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Method “Monte Carlo” in healthcare

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Abstract

In public health, simulation modeling stands as an invaluable asset, enabling the evaluation of new systems without their physical implementation, experimentation with existing systems without operational adjustments, and testing system limits without real-world repercussions. In simulation modeling, the Monte Carlo method emerges as a powerful yet underutilized tool. Although the Monte Carlo method has not yet gained widespread prominence in healthcare, its technological capabilities hold promise for substantial cost reduction and risk mitigation. In this review article, we aimed to explore the transformative potential of the Monte Carlo method in healthcare contexts. We underscore the significance of experiential insights derived from simulated experimentation, especially in resource-constrained scenarios where time, financial constraints, and limited resources necessitate innovative and efficient approaches. As public health faces increasing challenges, incorporating the Monte Carlo method presents an opportunity for enhanced system construction, analysis, and evaluation.

Key Words: Monte Carlo; Simulation; Healthcare; Modeling; Decision analysis; Stochastic methods; Statistical techniques; Health economics

Core Tip: The potential of the Monte Carlo method in healthcare spreads across decision-making, risk analysis, and modeling in healthcare. Emphasizing versatility, the method navigates uncertainties, offering insights for optimal resource allocation, cost-effectiveness evaluations, and strategic planning in the healthcare domain. The Monte Carlo technique could be demystified through clear illustrations and real-world examples, empowering practitioners to harness its power for robust analyses, enhancing decision accuracy, and contributing to improved healthcare strategies and outcomes.

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INTRODUCTION

In recent years, the Monte Carlo method has emerged as a powerful and versatile tool in healthcare research, revolutionizing how we approach complex problems[1]. Originating from statistical physics, this computational technique is increasingly applied to model intricate healthcare scenarios, offering a sophisticated approach to decision-making and analysis[1].

Analytical modeling involves preparing and using simulation tools to solve real-world problems. Simulation is based on a large group of methods and applications for imitating the behavior of real systems, usually through a computer and appropriate software[2]. Computer simulation allows us to make a computer representation of a real system and to experiment with the computer version. In this way, the behavior of the real system in different situations can be better understood and predicted[2].

However, simulation is particularly valuable for solving problems that cannot be solved by analytical mathematical approaches and for problems that involve random variables[3].

There has been a growing interest in using simulation (imitation) models in various fields in the last few decades. In business, they are primarily used to support analysis and decision-making under conditions of uncertainty and risk[4]. One of the approaches to account for the uncertainty of the business environment, respectively the risk, when preparing calculations in the field of investment analysis, financial analysis, and a number of other areas of business analysis is the use of stochastic (probability) models. Stochastic models' input variables (key factors) are random variables whose behavior is beyond decision-makers control[4-6]. These models can also be successfully used in the field of healthcare.

The Monte Carlo method simulates various possible outcomes using random sampling and statistical analysis[7]. In healthcare, this methodology has proven invaluable in treatment planning, risk assessment, and resource allocation. For instance, in cancer treatment, Monte Carlo simulations enable the exploration of various radiation therapy scenarios, optimizing dose delivery and minimizing adverse effects[7].

Furthermore, Monte Carlo simulations find applications in health economics, helping researchers evaluate cost-effectiveness and assess the economic impact of different healthcare interventions[5]. The method's ability to account for uncertainties and variability makes it particularly useful when dealing with intricate, dynamic systems inherent in healthcare[8].

As we navigate the complexities of modern healthcare, the Monte Carlo method offers a unique and powerful approach to enhance decision-making processes and refine our understanding of intricate medical phenomena. This review aims to provide a comprehensive overview of the application and practical utility of the Monte Carlo method in healthcare, emphasizing its role in the applications, benefits, and potential pitfalls of employing it in healthcare research, including decision-making, risk analysis, and modeling. Moreover, the Monte Carlo approach could shed light on its transformative role in shaping the future of medical investigation and decision support systems.

SEARCHSTRATEGY

To conduct a thorough review, we employed a systematic search strategy across the main databases, including PubMed, Scopus, and Medline, from inception to 14 February 2024. The search utilized a combination of relevant keywords, such as "Monte Carlo method," "healthcare," "simulation," "decision analysis," "modeling," "stochastic methods," "statistical techniques," and "health economics." Boolean operators (AND, OR) were strategically applied to refine the search and capture the breadth of literature on applying the Monte Carlo method in healthcare settings. Additionally, reference lists of critical articles were manually scanned to ensure inclusiveness.

