

What's New in Simulation ?



Benoît Beck

Nearly Nothing

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What Do You Think ?

Clinical trial simulation : Bonate 1999

Application of old technologies, e.g., Monte Carlo simulation, to a new problem, i.e., to maximize the information content obtained during the drug development process with an intent to have the greatest chance of “success” in a clinical trial.

Possibility of reducing the number of required studies, maximizing the chances of success in a clinical trial, possibly shortening development time

All outcomes which will reduce drug development costs.

Not So New ...

Maxwell C, et al. 1971. Instant experience in clinical trials: a novel aid to teaching by simulation. J. Clin. Pharmacol.

So What ...

Overview / Review

History

Techniques

Pharma Applications

Improvement in the Formalism

Object-oriented language

More Efficient Implementations

Computer speed – parallelism

A lot of New Applications

Clinical trial simulation is one example

Perspectives on the Evolution of Simulation

Nance – Sargent

Operations Research – 2002

Category I

Objectives of the Simulation Study

System Analysis

Mimic behavior to understand/improve system performance

Education and Training

Understanding and application of concepts

Acquisition and system acceptance

Answer questions related to Does the system meet the requirement?

Research

Testing, Comparing systems components in an Artificial Environment

Entertainment

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Category II

Representation of Time and State

Monte Carlo Model

State sequencing but no explicit representation of time

Discrete Event Model

Specify state changes at discrete points in time

Continuous Simulation Model

States change as continuous over time

(often : discretized approximate solutions of differential equations)

Hybrid Simulation Model

Incorporate an analytical submodel within a discrete event model
(Shanthikumar and Sargent 1983)

Not so New

First Book about Simulation 1960

Tocher, K. D. 1963. The Art of Simulation.

Set of steps for Conducting a Study

- Problem formulation
- System data collection
- Conceptual model formulation
- Validation of the conceptual model
- Construction of the simulation program
- Execution of the simulation program
- Operational (results) validation
- Output data analysis
- Documentation

Simulation precedes Computers

Artificial sampling : a manual Monte Carlo method
Buffon to estimate Pi in a study documented in 1777.

Monte Carlo computations on electromechanical calculators 1950s

Computer Simulation began during World War II

Monte Carlo models - term introduced by von Neumann and Ulam during their top-secret work on the atomic bomb at Los Alamos as a reference to the gambling casinos in Monte Carlo

Evolution

1960 - A deck of 80-column (also called “IBM”) cards represented both program and data

The revolution in computer hardware : Mainframes 1960, minicomputer 1970, parallel processors 1980, Networks of processors 1990, the net ...

The incredible advances in computer hardware must be acknowledged as making simulation a viable problem-solving technique for some and the preferred technique for many

Advances in Computer Software : Machine Language representations 1950, assembly language mid 1950, Fortran late 1950, Smalltalk (object-oriented) 1980



Identified major deficiencies in computerized models – 1970

Sensitivity to good software engineering practices
a requirement for major simulation modeling efforts

Arguments were advanced that model representation should generate model documentation, and that the common consideration of documentation as an after-the-fact “activity” was a major detriment to effective use of the model

Other external factors that influenced computer simulation

Computer Graphics – Human-Computer Interaction – Computer Networks
(1970s MIT) – Nowadays Web/Cloud

- Model : Specific Formal Domain Specific Languages – Languages for the transaction (GPSS - 1980) and activity (CSL - 1970) + Graphical Assistance in model specification
- Simulation Functions : Random Number/Variable Generators – Congruential generators (Lehmer 1951) – L'écuyer (2001)
Time flow Mechanisms and Event List Management
- Verification and Validation : is the model actually representing the truthful behavior of the referent system? Place validation in a cost-risk framework - verification focuses on the activities in developing the model (“producing the model correctly”) and validation focuses on comparison of the model with the referent system (“producing the correct model”).
 - Analysis Methodology : Output Analysis (Statistical Approaches Bayesian/Bootstrap/jackknife) – Experimental Design and Comparison of Alternatives – Metamodels and Optimization -

Variance-Reduction Techniques

Variance reduction (or reducing) techniques (VRTs) received much attention in the early days of simulation since computer time was extremely expensive, and reductions in run time represented valuable savings

