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Review Paper

Role of Mathematical Modeling in Controlled Drug Delivery

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Abstract

Controlled drug delivery occurs when a polymer or lipid (natural or synthetic) is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner. The aim of controlling the drug delivery is to achieve more effective therapies while eliminating potential for both under- and overdosing. Controlled delivery systems includes the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. Mathematical modeling of controlled drug delivery can help to provide a scientific knowledge base concerning the mass transport mechanisms that are involved in the control of drug release. Mathematically, it is identified for designing a particular pharmaceutical system and it can be used to simulate the effect of the device design parameters (viz., geometry and composition) on the resulting drug release kinetics. The objective of this review outlines the application of mathematical modeling to the controlled drug delivery mechanisms, focusing particular attention on drug transport in human breast cancer, treated with the drug Doxorubicin.

Keywords: Controlled drug delivery; Diffusion; Doxorubicin; Mathematical Modeling; Release Kinetics.

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1. Introduction

In what follows, a pharmaceutical agent is encapsulated within a polymer (or a lipid) drug safety and efficacy can be greatly improved and new therapies are possible. It gives the impetus for active study of the design of degradable materials, intelligent delivery systems and approaches for delivery through different portals in the body [1]. The developments of mathematical models, that can be predict delivery performance [2] will facilitate the design of various delivery systems. Application of materials for long-term controlled release of encapsulated agents is one of the principles used in drug delivery [1]. Some

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potential advantages of drug delivery are, continuous maintenance of drug levels in a therapeutically desirable range; reduction of harmful side effects due to targeted delivery to a particular cell type or tissue; potentially decreased amount of drug needed and decreased number of dosage and possibly less invasive dosing, leading to improved patient compliance with the prescribed drug regimen; and facilitation of drug administration for pharmaceuticals with short in vivo half-lives [1]. These advantages must be weighed against the toxicity of the materials (or their degradation products) from which the drug is released, or other safety issues such as unwanted rapid release of the drug; discomfort caused by the system itself or the means of insertion; and expense of the system due to the drug encapsulation materials or the manufacturing process. Thus, controlled delivery systems can be used to release the drug in a pre-programmed, desired manner over prolonged periods. The purpose of controlled release system (CRS) is to maintain drug concentration in the blood or targeted tissues at a desired value as long as possible [3, 4]. In other words, they are able to exert a control on the drug release rate and duration [5]. Mathematically, CRS may be classified according to the controlling physical mechanism of release of the incorporated [6] is based on the mechanism of transport in these systems as diffusion-controlled systems. Accurate mathematical model that take into account the mechanistic aspects of the transport processes in drug delivery systems and the structural characteristics of the polymer can help fulfill the above objectives. When developing new CRS or elucidating drug release mechanisms, the choice of the appropriate mathematical model strongly depends on the type of drug, type of excipients and composition of the device. Various procedures can be used to control drug release. Diffusion, water-triggered transport (swelling) and degradation/erosion are the most important ones. In this context, polymers are added to control or modify the release step of the drug. There is no over all mathematical model covering all the possible chemical and physical process that can occur. Thus, it is crucial to identify or develop an adequate mathematical theory for a specific drug delivery system.

2. Notations

Here we recall the notations which are used frequently:

- t - time,
- D - diffusion coefficient which is related to the breast tissue and drug properties ($2.7\text{ex}10\text{cm}^2/\text{s}$),
- K - drug consumption constant,
- ϕ_c - volume fraction of the interstitium,
- S_e - specific surface area of the interstitium,
- Q_2 - ratio of the total cell-averaged cell concentration over the free drug concentration in the second cell compartment,
- T_e - tortuosity of the interstitium,
- P_c - permeability of the first cell compartment,
- N_1 - number of intersections of the first cell compartment per unit length of the diffusion path,
- D_{f2}- diffusion coefficient in the fluid occupying the second cell compartment,
- D_{fe}- diffusion coefficient in the interstitial fluid,
- C_{dox} - concentration of drug (doxorubicin),
- (C_e, C_2) - dissolved drug concentrations,

(D_e,D_2) - true macroscopic drug diffusion coefficients,
($A_c \times S_e \times C_e$) - adsorbed drug accumulation per unit bulk volume in the outer cell compartment,
$\vec{\upsilon}$ - fluid velocity vector,
∇^2 - the Laplacian operator.