BASICSOF MONTE CARLO METHODOLOGY

Principles and concepts

The purpose of simulation is to simplify reality so that we can better understand it. Simulation is better than experiments because it "compresses" time and removes unnecessary details. Unlike actual processes, simulation is used for optimization and training[2,9]. The other feature of the simulation is that it is dynamic and active. Simulation involves creating a model of a system, conducting experiments with it, and analyzing the results to be applied to the actual system later. The purpose of these what-if experiments is to determine how the real system works and to predict the effect of changes on the system over time[8,9].

For example, business simulation is used to provide answers to the following questions: (1) Will the change in process increase yield/productivity/quality/revenue? (2) How many people are needed to maintain services at a certain level? (3) Can we create a system with a few components and keep it stable simultaneously[8,9]?

Development (construction) of a model of a system, usually mathematical and logical in nature, as well as actual or theoretical (virtual) includes the following stages: describing the real system in terms acceptable to computer systems; using a computer to run a simulation; and mimicking the action of the real system/process[3]. Since the simulation could also be considered an experiment, the goal is to find elements related to the real system, *i.e.* modeling and mimicking an actual process that can be modified by the simulation performer[3].

Mathematical procedures for modeling complex problems that cannot be solved theoretically are known as the Monte Carlo method[10]. The name of these techniques comes from the research of nuclear reactions at the beginning of the Second World War, when a solution to the problem of whether it was possible to induce a nuclear reaction was sought [10]. It was known that multiple neutrons moving in uranium could randomly cause the subsequent emission of other neutrons. Still, it was impossible to predict theoretically whether the chains of reactions forming a complex network would cause an atomic explosion or the prepared high explosive would break on the surface. The scientists investigating this problem used the first large computer ever built to model the random trajectories of neutrons through the atoms of the uranium charge. The project was classified under the code name ”Monte Carlo.” Its name was chosen because of the similarity of statistical simulation to games of chance in Monaco’s capital, the European gambling center[10].

Because this significant project was the first to use a computer and the theory of random trajectories to obtain a probabilistic solution to a complex physical problem, these mathematical experiments were called “Monte Carlo” methods[11]. McCracken, in 1955, when presenting the early “Monte Carlo” methods in the Journal of the American Statistical Association, wrote that “Monte Carlo” method is mainly used to solve problems that are determined in some critical way probabilistically-tasks where physical experiment is infeasible and the creation of an exact formula is impossible[11]. American mathematicians Metropolis and Ulam[10] are recognized as the inventors of the method in 1949.

From then on, Monte Carlo simulation became the primary technique for studying and modeling high uncertainty and risk events. The method is widely used in various scientific research and practice fields-from space exploration to predicting business bankruptcies and risk.

Furthermore, the “Monte Carlo” method is a universal simulation method with several healthcare applications[12]. The main advantages of the approach are its accuracy (builds a complete picture of risk), flexibility (allows risk managers to use different theoretical distributions and dynamic correlations), universality and possibility of integration in different risk modules[12].

The main drawbacks of “Monte Carlo” stem from the heavy computational procedure, requiring a considerable number of simulations (minimum 10000 simulations fora risky asset) and insufficient time to re-evaluate large bank portfolios under dynamic changes in financial markets[5]. The main idea of Monte Carlo simulation in economics is to construct a detailed picture of portfolio risk by computer simulation of many random numbers possessing the main characteristics of the empirical distribution of portfolio returns over a certain period[5].

Computer simulation models, including the Monte Carlo method, have advantages and disadvantages (Table 1).

APPLICATIONSOF THE MONTE CARLO METHOD IN HEALTHCARE

From a theoretical point of view, the Monte Carlo method can be thought of as a technique of numerical integration of a single random variable to deal with non-determinism[13]. An essential feature of the method is that the standard error decreases only with the square root of the model size, not the model’s size.

Monte Carlo simulation is essentially a numerical method, primarily described as a statistical simulation method. A statistical simulation could be any method that uses a sequence of random numbers to represent the simulation[14]. A simulation can typically involve over 10000 model evaluations using supercomputers. The Monte Carlo method is one of many methods for analyzing the distribution of uncertainty, where the goal is to determine how random variation, lack of knowledge, or error affects the sensitivity, performance, or reliability of the modeled system[13]. Monte Carlo simulation is categorized as a sampling method because the inputs are arbitrarily generated from the probability distribution to simulate the sampling process from the actual population. The data generated by the simulation can be presented as probability distributions (or histograms) or converted into error bounds, reliability estimates, tolerance zones, and confidence intervals[14].

