Review of Mathematical Modelling Techniques with Applications in Biosciences

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ABSTRACT: Modelling can provide intellectual frameworks that are necessary to translate data into knowledge. Mathematical modelling has played an important role in many applications, such as ecology, genetics, engineering, psychology, sociology, physics and computer science, in recent years. This study focused on reviewing mathematical modelling and its applications to biological systems by tracing many metabolic activities of cellular interactions on the one hand and between the spread of epidemics and population growth on the other hand. Various mathematical equations have played fundamental roles in the formation of these systems for model development procedures by describing them mathematically and establishing relationships that characterise the dynamics of a biological phenomenon. Consequently, the creation of new mathematical representations and simulation algorithms is important to the success of biological modelling initiatives. Finally, the optimisation approach performs its primary role in directing and controlling interactions by adjusting the parameters that provide the best possible result for the system.

Keywords: Mathematical modeling; Differential equations; Biological sciences applications.

1. INTRODUCTION

The idea of global or world modelling peaked in 1979, and it may be regarded as an effort to depict economic, political, social, demographic and/or ecological concerns rigorously, along with their interdependencies, on a worldwide scale [1]. These linkages are mapped as explicit mathematical equations that can be executed and assessed in terms of the dynamic behaviour of the models themselves [2]. Consequently, the models may be used to anticipate future developments under a range of scenarios. Such modelling may be regarded as the most advanced method for methodically utilising the nature of, and perhaps, solving global problems. The First Decade of Global Modelling describes the achievements of scholars working on global issues in prime math during the early 1970s [3]. At present, 42 years after the first hopeful phase of global modelling, we are slightly more cautious in our expectations of global models. Global modelling is still considered a research field in its infancy. Previous experiences have led to a consensus, with all experts agreeing that no model can or should be considered complete. The objectives of a system under examination are defined by optimisation models. These models may be used to investigate trade-offs between objectives, uncover extreme states and worst-case scenarios and pinpoint critical elements that influence system phenomena [4] [5]. Consequently, optimisation models are used to investigate a wide range of scientific, business and engineering problems [6]. Finally, given the considerable importance of describing nonobvious phenomena and finding relationships amongst them, an urgent need for modelling exists, in addition to the fact that its applications are extremely broad in various sciences; this concept is discussed in more detail to visualise it more closely and knowledgeably [7].
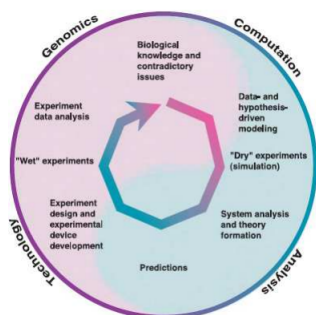
FIGURE 1. Modelling and experimentation cycle in biosciences.

2. MATHEMATICAL MODELLING STRUCTURE

2.1 PRINCIPLE OF MATHEMATICAL MODELLING

Three basic techniques are used for building models as shown in Figure 2. These methods are not mutually exclusive, and a model can be built by using a combination of these techniques. The first two methods are based on dynamic mathematics, whilst the third method is based on statistics [8] [9].
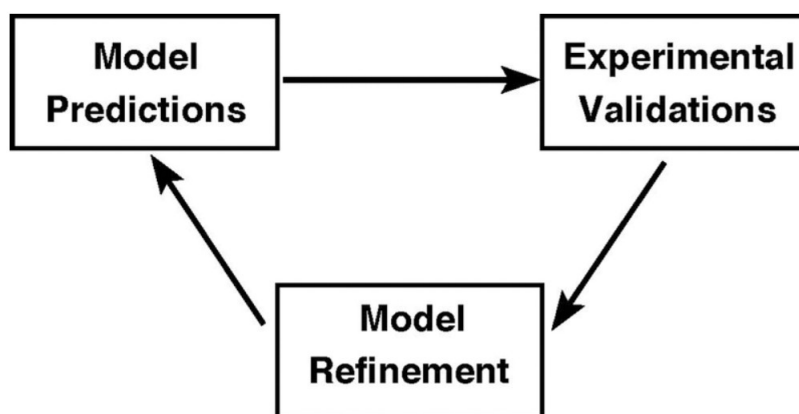

FIGURE 2. Three major steps in model building.