3. Models for Controlled Drug Delivery

In the study of CRS, mathematical modeling of the release process plays a significant role as it establishes a mechanism of drug (solute) release and provides more general guidelines for the development of other systems. It is accepted that numerous successful controlled delivery systems have been developed as a result of an almost arbitrary selection of components, configurations and geometrics. Here, we survey some of mathematical models as given below.

A large number of mathematical models were developed to describe the release rate of drugs from matrix systems. In 1961, Higuchi [7] published the probably most famous and most often used mathematical equation to describe drug release from matrix system. This model was then extended to different geometries and porous systems [8]. The extended model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility, (ii) drug diffusion takes place only in one dimension (edge effects must be negligible), (iii) drug particles are much smaller than system thickness, (iv) matrix swelling and dissolution is negligible, (v) drug diffusivity is constant and (vi) perfect sink conditions are always attained in the release environment. The basic equation of the Higuchi model is,

$$M_t = A\sqrt{D\left(2C_0 - C_s\right)C_s t} \quad C_0 > C_s \tag{1}$$

where, M_t is the amount of drug released until time t, A is the release area, D is the drug diffusion coefficient, C_0 the initial drug concentration in the matrix while C_s is drug solubility.

A simple semi-empirical equation to model the release kinetics is the so-called power law equation **[**9]

$$\frac{M_t}{M_\infty} = Kt^n \tag{2}$$

where $M\infty$ is the amount of drug released after an infinite time, K is a constant and n is the exponent characterizing the release process.

A mathematical framework was developed [10, 11] for the study of drug release from partially and not coated hydroxypropylmethyl cellulose (HPMC) tablets. This was based on the assumption that the release resistance is due to drug dissolution and diffusion through the developing gel layer surrounding the dry glassy core. A comprehensive model was developed [12-14] to describe the swelling/dissolution behaviors and drug release from cylindrical HPMC matrices. The advantage of this model lies in defining the polymer disentanglement concentration below which chains detaching from swollen network happens. An extension of this work was developed [15-17] to consider species diffusion in both radial and axial directions. This model consider as the most advanced model for drug release from amorphous polymers undergoing swelling and erosion.

Several attempts have been made to develop mathematical model for drug delivery systems. The first mathematical model for drug release [18] was formulated in a dissolving polymer-solvent system. The transport was assumed to be Fickian and mass balances were written for drug and the solvent at the glassy-rubbery interface and at the rubbery-solvent interface. This model can predict both Fickian as well as non-Fickian behavior. It is noticed that front synchronization (i.e., velocity of glassy-rubbery interface, velocity of rubbery-solvent interface) leads to zero-order release in dissolution-controlled systems.

The model [18] was modified [19] by accounting for macromolecular chain disentanglement. It is enabled a molecular understanding of the dissolution mechanism of the polymer. This information is important to design tailor-made drug delivery systems for specific applications.

Drug therapy to the central nervous system (CNS) is complicated by the presence of blood barrier**.** There exists a great interest in developing an effective method of administrating therapeutic drugs to the CNS for computing a wide variety of neurological disorders, ranging from brain tumors and epilepsy to Parkinson's disease.

The development of new drug delivery techniques to overcome this obstacle will be aided by a clear understanding of the transport processes in the brain. A finite element model [20] was developed for predicting the distribution of drugs delivered intracranially to the brain. The model has been used to predict transport and distribution of interleukin-2 (IL-2), a cytokine that has been shown to be a potent activator of the immune system and is currently under investigation in the immunotherapy of different types of cancer, in the brain and studies the major determinants of transport, at both early and late times after drug delivery. They used magnetic resonance imaging to track the true evolution of drug concentration distribution over time in the brain. It is observed that the distribution of any drug in the brain is strongly dependent both on the transport pathways present in the brain and on the drug properties, such as diffusivity, hydrophilicity and its interaction with brain tissue. The study of IL-2 demonstrates the complex nature of its transport in the brain, being affected by transport modalities that may vary temporally and spatially. To maintain high local concentration in the brain over long periods of time, a sustained release of the drug is necessary without a sophisticated theoretical framework of transport in the brain and consideration of factors such as edema, one could make serious errors in the estimation of transport parameters. The model is a preliminary approach at incorporating the effects of edema and time-varying convective forces on transport in the brain. A rigorous analysis will help define the potential and limitations of any mode of delivery to the brain and particularly aid the development and rational design of polymeric drug carriers for intracranial implantation.

