Number Generation

The underlying basis for Monte Carlo simulation is the ability to generate a sequence of independent random numbers having a given distribution with finite mean and variance. What many may not realise is that a computer does not exactly generate a random number, but generates a pseudorandom number using a software-specific algorithm. If a user starts a stream of random numbers at a specific point in the algorithm, and later on starts another stream of random numbers from the same point, both streams of numbers will be exactly the same. This starting point is called the seed and should be reported in all simulation reports. Also, random variates from any statistical distribution arise from a uniform distribution and are then transformed into the needed distribution. As an example, a common method to generate random variables from a normal distribution is the Box-Muller transformation.[7] If U_1 and U_2 are uniform random variates on the interval (0,1), then the variates Z_1 and Z_2

$$Z_1 = \sqrt{-2} \cdot \ln(U_1) \cos(2\pi U_2) \qquad \text{(eq. 1)}$$

$$Z_2 = \sqrt{-2} \cdot \ln(U_1) \sin(2\pi U_2) \qquad \text{(eq. 2)}$$

are independent standard normal deviates with mean 0 and variance 1. To generate 2 random variables, X_1 and X_2, with mean μ and variance σ^2, Z_1 and Z_2 are transformed using:

$$X_1 = \mu + Z_1\sigma \qquad \text{(eq. 3)}$$

$$X_2 = \mu + Z_2\sigma \qquad \text{(eq. 4)}$$

So, in order to generate standard normal variates (or any other distribution for that matter), one must first generate random uniform numbers. Note that in this instance, there is a 1 : 1 correspondence between the number of uniform random numbers generated and the number of standard normal random numbers generated. For some distributions, such as a Chi-square, γ or Weibull distribution, more than one uniform random number will be needed to generate a single random deviate from the desired distribution.

If a computer software package cannot generate random uniform numbers, then it cannot generate random variates from other distributions. Press et al.[8] state that most commercial RNGs should not be trusted and if the number of published simulations that used bad RNGs were pulled from library shelves, it would remove a block of research 'the size of a fist'. Just because a software package has a reputable and recognised name does not mean its RNG is any good. For example, McCullough[9,10] has shown that although the RNGs in SAS version 6.12 for Windows® (SAS Institute Inc., Cary, NC, USA) and SPSS version 7.5 (SPSS Inc., Chicago, IL, USA) both pass overall tests for randomness, the RNG in S-Plus version 4.5 (Mathsoft, Seattle, WA, USA) does not. It should be pointed out, however, that the studies challenging the overall randomness of RNGs are quite theoretical and involve examining millions of numbers. There have been no studies in the applied literature that have shown exactly how results obtained with a 'good' RNG differ from those obtained with a 'poor' RNG. Nevertheless, caution should be applied in using a RNG of poor quality, especially with simulations involving large numbers of calls to the RNG.

As a consequence of the large number of random numbers that are generated during any Monte Carlo simulation, the issue of random number burn-out must be considered. All RNGs have a limited period, in that eventually the stream of random numbers will cycle. Thus, Simulation 1 may be correlated with Simulation 994, Simulation 2 correlated with Simulation 995, etc., the result being that each iteration of the simulation is no longer independent of the other iterations. Many algorithms have a period of $2^{31}–1$ (about 2 billion numbers) since most computers are 32-bit computers. This means that after generating $2^{31}–1$ random numbers, the set of random numbers will begin again and start recycling.

But is this really important? Theoretically it is. Consider a simulation of a clinical trial where the pharmacokinetics and pharmacodynamics of a drug are characterised in 2 groups of 1000 patients, one group assigned to drug, the other to placebo. This is illustrated in figure 2. If we simulate the pharmacokinetics of the drug using a 1-compartment open model, we need to generate 1000 random numbers for clearance, 1000 for apparent volume of distribution, and 1000 for absorption rate constant. We will also assume that clearance is a function of age, so that 1000 random numbers are generated for the population receiving active treatment. We will assume that compliance is approximately 98% but that administration occurs at exactly the same time every day. Hence, 1000 random numbers are needed for the compliance model. Given the pharmacokinetic profile, the pharmacodynamic end-point is simulated using a maximum effect (E_{max}) model with trough drug concentrations as the dependent variable. First, 1000 random numbers each for the baseline activity of the drug and placebo groups and 2000 random numbers for measurement error in the active and placebo groups are simulated. After 7 days of treatment, the pharmacodynamic endpoint is again assessed. For the E_{max} model, 1000 random numbers for E_{max} and 1000 random numbers for EC_{50} are needed to simulate the effect at end-study in the active treated group. Assuming no intra-occasion variability in the pharmacodynamic end-point, only measurement error for the 2 groups needs to be simulated (2000 random numbers). Thus for each simulation