The mathematical representation of a model depends on knowledge of a system, on specific modelling decisions (e.g. the spatial scale of representation) and on the purpose of the modelling process. A researcher can choose from a wide range of mathematical and computational techniques, and the correct method is frequently determined on the basis of experience. The choice of an appropriate computational approach appears to be straightforward at first glance. Many of these interests revolve around how a system should be described in terms of its components, biological and physical variables, space and time, type of interactions between objects and the representation of the object itself. Organs are considered separate systems in systems biology because they perform distinct roles. Various modelling options can result in single or multipart models, including transfer, evolutionary differential equations, algebraic or spatial differential equations, differential equations versus differences and ordinary differential equation (ODE) versus partial differential equation (PDE) [10]. Figure 3 represents a modelling of the kinetics of an enzyme substrate. On the left, a schematic depicts the system's principal biochemical species and their interactions. The biological processes are shown in the middle of this detailed diagram. On the right, a set of ODEs characterising each biological species' rate of change is presented.

2.2 MODELLING PROCESS

A mathematical model is a mathematical tool and linguistic representation of a system. Mathematic modelling is the process of creating mathematical models. An initial model typically only depicts an extremely crude description of a system, and thus, it must be improved in subsequent phases. When the model structure and kinetic parameters are
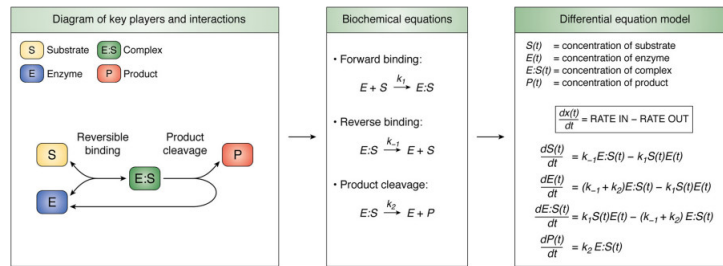
FIGURE 3. Example of building a model for the result of enzymatic reactions.

compared with experimental data, the model structure and kinetic parameters are changed. The basic step for the modelling process is model calibration, and whether it is useful or not can be determined by comparing its output with ? [11–13].
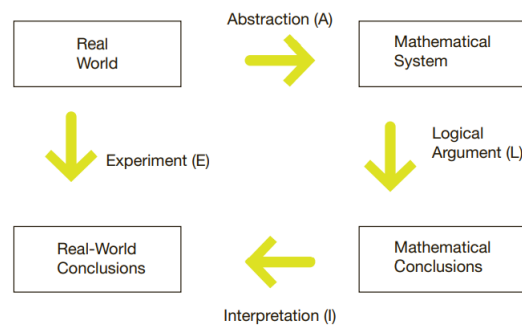
FIGURE 4. Modelling cycle.