A mathematical model was published to describe drug release from dissolving hydroxypropyl methyl cellulose (HPMC) matrices [15, 16, 21] by considering cylindrical devices and accounting for both radial as well as axial transport. In this technique, dissolution rate is treated as an adjustable parameter. The model has been shown to possess predictive capabilities by comparison with experimental data on release of propanolol-HCl from HPMC matrices. When dissolution rate has been treated as a constant, the model prediction can at best be treated as qualitative, as evidenced from the over-prediction of the release rate at short times, and under-prediction of the release rate at long times. Dissolution rate is a function of time, incorporation of that effect into the model might lead to more meaningful predictions [22].

Mathematical modeling was used to elucidate the transport mechanisms involved in drug release from hydrophilic matrices [17] and allowing quantitative predictions of the resulting release kinetics. The practical benefit of this work was an improved design model that can be used to predict accurately the required composition and dimensions of drug-loaded hydrophilic matrices in order to achieve desired release profiles, thus facilitating the development of new pharmaceutical products.

Mathematical modeling [23] was used as a tool for (a) determining the principal mechanisms governing the pharmacokinetics and pharmacodynamics during localized paclitaxel delivery and quantitatively simulating interatumorel drug concentration, and (b) determining a drug release profile which maximizes tumor cell kill.

From these techniques a reaction diffusion model was derived which describes the principal process governing drug transport inside a solid tumor: diffusion and binding in the interstitial medium, drug clearance from the interstitial medium through the leaky micro vessels, passive uptake of free interstitial drug by the intracellular medium, and specific and nonspecific binding of drug in the intracellular medium

A mathematical model was developed for drug transport in human breast cancer tissue [24] on the basis of clinical study of patients with breast cancer, treated with the drug doxorubicin and of drug transport experiments using cultured human breast cancer cells. The clinical study revealed doxorubicin gradient in tumor islets of densely packed cancer cells, but not in connective tissue. This model allows simultaneous drug transport through the cellular network (transcellular path way), through the interstitium (paracellular pathway) and across the boundary between the two networks.

A mathematical model was proposed to predict the release kinetics and distribution profile of Doxorubicin from Pluronic gel into the breast tissue [25]. This model accounts for the two dimensional distribution of the drug inside a physiologically realistic breast geometry, it helps specialists to understand the drug delivery mechanism and allow physicians to make decision on an optimal dose to treat patients. In the above modeling only diffusive condition was considered. Next, a 3D mathematical model [26] was developed to predict the release of Doxorubicin from pluronic gel to treat human breast cancer and it is very useful to observe the side effect to adjacent tissue while concentration profile is releasing. Here, only diffusion coefficient was taken. A three dimensional simulation platform for controlled drug delivery of doxorubicin in breast model was developed and extended from the two dimensional controlled- release drug delivery model.

Recently, many models have been developed to study the release kinetics of polymer matrices [27-29]. Numerous mathematical models that predict drug release from degradable systems have been reported. A simple mathematical model was developed [30] to predict the release of many different types of agents from bulk eroding polymer matrices without regression. The comparison of model predictions and experimental data strongly suggests that the magnitude of the initial burst is directly proportional to the amount of agent localized to occlusions residing just inside the matrix surface. A unified model was developed [31] to predict release not only from bulk eroding and surface eroding systems but also from matrices that transition from surface eroding to bulk eroding behavior during the course of degradation.

Outlines and importance of the above technique of cancer treatment to emphasize the need for further investigations into the mathematical models capable of describing clinical responses to these therapies as given below.