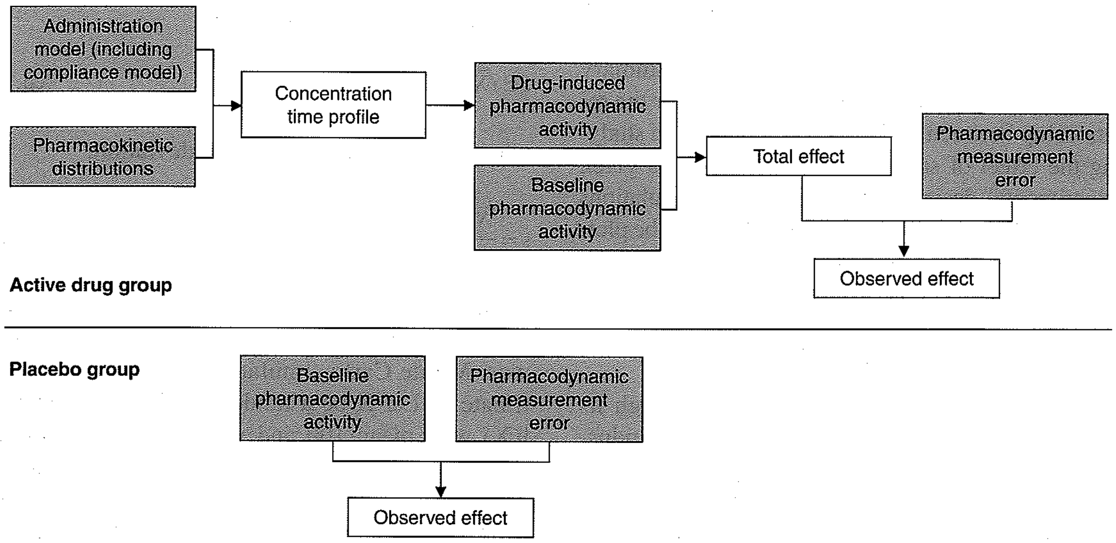
Administration model (including compliance model)
Pharmacokinetic distributions
Concentration time profile
Drug-induced pharmacodynamic activity
Baseline pharmacodynamic activity
Total effect
Pharmacodynamic measurement error
Observed effect
Active drug group
Placebo group
Baseline pharmacodynamic activity
Pharmacodynamic measurement error
Observed effect

Fig. 2. Simplified block model of a phase III clinical trial comparing pharmacodynamic end-point of drug and placebo at end-study. Shaded boxes denote where random variables must be generated.

we need to generate 13 000 random variables (assuming a 1 : 1 correspondence between calls to the RNG and generation of the random variable in question). If this process is simulated 10 000 times, 130 million random numbers need to be generated, a number that represents 6% of the period of the RNG. This is a simple example. If many covariates need to be simulated using a software package with a period near 2^{31}, the resulting simulations may not have sufficient 'randomness' for validity.

A good RNG for simulation should have period of at least 2^{50}.[11] Some argue the number should be as high as 2^{100}. This example was provided to show how the results of a simulation are not only dependent on the model, but also on the underlying algorithms, some of which are never questioned by the user.

4. Output Formats

Once the inputs are defined and the simulation is performed, the outputs must be examined. Most simulation reports present 'typical' plots from a single replication, for example concentration-time profiles in a group of participants receiving a fixed dose from simulation 1. Also, since in most simulations a large number of outputs are collected, summarising the results across all simulations is crucial for presentation of the results to an outside audience. Usually, graphical results or summary statistics are used to summarise a variable or the relationship between variables. For example, in studying the effect of sample size on power for a given experimental design, the percentage of simulations rejecting the null hypothesis of no effect may be plotted against sample size or as a surface plot of power as a function of sample size and compliance.

5. Why Use Simulation?

Simulation is really nothing new, although its use is relatively new in the pharmaceutical industry. For years, statisticians have been using Monte Carlo simulation to find the standard error and sampling distribution of statistics for which parametric theory has no answer. There are a number of advantages to using simulation. First, simulation can provide answers where no analytical solution exists, whereas the converse is not true. Secondly, simulation is easier to understand by the layman than complex mathematical equations. It has been shown that students studying both analytical methods and simulation are more apt to get the correct answer using simulation than with the analytical methods.[12] In fact, there is a $US5000 dollar offer to anyone who can show the superiority of analytical methods over simulation methods, although no one has yet claimed the prize.[13] Currently, statisticians are using simulation to solve very complex problems, for example Markov Chain Monte Carlo.[14]

As a simple example, Monte Carlo simulation will be used to calculate the standard error of a statistic. It is common knowledge that if **X** is a vector of normally distributed random variables of size n having mean μ and variance σ^2, then an unbiased estimate of μ can be estimated by the maximum likelihood estimator $\overline{X}$, where:

$$\overline{X} = \frac{\sum_{i=1}^{n} X_i}{n} \quad . \qquad \text{(eq. 5)}$$

Parametric theory states that the precision or standard error of $\overline{X}$ is given by:

$$SE(\overline{X}) = \frac{s}{\sqrt{n}} \qquad \text{(eq. 6)}$$

where s is the sample standard deviation,

$$s = \frac{\sqrt{\sum_{n=1}^{n} (X_i - \overline{X})^2}}{n-1} \qquad \text{(eq. 7)}$$

Suppose that the analyst did not know what the parametric theory estimate for the standard error was. Monte Carlo simulation may be used to estimate it. Let **X** be a random variable distributed f(X) with mean 100 and variance 100. Theoretically, $\overline{X}$ computed from 25 draws from f(X) should have mean 100 and standard error 2.0. Using the Monte Carlo approach, a set of 25 random values from **X** is repeatedly drawn, the mean computed each time, and saved for further analysis. This process is repeated 10 000 times with the resulting histogram shown in figure 3.

