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Physiology

Computer Simulation– A Future Perspective in Understanding the Concepts of Physiology

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Review Article

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Abstract: Computer simulation has contributed heavily in escalating our current knowledge of human physiology. A coalition of interconnected operations is known as system and a simulation model mimics the original system. The primary goal of a model system is to predict accurately future performance of the physiological system using quantitative statistical measurements. A strong future for simulation models will be realized when they will be comprehensively incorporated into diagnostic, therapeutic and research areas of the healthcare system.

Keywords: Computer simulation, Simulation model, Deterministic stochastic model, Parametric Non-parametric model, modeling chaos.

INTRODUCTION

Recent advances in the field of biological, medical and pharmaceutical research ameliorate our understanding of cellular mechanisms. Conscientious efforts are constantly being done to develop physiological cell models. Many models of physiological cell functions are, despite being already published, constantly being improved and extended towards more precise and comprehensive ones [1]. Biological systems are naturally multiscale and to understand their behavior fully, we must understand the interaction of a number of processes that may occur on diverse temporal and spatial scales. Simulation models have progressed greatly since the first use of mathematical equations to describe physiological functions. The potential use of mathematics for interpreting existing data illustrates the insight of theoretical models. Computer simulation is one such scheme which has contributed heavily in escalating our current knowledge of human physiology and pathophysiology.

In this scheme, the operation of an actual process is imitated with time [2].This technique came into being around hundred years back and has helped considerably in discerning molecular biology . Its use involves application of one or more mathematical equations adding quantitative diligence to the existing notion. Physiological simulation models provide an ideal platform for designing techniques evaluating pathological conditions.

Physiological system modeling and simulation

Introduce some main terminology at this point. A system may be considered to be any collection of interconnected processes and/or objects. A model is a representation that approximates the behavior of an actual system. This representation is descriptive in a certain level of detail, for that system. By using a set of simplifying assumptions, the system is conceptually reduced to that of a mathematical model. Therefore, the results of each model have significant limitations and are valid only in the regimes of the real world where the assumptions are valid. A model is always connected to an experiment from which we obtain data. To optimize the experiment, we need to have access to the data related to important variables of the model. Consequently, designing and executing an experiment is a crucial step in modeling that usually involves a careful and usually time-consuming selection of the model's variables. Next, we will discuss the two most important classes of variables introduce some main terminology at this point. A system may be considered to be any collection of interconnected processes and/or objects.

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A coalition of interconnected operations is known as system and a simulation model is something that mimics the original system. This close resemblance with the system is achieved by generating a series of mathematical calculations that conceptually reduce the actual system to a simulation model which subsequently originate data for the desired experiment by generating necessary variables. But design, execution and variable choice are perhaps the key steps using an input and an output signal. The input signal constitutes a series of information which flows inside the system, which may be manipulated accordingly and finally retrieved as the output. This information is termed as "measure" and it can be a physical quantity, property or condition that can be measured e.g. relevant measures include electromyography (EMG), electrocardiography (ECG), etc.

Use of quantitative statistical measures played a huge role in assessing the accuracy of the simulated model systems. It is empirical to clarify the distinction between the terms "accuracy" and "precision" used interchangeably in most of the simulation studies so far. "Accuracy" is the difference between the predicted value and true value. "Precision" on the other hand primarily deals with the reproducibility of the results on a constant basis. The aforementioned objectives can solemnly be achieved on the basis of statistical analysis [3]. For instance; 'Goodness of fit test', a variant of chi-square compares the difference between the observed and expected values often illustrated as observed/expected (O/E) ratio. Also, the output values of the simulated model are collated with the values obtained from tests optimizing repeated measures. However, the importance in both the scenarios remains in the minimally obtained difference between the actual and simulated system values reemphasizing the role of precision.

The primary goal of a model system is to predict accurately future performance of the physiological system. To achieve this, a simulated physiological model formulates a hypothesis based on a number of near approximated experimental values. A mathematical model is then designed which continues to generate new data through equations until a satisfactory set of values obtained. A simulated model can either refine or modify the understanding of an existing system or uncover a hidden phenomenon (Fig 1).