3. MATHEMATICAL MODELS AND APPLICATIONS

3.1 MODELS OF DIFFERENTIAL EQUATIONS AND ECOLOGY

Many relevant tools for examining dynamical models may be found in the field of linear algebra. Linear algebra is a set of bookkeeping techniques for solving linear equations. Complicated equations that involve more than one variable can be expressed in a concise manner by using these strategies. An even more significant advantage is the utilisation of linear algebra theorems to prove certain facts about a model's behaviour. For example, a community or group of living organisms that exist in and interact with one another in a certain environment is the most basic definition of an ecosystem. Air, water, sunlight, soil, plants, microorganisms, insects and animals are all important components of most ecosystem states. Changes in the number of ecosystem states that may be indicated to fluctuate continuously over time, such as individual concentrations per unit area and mass, are frequently anticipated in ecology by using PDEs and age-/size-structured dynamics; integrodifferential and matrix equations can be used to depict spatiotemporal dynamics [11]. Lutka suggested a mathematical model of population dynamics based on ODEs [14] [15]. Lotka–Volterra (LV) models have been widely used to characterise ecosystem temporal development [16]. Volterra constructed an independent population dynamics mathematical model based on ODEs and LV models (Figure 5). Moreover, the mathematical features of expanded LV models have been explored by extending LV equations to a random number of coexisting populations (gLV) [17]. In 2013, an environmental model was developed by Stein et al. by taking a new model and more space for prediction [16]. Here, we review the summary of the course of environmental models and their evolution over time.

We provide an example of a simple mathematical model.

Example 3.1. *Consider developing a deterministic model for the basic network shown in Figure 6 [18].*

The description of this model's assumptions is as follows: homogeneous, not compartmented, first-order reactions and parameters $i, j = 1, 2, 3$, such that P_{ij} is reaction rate constants and Hi is the rate of transport of each metabolite in/out of the cell
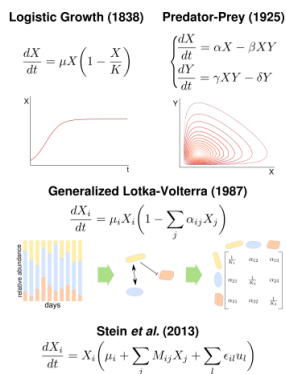
$$H_i = K_{i,\,\text{in}} - K_{i,\,\text{out}}$$
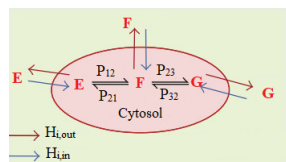
FIGURE 5. Modelling communities with ODE systems.

FIGURE 6. Modelling communities with ODE systems.

However, the model equations can be formulated as follows:

$$\frac{dE}{dt} = 0.E + P_{12}F + 0.G + H_1$$
$$\frac{dF}{dt} = P_{21}E + 0.F + P_{23} \cdot G + H_2.$$
$$\frac{dG}{dt} = 0.E + P_{32}F + 0.G + H_3$$

These equations can be expressed as a matrix:

$$\begin{bmatrix} \frac{dE}{dt} \\ \frac{dF}{dt} \\ \frac{dG}{dt} \end{bmatrix} = \begin{bmatrix} 0 & P_{12} & 0 \\ P_{21} & 0 & P_{23} \\ 0 & P_{23} & 0 \end{bmatrix} \begin{bmatrix} E \\ F \\ G \end{bmatrix} + \begin{bmatrix} H_1 \\ H_2 \\ H_3 \end{bmatrix} \Rightarrow \frac{dk}{dt},$$

where (K, M) are vectors that comprise the concentrations of the species (E, F), and ($G, dK/dt$) indicate the rate of change. K, θ are vectors of the model parameters.

3.2 MATHEMATICAL MODELLING OF INFECTIOUS DISEASES

A mathematical model of the transmission process of an infectious disease may be presented as follows. When infectious people are introduced into a vulnerable population, the disease is transmitted to other people through its modes of transmission, spreading the disease across the population [11] [19]. During the early stages of infection, an infected person may be asymptomatic. He/She may later acquire clinical symptoms and be identified as a case of the disease. Hence, mathematical modelling that adopts a specific approach to disease tracking and develops effective solutions for control is urgently required [20]. With an increasing number of models being built to track and forecast the spread of a disease, along with significant choices being made on the basis of the findings of these studies, mathematical modelling has played a prominent and crucial role in the current coronavirus disease 2019 (COVID-19) pandemic [21]. A proliferation of models, many of which differ considerably in their forecasts, have been followed by questions regarding the validity of modelled studies and whether and to what extent conclusions may be believed. The mathematical modelling of the propagation of COVID-19 in various nations is explored to predict future instances and prepare for them. A large number of new mathematical models for the spread of COVID-19 have been developed [22]. For example, analytical data accessed through mathematical modelling indicate that the United States and Italy are in the third stage of the COVID-19 pandemic, whilst India is in the second stage [21]. Amongst the proposed modelling methods is the closure method, which has been an effective model for limiting the spread of infection, as shown in Figure 7 [23]. Several techniques have been used to improve the validity of the conclusions obtained from these studies, along with approaches that will assist decision makers in the current COVID-19 pandemic and beyond [24]. Finally, a mathematical model is critical when adopting a segmented