One of the earliest applications of the Monte Carlo method in medicine was in risk analysis for human tetrachlorethylene carcinogenicity using no pharmacokinetic models[15]. The authors treat the parameters of the pharmacokinetic model as random variables and determine the bounds of the risk estimates after accounting for parameter uncertainty through Monte Carlo simulations. They further assessed the sensitivity of the pharmacokinetic model predictions to its parameters by analyzing the results of Monte Carlo simulations, demonstrating that the kinetic parameters that define the percent metabolized tetrachlorethylene are the most important for assessing the risk of carcinogenicity in humans[15].

Population pharmacokinetic modeling coupled with Monte Carlo simulations has proven a powerful tool for science-based decision-making. Early stages in the clinical evaluation of new drugs face three critical issues: (1) Extrapolation of

Table 1 What computer simulation models allow and what cannot

Advantages[8,9]	Limitations[2,3]
Allow conclusions to be drawn about a new system without having actually to build it or to make changes to an existing one without disrupting its operation	Cannot optimize but can only generate results from "WHAT-IF" queries
Allow the manager to visualize the operations of a new or existing system under different conditions	Cannot obtain correct results from inaccurate data
Allow us to see how different components interact and how this affects the overall system performance	Cannot describe system characteristics that were not included in the model
Allow general insight into the essence of the process	Cannot solve problems; they can only provide information that aids the process of developing a solution
Allow recognition of specific problems and problem areas in the studied system	Cannot give simple answers to complex problems
Assist in the development of particular policies and process plans	
Improve system efficiency	

preclinical data to humans; (2) Safety and tolerability concerns regarding dosage; and (3) Scientifically based drug combinations[13]. The Monte Carlo method has shown great promise in drug development, particularly in designing phase II/III clinical trials of antimicrobial agents and the appropriate dosage prescribed for humans[16]. In real life, interindividual variability in the pharmacokinetic values of a given drug cannot be excluded or ignored. Furthermore, there is a spectrum of variable susceptibility to each test drug among microorganisms of clinical interest. Therefore, any method for examining the adequacy of a fixed-dose regimen must also explicitly account for sources of variability (pharmacokinetic and microbiological). The method used by the authors consists of applying data from preclinical microbiological and animal models together with data from early phase I pharmacokinetic studies[13].

The Monte Carlo method is also flexible enough to assess the impact of changing dosage. It can also accurately compare drugs from different classes (*e.g.*, fluoroquinolones with macrolides or beta-lactams with aminoglycosides) because different targets are set for each drug class[13].

The third major issue in drug development is the reliable judgment of doses and the scheme of combining with other drugs. The ability to assess the impact of both dose and regimen in combination with other medications can streamline the search for an optimal dose regimen to be studied in clinical experience in the shortest possible time and with the smallest possible number of patients[17]. Integrating population pharmacokinetic modeling with the Monte Carlo simulation method offers a new opportunity to develop optimal and more reliable alternative dosing strategies with antibacterial drugs (*i.e.* beta-lactams) to achieve a predefined therapeutic goal. Alternative regimens optimize dosing with a lower total daily dose than would be used with traditional dosing methods[17,18].

A promising area of application of the Monte Carlo method is the emerging approach of simulating clinical trials to maximize the information gained during the drug development process to achieve the most significant success in clinical trials[19]. From a financial perspective, simulation allows pharmaceutical companies to reduce the number of studies required, maximize the chances of success in clinical trials and possibly shorten development time. All these results will reduce the cost of drug development[19].

The significant clinical benefit of the nonparametric population pharmacokinetic modeling approach is that multiple reference points, with their various sets of pharmacokinetic parameter values, provide multiple predictions of future plasma concentrations and other responses from future doses[13]. The ultimate benefit of Monte Carlo simulations are seen in drug phenotyping when dealing with clinical data that are inherently limited and sparsely distributed[13].