The distribution is normally distributed with mean 100.0038 and standard deviation of 2.005. Thus, the standard deviation of the distribution of simulated values of $\overline{X}$ is equal to the theoretical standard error. Similarly, a (1–α) 100% confidence interval for $\overline{X}$ can be determined from the α/2 tails of the distribution.

Simulation is a truly powerful tool that has been shown to be of great merit in many industries, but a number of caveats need to be expressed. First, simulation is time consuming. Secondly, not all simulations will lead to useful results. The more information that is known about a drug, the greater the likelihood for success. Thirdly, it is unclear if simulation will speed drug development. Hence, simulation should be discriminately applied when the probability of success is high. Naylor et al.[15] present a variety of situations where simulation may be useful:

- It may not be possible to even do an experiment. Simulation may provide the outcome without the need to conduct an experiment.
- The system is so complex that it cannot be easily described by a set of mathematical equations. Simulation can be used to show how a set of inputs produces a series of outputs and which variables are important.
- It may be impossible for fiscal, time or practical restraints to perform a large number of validation experiments on a model, so a few key experiments will be chosen to obtain the maximum amount of information from each individual experiment.
- Simulation may be used to answer 'what-if' questions about a system. What happens if we use 200 participants as opposed to 400? What happens if we collect data for 1 week as opposed to 6 weeks?

There are a number of very good books on Monte Carlo simulation, to which the reader is referred.[2,16,17] There are also a number of references with regard to simulation of clinical studies, notably Holford et al.[18] and Bonate.[19]

Despite the enthusiasm evidenced by the pharmaceutical industry for the potential role of Monte Carlo simulation of clinical trials or as a substitute for clinical and/or preclinical studies, it is unclear whether this enthusiasm is shared by regulatory agencies. The Holy Grail of clinical trial simulation is to submit a simulation in lieu of a phase III study and have it accepted by regulatory agencies. It is clear that at least the US Food and Drug Administration (FDA) supports the role of simulation

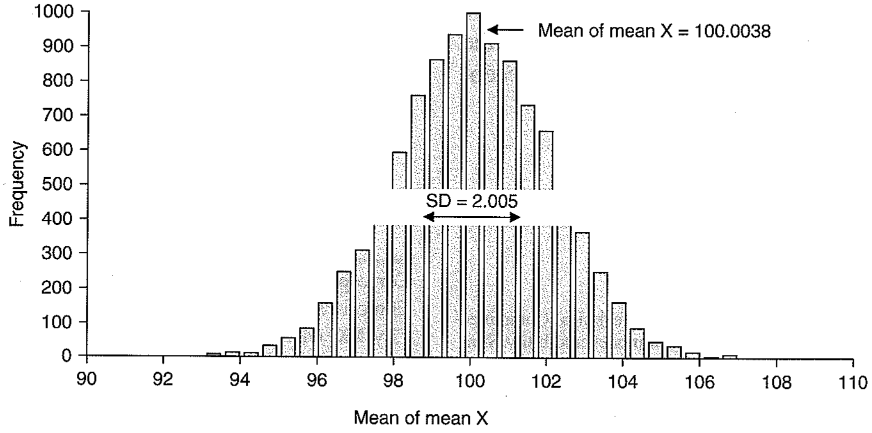

Fig. 3. Histogram of the means resulting from a Monte Carlo simulation where 25 random variates from a normal distribution with mean 100 and variance 100 were simulated 10 000 times. The mean was calculated on each iteration and is plotted here.

in the design of clinical studies,[20] but it is unclear to what extent they, or any other regulatory agency, are willing to accept simulation data in support of an New Drug Application. It should be noted that currently the FDA does have on staff recognised experts (within the Office of Pharmaceutical Science) who are qualified to review submissions containing simulation data, so they are cognisant of the issue and are preparing for it. Still, it is unclear to what extent Medical Reviewers would be willing to accept simulation data in lieu of actual data. Only time will tell in this regard.

6. Conclusions

Simulation is a very useful research tool that is only now being exploited by the pharmaceutical industry. Two types of simulation are seen in clinical research, deterministic and stochastic or Monte Carlo simulation. Stochastic simulation looks at the long term effect of random variability in the model parameters on the outcome of a model. Deterministic simulation is a special case of stochastic simulation where variability is set equal to zero. As such, there is only one possible outcome for a set of inputs. Monte Carlo simulation differs from deterministic simulation in that the variability of the model parameters is included in the model and the long term impact of that variability is examined. As such, there are many possible outcomes. Monte Carlo simulation is not new, but is new to the pharmaceutical industry, and the possibilities for its use are limited by lack of knowledge, the vision of the pharmaceutical industry, and acceptance by regulatory agencies.

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