method to explain the transmission mechanism of an infectious disease. The host population is first divided into mutually exclusive groups or compartments in accordance with the natural history of the disease [25].
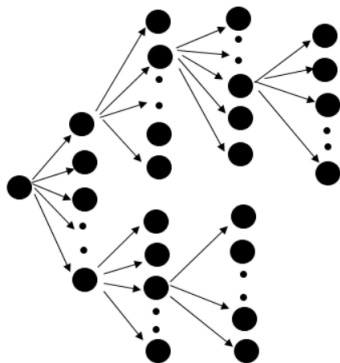

FIGURE 7. One of the proposed models for the spread of COVID-19.

3.3 SIR MODEL TO PREDICT COVID-19

A system of three linked nonlinear ODEs comprises the SIR model, where S represents susceptible hosts, I represents infectious hosts and R represents recovered hosts.

The modelling mechanism for the transmission of an epidemic is in accordance with the following model:
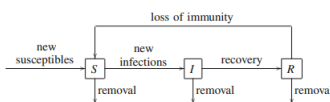
FIGURE 8. Transfer diagram of SIR compartment model.

Modelling aims to keep track of the number of hosts in each of the three compartments at any given time t, which we label as *S(t), I(t)* and *R(t)*.

Given the urgency and due to the outbreak of COVID-19, this modification is implemented into the SIR model because the proposed approach includes unique policy features to capture interactions during the spread of infection. The model assesses pandemic vulnerability by predicting new cases through the estimation of a model that varies over time to reflect changes in the behaviour of the SIR model related to new policies implemented in different periods and locations world-wide. The modified SIR model can be applied with variable values to different country scenarios. Finally, this modification can be applied to the case of closing or opening a country depending on the imposed policies [20] [26] [27] [28].

3.3.1. MATHEMATICAL BEHAVIOUR OF THE SIR MODEL DURING THE PANDEMIC

In accordance with the mathematical principle, the logarithmic function cannot be negative. Physical contact amongst people was mostly cut off during the outbreak of the pandemic, limiting its spread. Thus, variable ρ is used to express the rate of infected people on the basis of the following logarithmic function:

$$\log(\rho_t) = \log(\rho_0) - \alpha_I t_I / N_t$$

However, given the lack of adequate ongoing testing, forecasting the number of infected individuals at any one moment is impossible . Consequently, the model for continued expansion may be written based on death rate as follows:

$$\log(\rho_t) = \log(\rho_0) - \alpha_D \Delta D_t / N$$

The logarithmic function is adopted to obtain the concept in early decreases [21] [29] [30].

3.4 MATHEMATICAL MODELLING WITH BIOLOGICAL SYSTEMS

The genotype-to-phenotype map is necessary in developmental biology to complete the evolutionary loop postulated by selection heritable variation. Understanding the relationship between genotype and phenotype in a multicellular organism
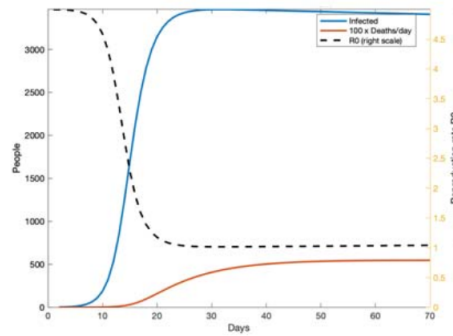
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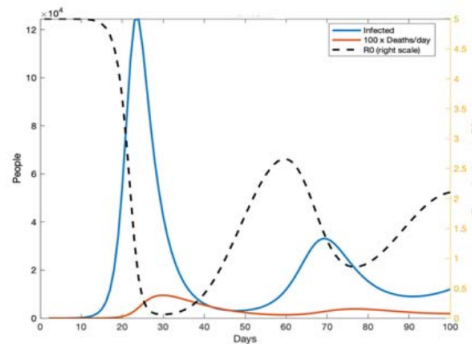**FIGURE 9.** SIR behavioural model with R_0