Parallel and Distributed Simulation

A series of conferences bearing the name PADS began in 1985

Book Review

Sheldon Ross – Simulation

1990 – 1997 – 2001 – 2006 – 2013

Probability – Random Discrete/Continuous
Number Generator – Discrete event simulation –
Statistical Analyses – Variance Reduction
Techniques – Statistical Validation Techniques –
Markov-chain-Monte-Carlo techniques

Book Review

Stochastic Simulation and Monte Carlo Methods Mathematical Foundations of Stochastic Simulation

Carl Graham – Denis Talay

- * Principles of Monte Carlo Methods

 - Strong Law of Large Numbers and Monte Carlo Methods

 - Non-asymptotic Error Estimates for Monte Carlo Methods

- * Exact and Approximate Simulation of Markov Processes

 - Poisson Processes as Particular Markov v Processes

 - Discrete-Space Markov Processes

 - Discretization of Stochastic Differential Equations

- * Variance Reduction, Girsanov's Theorem and Stochastic Algorithms

 - Variance Reduction and Stochastic Differential Equations

 - Stochastic Algorithms

Book Review

An Introduction to Statistical Computing a Simulation-based approach

Jochen Voss

Beyond Monte-Carlo
Approximate Bayesian Computation
Resampling Methods
Continuous-time models

Book Review

Handbook of Markov Chain Monte Carlo

Brooks – Gelman – Jones -Meng 2011

Reversible Jump MCMC

Optimal Proposal Distributions and Adaptive MCMC

MCMC Using Hamiltonian Dynamics

Inference from Simulations and Monitoring Convergence

Implementing MCMC : Estimating with Confidence

Perfection Within Reach : Exact MCMC Sampling

Spatial Point Processes

The Data Augmentation Algorithm: Theory and Methodology

Importance Sampling, Simulated Tempering, and Umbrella

Sampling

Likelihood-Free MCMC

Book Review

Handbook of Monte-Carlo Methods

Kroese – Taimre – Botev

Nearly Everything

New Techniques : Stochastic Differential Equations

Using Stochastic Differential Equations for PK/PD Model
Development - 2005

Non-Linear Mixed-Effects Models with Stochastic Differential
Equations: Implementation of an Estimation Algorithm - 2005

Predictive performance for population models using stochastic
differential equations applied on data from an oral glucose
tolerance test - 2010

Journal of Pharmacokinetics and Pharmacodynamics

New Techniques : ABC

The first ABC-related ideas date back to the 1980s. Rubin discussing the interpretation of Bayesian statements
Rubin DB (1984) Bayesian Justifiable and Relevant Frequency Calculations for the Applied Statistician

Inference for SDE models via Approximate Bayesian Computation
U. Picchini (2014)

Coupling Stochastic EM and Approximate Bayesian Computation for Parameter Inference in State-space models U. Picchini and A. Samson (2015)

Approximate Maximum Likelihood Estimation using Data-Cloning ABC - U. Picchini and R. Anderson (2015)

Applications

Monte Carlo Simulation for the Pharmaceutical Industry
Concepts, Algorithms, and Case Studies - Mark Chang - 2011

Meta-Simulation for the Pharmaceutical Industry
Macroeconomics – Health Economics and Pharmacoeconomics
Pharmaceutical Games – Multi-Players

Macro-Simulation : MDP for a Clinical Development Program
- Out-Licensing – Portfolio Optimization

Clinical Trial Simulations – Adaptive

Clinical Trial Management and Execution
Patient Recruitment and Projection – Randomization – Dynamic
and Adaptive Drug Supply

Applications

Prescription Drug Commercialization

Molecular Design and Simulation – Structure-Activity Relationship

Disease Modeling and Biological Pathway Simulation
Computational System Biology – Cellular Automata – Eq Diff –
Agent-based – Network – Petri Net

Pharmacokinetic Simulation
Pharmacodynamic Simulation
Enzyme Kinetics – PD (Emax) Models – Drug-Drug Interaction

Monte Carlo for Inference and Beyond
Resampling Methods