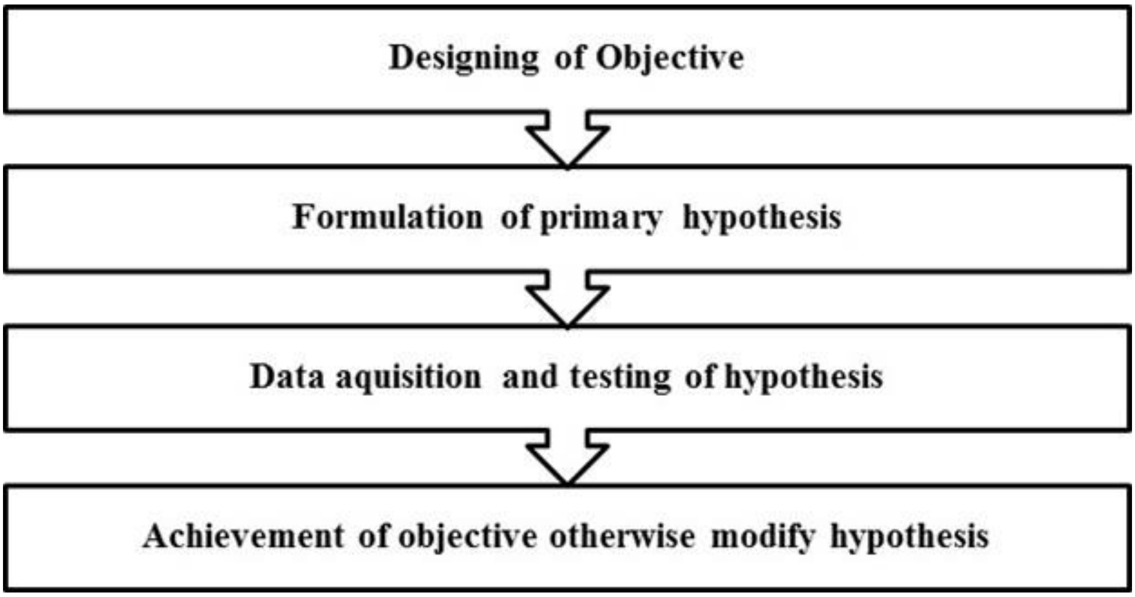

Fig-1: Basic framework of simulation model

Levels of modeling

From a historic perspective, the works of Hodgkin & Huxley (nerve excitation model), Denis Noble (cardiac cell model) and Beeler & Reuter (electrical activity in ECF and ICF) form the cornerstones of modern simulation research (4). It laid the foundation of 'System Biology', which is a quantitative technique in biological research that uses huge experimental data available across various laboratories globally. This is subsequently employed in organizing a model system level ranges sub-cellular to complete organ system (cellular, intercellular, tissue, organ, and organism) (Fig 2).

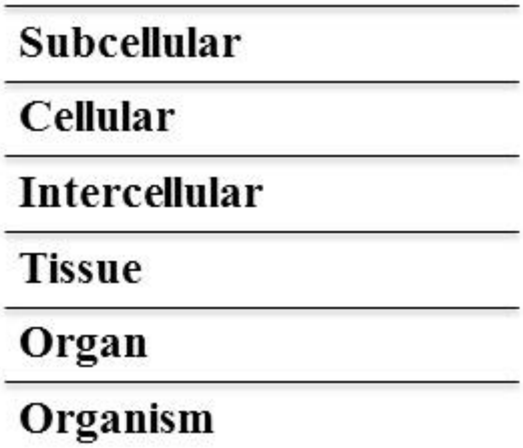

Fig-2: Levels of simulation model

Classification of Models

Simulated models can be broadly classified into various categories (Fig 3). These models formulate hypothesis, consider randomness and maintain original model structure using computational mathematical tools.

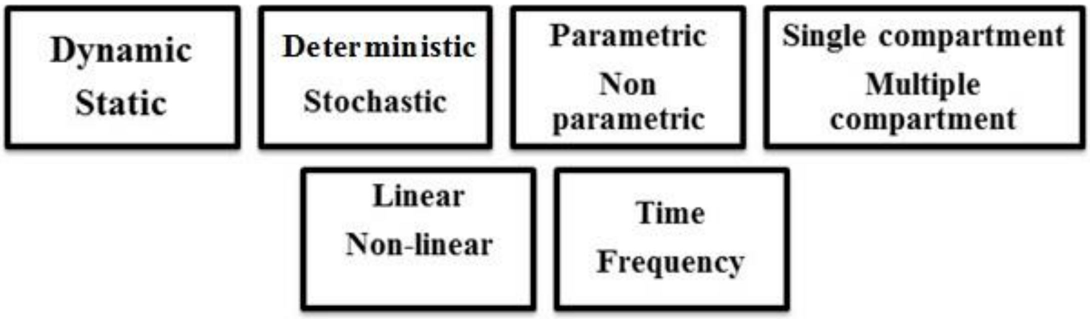

Fig-3: Classification of simulation model

A static model has direct simultaneous connection amongst all variables while the dynamic model deals with a large number of variables, known as state variables whose values change with time even in the absence of external inputs (5). A physiological simulation system can either be based on a deterministic or stochastic model. The deterministic model has an edge over stochastic model in predicting the future course of the system with fair accuracy once it is provided with sufficient information about the dynamics and the values of the state variables at a given point of time. On the other hand the stochastic model's outcome carries some degree of chance and it is not fully predictable. Hence, it is difficult to choose a model for a particular system[6].