FIGURE 10. SIR form with behaviour and policy responses in accordance with a new approach.

is essentially a multi-scale, and therefore, challenging task [31]. That is, if it can address highly heterogeneous mathematical dynamics, such as stochastic reaction networks, dynamic spatial structures at the molecular and cellular scales and PDEs that govern pattern formation and dynamic geometry within a dynamic topology, then partial automation has the potential to reduce the complexity for human scientists [32] [10]. The unifying idea of rewriting rules that define operators in operator algebra underpins a mathematical modelling framework. This framework is declarative because rewriting rules allows it to express high-level mathematical notions in a symbolic and computationally manipulable manner [33] [34]. As shown in Figure 11, the modelling process in biosciences is based on four facts: conceptualisation, mathematical formalisation, management and optimisation [12, 35–37].
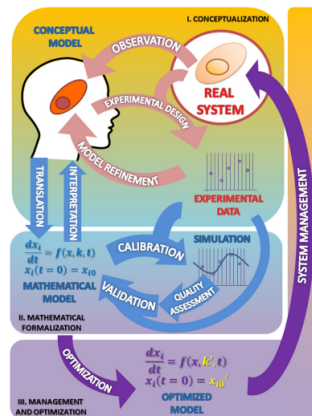

FIGURE 11. Modelling process with biological systems.

3.4.1. *MATHEMATICAL MODELLING AND CONTROL OF CELL GROWTH PATHWAY SINGLE TRACKING*

The mechanical target of rapamycin (mTOR) is a key regulatory mechanism that combines a range of environmental input into complex molecular reactions to control cellular development and homeostasis. Despite the intrinsic knowledge of their components, the molecular understanding of how they interact in space and time remains furtive; nevertheless, it has become clearer through the use of mathematical modelling, which has added many properties, the most important of which is tracking the progress of cell growth by understanding the signals of interactions that occur within cells as shown in Figure 12 [38] [39] [13] [40] [41].
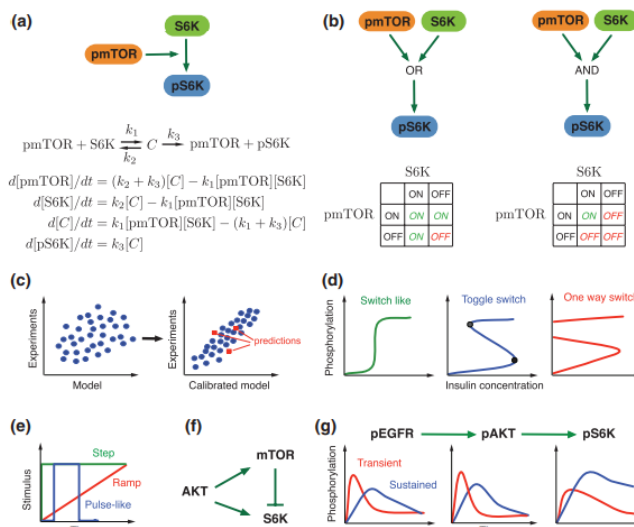

FIGURE 12. Modelling process with biological systems.