3.1. *Models for polymeric controlled release system*

Polymer based drug delivery systems [1] have had enormous impacts on drug therapies. Not only can the drug delivery platform transport drug molecules effectively, it can also improve patient compliance, offer greater patient convenience, and extent product life cycles as patents expire. The development of advanced drug delivery can be facilitated through mathematical modeling of controlled release systems. Mathematical modeling aids in predicting the drug release rates and diffusion behavior from these systems by the solution of an appropriate model, thereby reducing the number of experiment needed. It helps an understanding the physics of particular drug transport phenomenon; thus facilitating the development of new pharmaceutical products. One of the objective of this article is to review some of recent mathematical models that have been developed to describe drug release from polymeric controlled release systems.

3.2. *Model of drug transport in human breast cancer*

There are so many studies have been conducted for the development of a drug delivery model in a cancer tissue and numerous papers have tried to design mathematical models of drug delivery for cancer treatment. Mathematical models can predict the drug concentration in the region of interest under different conditions such as various drug concentrations, tumor's location, various geometries, and a range of drug's diffusion coefficients in the tumor tissue etc.

A mathematical model of drug transport in tissue has been developed on the basis of a clinical study of patients with breast cancer, treated with the drug Doxorubicin and of drug transport experiments using cultured human cells [24]. This model allows simultaneous drug transport through the cellular network (transcellular path way), and across the boundary between the two networks. Drug transport across this boundary has been modeled using the results of the cellular drug uptake and efflux experiments. In this sequel, a mathematical model of drug transport in human breast cancer islets has been developed, in order to asses the effectiveness of drug treatments.

Drug transport in the interstitium,denoted by subscript '*e',* and in the second cell compartment, denoted by subscript '*2*', forming part of the cellular network, can be described by the following diffusion equations:

$$(\phi_e + A_c \times S_e)\times (C_e)_{,t} = D_e \times \nabla^2 (C_e) - S_e \times P_c \times (C_e - C_2) \tag{3}$$

$$Q_2 \times (C_2)_{,t} = D_2 \times \nabla^2 (C_2) + S_e \times P_c \times (C_e - C_2) \tag{4}$$

For radial diffusion in a sphere, we have

$$\nabla^2 = (1/r^2)\times(\partial/\partial r)\{\{r^2 \times (\partial/\partial r)\}.$$

The total volume- averaged drug concentration in the cells, C_a, is defined by:

$$C_a = (A_c \times S_e)\times C + Q_2 \times C_2 \tag{5}$$

The macroscopic drug diffusion coefficient of the interstitium can be expressed as

$$D_e = \phi_e \times D_{fe}/T_e \tag{6}$$

Drug transported through the cellular network must cross the outer cell compartment of each cell twice.

The microscopic drugs diffusion coefficient D_2 of the cellular network can be expressed as:

$$D_2 = D_{f2}/\left(1 + N_1 \times D_{f2}/P_c\right) \tag{7}$$

The derivation of Eq. (7) for D_2 is obtained as follows. The average drug concentration gradient in the cellular network is the sum of the concentration gradient in the second cell compartment and the concentration drop over a first cell compartment multiplied by $N_1 : \left(\partial C_2/\partial x\right) = -J_x \times \left(1/D_{f2} + N_1/P_c\right)$. The number of intersections of a straight line of a unit length in a tumor with a number density of cells given by $10^6/V_c$, and an average cell radius a_c is given by $V_c = \left(4 \times \pi/3\right) \times a_c^3 \times 10^6$ is equal to $N_1 = 2 \times \pi \times a_c^2 \times 10^6/V_c = \left(3/2\right)/a_c$. Tortuosity may result in lower value of N_1, but not much lower, since theoretically $N_1 > 1/a_c$. Substitution of Eqs. (6) and (7) in (3) and (4) gives:

$$\left(C_e\right)_{,t} = A_1 \times \nabla^2\left(C_e\right) - B_1 \times \left(C_e - C_2\right) \tag{8}$$

$$\left(C_2\right)_{,t} = A_2 \times \nabla^2\left(C_2\right) - B_2 \times \left(C_e - C_2\right) \tag{9}$$

where, $A_1 = D_e/\left(\phi_e + A_c \times S_e\right)$, $B_1 = \left(S_e \times P_c\right)/\left(\phi_e + A_c \times S_e\right)$, $A_2 = D_2/Q_2$, and $B_2 = \left(S_e \times P_c\right)/Q_2$, ($A_1$ and A_2 are the effective drug diffusion coefficients in the interstitium and in the cellular network). The boundary condition $C_e\left(R,t\right)$ for the boundary $r = R$ of tumor islet is given by the time dependent concentration in the blood of a patient, while the boundary condition $C_2\left(R,t\right)$ is given by the Eq. (9) with out the diffusion term.