A parametric model obeys the physical principles, and perhaps integrates variables and constants with physical constraints to develop a mathematical model of the system. It utilizes basic scientific facts and established known values to postulate algebraic equations, which represent the system either intermittently or continuously. On the contrary, output of a non-parametric model depicts true relationship between the input and output without using equations and making least assumptions. They use black-box approach or data tables instead of mathematical formulas. However, the choice of using a particular system depends upon the expected behavior of the output and nature of the system. Estimation of domains with physical interpretation usually employs parametric system while non-parametric system is more suitable in determining locations of resonances, notches etc. [3]

The use of compartmental modeling in respiratory and circulatory system revolutionized simulation technique in the field of medicine [7]. They are divided into homogenous compartments with well demarcated entity feasible allowing transfer of solutes across them. In pharmaceutical sector models analyze distribution of hormones and drugs among different compartments in the body, thus predicting pharmacokinetics and fluid transport characteristics of an unknown salt. This modeling makes significant contribution in modeling neural entities through General Neural Simulation System (GENESIS), a specific purpose object oriented software platform which simulates existing biological environment of neural components at subcellular and cellular levels in humans. However, the two difficulties in this type of model are the number of compartments used and inter-compartmental accessibility of data [3, 8].

Linear modeling is another approach in modeling which uses the principal of superposition to determine linearity which means that the shape of the output remains same even after using same inputs at different amplitudes. Many systems respond linearly only to a limited range of inputs and an increase in the number of inputs disrupts their linearity. Thus, determination of range is essential while using these systems. Linear systems with more than one range also exist and these show variability among different ranges. However, these systems remain popular due to their simplicity and exquisite nature. An appropriate model of a system is always guaranteed in a linear system. It works by determining the response to an arbitrary input in three basic steps; initially the input is broken down linearly into basic functions, then the proportionality principal is used to determine response to each element and finally, the overall result is interpreted by super positioning the above obtained responses. A non-linear system on the contrary deals with the linear range with variable frequency by modulating the input or output which results into a linear input output relationship [6, 9].

Now, the final response can be a time domain model if the basic functions form a series of impulses, but if they become sinusoids then the analysis will be transformed into frequency domain model and this response to any input can simply be visualized using “impulse response function” [10].

Modeling chaos in physiology

Classically, maintenance of milieu intérieur (internal environment) inside the human body is attained through an extremely balanced series of interconnected feedback mechanisms. Simulation describes physiological system as stochastic, determinism or chaotic system i.e. an immensely complex deterministic system [11]. For example, activity in one part of a brain is dependent on the accurate functioning of numerous other factors acting via different pathways. Other key characteristics of chaotic system include hierarchy, randomness, and more significantly landing into an unusual, unfamiliar and stressful situation and defying it through alternative routes on its own. For an instance, periodic beating of SA node in the heart typically describes a chaotic system where inter-beat variability is influenced primarily by antagonistically acting parasympathetic and sympathetic nervous systems. There is also spilling over of respiratory impulses on it modulating its activity to some extent. It’s worth noticing that chaotic systems operate purposefully as evident from the inter-beat different in rhythm of heart which allows it to relax and limits fatigue. An increase of cardiac output from 5L to 25L during strenuous exercise sessions shows that chaotic systems have high compensatory power too [6, 12-14].

A new stimulus in human brain initially creates chaos but it advents a new circuitry shortly reiterating the ability of a chaotic system to adapt to new stimuli. Learning function of cerebellum is primarily associated with the above mentioned discussion. Thus, chaos allows a system to ‘adapt’ and enhances its ability to learn. But the abovementioned chaotic theory is in opposition to the “Neuron Doctrine” proposed by Waldeyer-Hartz in 1891 which strongly opposes prediction of future action by an organ, e.g. human brain, as its action is largely instantaneous, invariably depending on various feedback mechanisms [15,16].

Health is defined as a ‘state of balance’ and a disease will make system ‘out of balance’ [17, 18]. From a simulation perspective, output of a linear system is derailed if it gets an odd input; however a non-linear system resets itself in case it receives a bizarre stimulus. Off late, physicians classify epileptic seizures, Parkinson’s disease, and heart attack as dynamical diseases caused by chaos or abnormal periodicity, and aging is also related to loss of deterministic variability [19].They create chaos of impulses inside sub-thalamic nuclei of basal ganglia (deep brain stimulation) to treat Parkinson’s disease [20]. An ordered and calculated input to known systems is widely implicated to obtain clinically relevant outputs. But to work successfully the mathematical models should cope with the anisotropic, multi-scale sensitive physiological features of the human body in real time. Thus, it seems apparent to advent a universal modeling language through an interdisciplinary approach from a futuristic point of view.

Summary

An insight of this review suggests the use of computer modeling with experimental design in order to formulate predictive equations. The fundamentals of physics and biology are implicated to design simulation models with an ability to extract indispensable data information. More recently simulation is used to study and improve clinical labs e.g. diagnostic accuracy of pap smear, mammogram, HIV and hepatitis etc. It illustrates the benefits that result from close collaboration between experimentalists and theoreticians and takes us back to the key point made by Huxley and noble that physiological modeling must be thoroughly grounded in experimental data if it is to be successful. The current challenges include development of latest, relevant statistical techniques and software. With computer simulation still in its infancy, further development is required via coalition of simulation modeling with relevant clinical data to achieve the desired pivotal point in healthcare systems.

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