4. TYPES OF MATHEMATICAL MODELS FOR TRANSCRIPTION REGULATION

4.1 MODEL FOR TRANSCRIPTION REGULATION WITH INDEPENDENT BINDING SITES

Assuming independent binding sites for repressors (C), we begin by describing the model of repressor molecules (B) [42]. In this case, we are interested in the reactions that will be (binding) for the forward reactions and (disengaging) for the reverse, as follows:

$$C + B \overset{kf}{\underset{kr}{\leftrightarrow}} CB$$
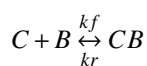
Then, we have

$$\frac{dC}{dt} = K_r(1-C) - K_f C[B]$$

We may observe the steady state and assume that $dC/dt \approx 0$ if we assume that B-to-C binding and dissociation are faster compared with other cell activities. Thus, we derive

$$K_r = C\left(K_r + K_f[B]\right)$$

which refers to the likelihood that a particular is free. Assume that all m sites must be available for copying. Gm, which implies that correlations to various sites are independent, is the proportion of time that this phenomenon will occur. Copying will proceed at the maximal K_{max} rate once all the m sites are free [43]. Consequently, the overall rate of conversion is

$$\frac{K_{\max}}{\left(1 + \frac{K_f}{K_r}[B]\right)}$$

4.2 HILL EXPRESSION MODEL

The DNA is the molecule that contains the genetic information of all living organisms. Formed by two threads winding around each other, the DNA structure is called a double helix. Sugar (deoxyribose) and phosphate groups form the backbone of each strand. Adenine (A), cytosine (C), guanine (G) and thymine (T) are attached to sugars (T). Adenine binds with thymine, and cytosine binds with guanine, providing the bonds that hold the two strands together. The assembly of proteins and RNA molecules is guided by the base sequence along their backbones. The hypothesis of this model is that protein molecules are united in their work, which is achieved through two major approaches. The first approach lies in the rapid formation of a complex of M-proteins. This complex consists of a mixture of proteins that quickly bind and unlink from the DNA in accordance with certain mathematical formulas. In the second approach, the two stable states of DNA are only the state with M-molecules bound to the DNA and the state without M-molecules bound to the DNA [44] [45]. In both cases, we have

$$C + mB \underset{kr}{\overset{kf}{\leftrightarrow}} CB^m$$
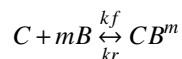
Consequently, the probability C of a differential equation is

$$\frac{dC}{dt} = K_r(1 - C) - K_f C[B]^m$$

We are only interested in stable states with regard to quick binding. Therefore,

$$C = \frac{1}{\left(1 + \frac{K_f}{K_r}[B]^m\right)}$$

Thus, transcription is, on the average, in accordance with the following mathematical formula:

$$C = \frac{K_{\max}}{\left(1 + \frac{K_f}{K_r}[B]^m\right)}$$

which is referred to as a Hill expression.

Table 1. **Advantages and disadvantagesof the presented mathematical models.**

Mathematical model	Advantages	Disadvantages
SIR	Simple, easy to use	Other factors relevant to COVID-19 are not included.
Logistic growth	Better fit with existing data	Inaccurate for long-term predictions
Transcriptional regulation with independent binding sites Hill expression	Less expensive than other models Equations are simple to write and evaluate.	High coverage required It can lead to incomplete predictions if not all theparameter values are provided accurately.

5. CONCLUSION

A significant reason for studying mathematical biology is the fact that mathematical equations frequently 'tell' more than the surrounding material. Many publications have length constraints, and thus, authors frequently omit intermediate stages or fail to specify all their assumptions. The ability to comprehend and analyse mathematical equations is critical for verifying the findings of authors and assessing the constraints of unspoken assumptions. Without understanding mathematical conclusions, describing biological insights gained via mathematical models will be difficult. Accordingly, the current research focused on the concepts gained through mathematical models in a small but critical biological area known as the environmental and mathematical modelling of infectious diseases. COVID-19 serves as an example of how a pandemic spreads. In addition, we discuss the modelling process in biological systems and present mathematical models of transcriptional control based on DNA handling.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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