3.3. 2*D model for doxorubicin controlled release system*

Doxorubicin is one of the most widely used anticancer drugs in chemotherapy treatment. It exhibits a broad spectrum of anticancer activity and has been used to treat a variety of human and animal solid tumors. Due to the short therapeutic life time of this drug, patients are required to receive the drug very often; and it may causes to severe side effects. When the drug is introduced to the patient, the drug concentration inside the patient's body sometimes exceeds the maximum effective level, resulting in toxicity, while it is below the therapeutic range [32], as shown in Fig. 1(a).

To better control the concentration of drug in the body, a localized delivery is introduced. The drug concentration can be maintained at the effective level for a prolonged period of time. In this delivery method, drug is encapsulated into a polymer matrix and is slowly released through polymer pores, as shown in Fig.1 (b). Polymeric device can control the concentration and the release rate of the drug [32]. Therefore, the drug can be released at the controlled rate, time and concentration.

A mathematical model with the reconstructed breast cancer has been proposed to account for an understanding of the drug delivery mechanism and aid specialists to test various hypotheses before performing clinical experiments which can be costly and time

consuming [25]. The drug delivery of two dimensional model for Doxorubicin can be modeled in terms of convection and diffusion and is given by

$$\frac{\partial C_{dox}}{\partial t} + \vec{\upsilon}\Delta C_{dox} = \nabla\left(D\nabla C_{dox}\right) - kC_{dox} \tag{10}$$

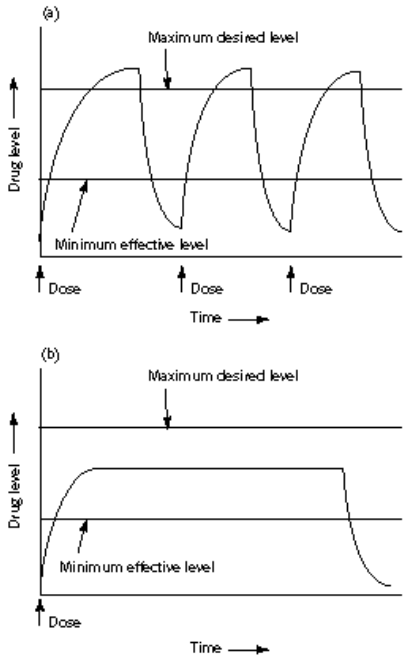

Fig. 1. Drug levels in the blood with (a) traditional drug dosing and (b) controlled-delivery dosing.

In order to verify the 2D model was developed [25], the prediction was compared with the experiment result from an *in vitro* study. The mathematical model was developed such that it would closely mimic the desired *in vitro* setting. The comparison between the model prediction and experimental result shows that the diffusion coefficient of doxorubicin plays an important role in developing an accurate model. In this sequel, the effect of diffusion and polymer degradation were considered while the effect of convection was initially neglected.

The mathematical model, used to explain this drug delivery system, contains only the continuity equation, because the system has no fluid flow and temperature change is neglected, i.e., $\vec{\upsilon}$ = 0 and K = 0, then the equation becomes,

$$\frac{\partial C_{dox}}{\partial t} = \nabla\left(D\nabla C_{dox}\right) \tag{11}$$

The diffusion rate in the above equation was calculated using by finite element method. The diffusion of doxorubicin inside the gel is significantly small which can be assumed to be zero. i.e.

D_{dox} = 0 within the polymer; ($r \leq R - K.t$).

Doxorubicin is freely diffused once out side the gel with the diffusion coefficient of D. That is,

D_{dox} = D in normal tissue; ($r > R + K.t$).

D_{dox} = D in Malignant tissue; (r > R + K.t),

where r is position of doxorubicin in the system (cm) and R is the radius of polymer (cm).