The method of Monte Carlo also serves as a useful tool in the pursuit of precision medicine, empowering clinicians and researchers to navigate the complexities of individualized patient care and enhance drug efficacy in diverse clinical scenarios[20]. By simulating the diverse biological and physiological factors influencing drug response, Monte Carlo simulations enable researchers to tailor treatment strategies to the unique needs of patients, optimizing therapeutic effectiveness while minimizing adverse effects[20]. Furthermore, Monte Carlo techniques facilitate the exploration of alternative dosing regimens, drug combinations, and patient stratifications, fostering a more precise and personalized approach to healthcare delivery. The Monte Carlo method simulates the dynamic interactions between pharmaceutical compounds, biological systems, and patient-specific factors to predict and optimize treatment outcomes in drug efficacy modeling[20]. By incorporating parameters such as drug pharmacokinetics, pharmacodynamics, and individual patient characteristics, the method simulations provide a comprehensive framework for assessing drug efficacy in diverse populations. For instance, researchers can utilize Monte Carlo techniques to model the distribution of drug concentrations in different tissues and organs over time, accounting for variability in absorption, distribution, metabolism, and excretion processes[20]. This enables the exploration of optimal dosing regimens to achieve therapeutic concentrations while minimizing toxicity risks. Moreover, by simulating the effects of genetic polymorphisms, comorbidities, and concomitant medications, researchers can assess interindividual variability in drug response and identify factors influencing treatment efficacy and safety[21]. Through Monte Carlo simulations, researchers can also conduct virtual clinical trials to assess the impact of different treatment protocols, dosage adjustments, and patient stratifications on therapeutic outcomes. The method has been applied to models and simulates drug development for various pathologies, such as thromboembolism, diabetes, rheumatoid arthritis, *etc*[21]. Monte Carlo methods also facilitate risk assessment and stratification by estimating the probability of specific clinical events, such as disease recurrence, complications, or mortality, based on individual patient characteristics and treatment interventions. By simulating large populations of virtual patients with varying risk profiles, Monte Carlo simulations enable the identification of high-risk subgroups and the development of targeted interventions to mitigate adverse outcomes. This enables clinicians to anticipate disease milestones, evaluate treatment effectiveness, and inform patient management strategies[21].

The method may serve as a cornerstone in economic impact assessments of interventions and treatments, offering a robust computational framework to evaluate the potential economic consequences of healthcare policies and medical innovations[5]. Through iterative sampling of key variables such as treatment costs, healthcare utilization, and productivity gains, Monte Carlo techniques provide probabilistic estimates of economic outcomes, including cost-effectiveness, budget impact, and return on investment. These simulations facilitate sensitivity analyses to assess the robustness of economic evaluations to variations in input parameters and model assumptions, enhancing the credibility and transparency of decision-making processes[5]. In essence, Monte Carlo simulations are pivotal in advancing evidence-based healthcare decision-making by quantifying the economic implications of interventions and treatments, ultimately guiding policymakers, payers, and healthcare stakeholders toward more informed and efficient resource allocation strategies.

Some of the major fields where the method Monte Carlo takes part are presented in Table 2[22-26].

CHALLENGESAND LIMITATIONS OF THE MONTE CARLO METHOD

Sensitivity to input parameters

The results of the Monte Carlo simulation are sensitive to input parameters. Thus, data quality is crucial. The input data have to be reliable. In addition, they should cover as long a period of time as possible[27].

Another challenge regarding the data is their distribution. Most of the phenomena generally follow Gaussian distribution, but not all of them. Datasets covering longer periods could help reveal the distribution's true shape. If the distribution cannot be identified based on available data, then a goodness-of-fit technique could be used. Further bootstrapping could be performed if the distribution is still unknown. The last option proposed by the literature is to use the "default" distributions: normal, log-normal, and uniform[27].

Computational demands

Increasing the number of input parameters increases the accuracy of the simulation. From a certain point forward, adding additional variables makes the analysis harder and time-consuming, even with the help of computer programs. There are different techniques for variable selection[28].

Monte Carlo simulation requires using specialized software such as MATLAB or add-ins for Excel. More than 20 years ago, Brian O'Connor wrote syntax codes for creating simulations for the most popular statistical software packages[29]. Thus, the Monte Carlo simulation could be performed not only by mathematicians.

Ethical considerations

Due to ethical reasons, not all types of experimental studies in the field of medicine and healthcare can be performed. The simulations fill in that gap in the knowledge and provide valuable information for unknown parameters that could not be studied in reality.

The conclusions from the Monte Carlo method application are based not on actual data but on simulations. There might be limitations in the design of the simulation, the selection of variables and their distribution. This means that the results applied in the practice could also affect human health in a negative aspect.