Doxorubicin concentration remains quite high inside the gel and drops sharply when moving away from the gel interface, indicating minimal doxorubicin diffusion. After about thirty minutes the gel interface starts with moving inward, while the concentration of doxorubicin in PBS solution increases. As time proceeds, doxorubicin diffuses further, creating a concentration gradient.

This model helped to predict the release kinetics and distribution profile of Doxorubicin from Pluronic gel into the breast tissue and also it accounts for the two dimensional distribution of the drug inside a physiologically realistic breast geometry. This model can help specialists to understand the drug delivery mechanism and allow physicians to make decision on an optimal dose to treat patients.

3.4. *3D model for a doxorubicin controlled release system*

A 3D mathematical model was developed [26] to predict the release of Doxorubicin from pluronic gel to treat human breast cancer and it is very useful to observe the side effect to adjacent tissue while concentration profile is releasing. They considered only diffusion coefficient in this study also. Their aim of this research was to develop a three dimensional simulation platform for controlled drug delivery of doxorubicin in breast model extended from the validated two dimensional controlled- release drug delivery model.

The diffusion coefficient of doxorubicin inside pluronic gel is significantly small which can be assumed to be zero and can be gradually increased to be higher value in PBS solution by sigmoid function. As time proceeds, gel's dissolving distance is $K\,t$ mm. Then the diffusion coefficient inside gel will be increased as the gel surface transform from a solidified surface into a rubbery surface. The drug is released near the gel's erosive surface while the gel is dissolving. The drug concentration inside the gel seems to be moving in a sigmoid pattern towards the center of the polymer based on equation (12). And the released drug is freely diffused once outside the gel with the diffusion coefficient of D as in equation (13).

D_{dox} = sigmoid function; ($0 < r \leq R - K.t$). (12)

D_{dox} = D in PBS solution (2.96×10^{-5} cm^2/s) ; (r > R + K.t) (13)

The diffusion rate in equation (11) was calculated using Finite Element Method.
Initial condition:

C_{dox} = 5.02x10^{-3}M; $(0< r \leq R)$

C_{dox} = 0M; (r > R)

Boundary condition:

D_{dox} = sigmoid function; $(0< r \leq R - K.t)$.

D_{dox} = D in normal breast tissue (2.7 x 10^{-10} cm^2/s) ; (r > R + K.t)

Observation

A 2D model was developed [25] to predict the release profile of doxorubicin from pluronic gel. The diffusion coefficient of doxorubicin inside pluronic gel is significantly low that the diffusion inside the gel is considered negligible. As time increases, the gel's surface gradually decomposes and doxorubicin can be released into breast tissue at higher diffusion coefficient. This drug's diffusion looks similar to a soft threshold which is defined by sigmoid function.

The 3D model developed [26] will be useful to observe the side effect to adjacent tissue while concentration profile is releasing. This model accounts for the three dimensional distribution of the drug inside a physiologically realistic breast geometry. Only diffusive condition was considered in this work. In the future work, one can modify this model to accommodate the convective condition as well as a more complex geometry. Mesh refinement and adaptive mesh will be used to improve for better accuracy.

4. Applications

The mathematical model equation can be used to design new systems by selecting the optimal geometry, method of formulation and size [2]. Mathematical modeling aids in predicting the drug release rates and diffusion behavior from these systems by the solution of an appropriate model, there by reducing the number of experiments needed. Mathematical modeling of controlled drug delivery can help provide a scientific knowledge base concerning the mass transport mechanisms which are involved in the control of drug release. Thus mathematical modeling can significantly facilitate the optimization of existing and the development of new pharmaceutical products. The systematic use of models can save money and time. The mathematical approaches may help researchers to develop highly effective drug formulations and more accurate dosing regimens.

5. Conclusions

The interest of this work was to discuss some mathematical efforts which were established to understand the mechanisms ruling controlled drug delivery. This represents the fact that mathematical models play a pivotal role in the design of drug delivery systems. The mathematical models discussed above will aid specialists to understand the drug delivery mechanism and allow physicians to make a decision on an optimal dose to treat patients. Mathematical modeling for controlled drug delivery will prove invaluable in the ongoing struggle to develop new and more effective therapeutic for the treatment of cancer. In

closing, we consider the generality of our approach, discuss related research on mathematical modeling, and suggest directions for further endeavors.

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