FUTUREDIRECTIONS AND INNOVATIONS

As the healthcare landscape continues to evolve, future directions for applying the Monte Carlo method in healthcare simulation hold great promise. Advancements in computational power are anticipated to play a pivotal role, enabling the development of more intricate and realistic models that capture the complexity of healthcare systems. The integration of artificial intelligence (AI) represents a paradigm shift, where machine learning algorithms enhance Monte Carlo simulations' adaptability and predictive capabilities. This synergy empowers healthcare professionals to derive actionable insights from vast datasets, facilitating personalized treatment strategies and resource optimization. Furthermore, the Monte Carlo method is poised to extend its reach into emerging healthcare fields, such as precision medicine, genomics, and digital health[30]. Innovations in simulation techniques will likely contribute to refining decision-making processes, policy formulation, and healthcare planning. The convergence of computational power, AI, and the expanding horizons of healthcare applications positions the Monte Carlo method as a dynamic and indispensable tool in shaping the future of evidence-based healthcare practices.

CONCLUSION

The benefit of simulation modeling is in evaluating new systems without having to build them, experimenting with

Table 2 Application of Monte Carlo method in cancer treatment optimization, personalized medicine and drug efficacy modeling, predictive modeling for disease outcomes, evaluation of treatment risks and benefits, and economic impact assessment of interventions and treatments

Field	Specific issue	Outcomes	Ref.
Cancer treatment optimization	Radiation therapy simulations	Applications of the Monte Carlo method to model treatment heads for neutral and charged particle radiation therapy and specific in-room devices for imaging and therapy purposes	Park *et al* [22], 2021
	Dose delivery strategies	The method may be used to calculate dose distributions and further investigations aimed at improving dose delivery and planning in cancer patients	Chiuyo *et al* [23], 2022
Personalized medicine and drug efficacy modeling	Antibiotic dosing regimen analysis	The simulated therapeutic curve was virtually identical to that obtained experimentally	Milligan *et al*[21], 2013
Predictive modeling for disease outcomes	Infectious disease	The employed Bayesian Monte Carlo regression framework allows for incorporating prior domain knowledge, which makes it suitable for use on limited yet complex datasets as often encountered in epidemiology	Stojanović *et al*[24], 2019
	COVID-19	The method of the Monte Carlo algorithm was used to conduct Bayesian inference and illustrate the proposed approach with data on COVID-19 from 20 European countries. The approach performs well on simulated data and produces posterior predictions that fit reported cases, deaths, and hospital and intensive care occupancy well	Rehms *et al* [25], 2024
Evaluation of treatment risks and benefits	Application to the prophylaxis of deep vein thrombosis	The simulation was feasible to model the joint density of therapeutic risks and benefits of prophylaxis in patients with deep vein thrombosis	Lynd *et al* [26], 2004
Economic impact assessment of interventions and treatments	A Monte Carlo simulation approach for estimating the health and economic impact of interventions provided at SRCs	Using Monte Carlo simulation methods, the health and economic impact of SRCs can be reasonably estimated to demonstrate the utility of SRCs and justify their growing importance in the healthcare delivery landscape of the United States	Arenas *et al* [5], 2017

COVID-19: Coronavirus disease 2019; SRCs: Student-run clinics.

existing systems without changing them, and testing the limits of systems without destroying them, *i.e.* simulation can be used to construct, analyze and evaluate various systems.

We can formulate the following take-home messages: (1) Through analytical modeling, one could understand and predict the behavior of a real system in various situations and problems, especially those that cannot be solved by mathematical approaches or involve quantities of a random nature; (2) Simulation is better than experiment because its "compresses" time and removes unnecessary details. Moreover, it is dynamic and active; (3) Simulation involves creating a model of a system, conducting experiments with it, and analyzing the results to later apply to the real system; (4) Mathematical procedures for modeling complex problems that cannot be solved theoretically are known as the "Monte Carlo" method; (5) The approach's main advantages are its accuracy (building a complete risk picture), flexibility (allowing risk managers to use different theoretical distributions and dynamic correlation dependencies), universality and the possibility of integration into different risk modules; (6) The main drawbacks of "Monte Carlo" stem from the heavy computational procedure, requiring a considerable number of simulations (minimum 10000 simulations for a risky asset) and insufficient time for re-estimation under dynamic changes in financial markets; and (7) One of the earliest applications of the Monte Carlo method in medicine was in risk analysis of carcinogenicity of certain drugs in humans, in the design of clinical trials phase 2/3 in clinical studies, for accurate comparison of drugs of different classes, combining with other medications, and other.

The Monte Carlo method is not yet a mainstream tool in healthcare, but it is a technology with immense potential to reduce cost and minimize risk. Experience gained through simulated experimentation is critical in situations of limited time, money, and resources.

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FOOTNOTES

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