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Application of Ordinary Differential Equations in Pharmacodynamics-Pharmacokinetics and Cancer Treatment

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ABSTRACT

With the prevailing critic situation due to Covid – 19 pandemic, I felt that there is a great need to determine the accuracy in the vaccine or medicine we take. The surging health crisis due to environmental and habitat change challenges the experts to look for efficient medicines. This is the reason I chose for this topic as my thesis project. This paper reports the required mathematics for a typical challenging problem from computational medicine and the cancer therapy planning . Nonlinear ordinary differential equations (ODEs) that emerge in the pharmaceutical sciences require quick and precise solutions. For medical therapy, the efficiency of numerical algorithms, i.e. computing speed and monitoring dependability, was critical. This is especially true when it comes to pharmacokinetic–pharmacodynamics modeling and design. Models of tumor growth and treatment based on one or two ordinary differential equations are also often employed in practice because they are straightforward but may often capture the core of complex interactions. Furthermore, careful mathematical modeling was required before numerical algorithms could be used to solve the difficulties. The method is demonstrated by applying inductive approximations to a simple nonlinear pharmacokinetic (PK) model, i.e. a model that is nonlinear when expressed as an ordinary differential equation. The inductive method is particularly well suited for parameter estimates and optimal design approaches since the approximations are continuously dependent on the parameters and tome. This work also proposes a general method for modeling and analyzing cancer-immune interactions, with a focus on immune-induced tumor dormancy, utilizing ODEs.

Key Words: PKPD, parameter estimations, , tumor growth kinetics, angiogenic inhibitors, Michaelis – Menten concentration, efficacy, pharmacology, oncology,,substrates, inhibition, logistic equation ,

Introduction

Differential equations are equations that relate a function to one or more of its derivatives. One of the most fascinating and helpful areas in mathematics is differential equations. Differential equations can be used to describe a variety of fascinating natural events involving change. From a standard functional with penalized temperature restrictions to a medically preferred functional with ODEs equality requirements and stringent temperature inequality constraints, the therapeutic goal is transformed into a range of mathematical optimization problems of increasing difficulty. PKPD models are used to represent the time course of drug effects, and research into these processes has received a lot of interest. Pharmacokinetics models describe drug concentration variations in the body, whereas pharmacodynamics addresses the link between concentration and effect. Because of the nonlinearities in the structure of PKPD models, they are frequently described as ODEs. This research also emphasizes the dynamics of solid tumors that are large enough to be directly observed, at least before therapy. The application of ODEs can be used to forecast the models and treatment of such growth.

The modern era of cancer treatment is continually changing, with new breakthroughs and discoveries rapidly altering the course of treatment. It's crucial to figure out which treatment combination is best for the patient.

Problem Statement

2.1 Overview

The comparison of experimental states is required for parameter identification. A differential equation is a mathematical equation that connects the values of a function and its derivatives of various orders for an unknown function of one variable. The differential equation is known as an ordinary differential equation if it just has one independent variable. Ordinary differential equations (ODEs) explain how a function changes and contain derivatives of unknown functions. They're especially common in applied mathematics since they explain phenomena that change over time.The ODEs have to be supplements to cope with memory effects and noise. The change in the value of parameters is the aspect which parameter identification deals with.

2.2 General Formulation and Parameter Identification method

The governing equations:

i) The general form of first order nonlinear systems :

$dy/dt = F(t,y)$; $y(t_o) = y_0$ (1)

where t is the time, $y(t) = (y_1(t), y_2(t), \ldots\ldots\ldots, y_m(t))$ is a mX1 vector of response variables (i.e. concentrations or effects), and F: $\mathbf{R}X\mathbf{R}^{\mathbf{m}}$ $\mathbf{R}^{\mathbf{m}}$ is non – linear function of y.

The above equation can be rewrite as:

$dy/dt = A(t.y)y + f(t,y)$; $y(t_0) = y_0$ (2)

where A(t,y) is an m X m non - singular matrix, y(t) and f(t,y) are column vectors, and $A(t,y)y + f(t,y) = F(t,y)$.

ii) We also propose an integrated approach that allows immune actions to modify the net growth term through the following form:

$$dC/dt = \mu/\alpha(1 + \Psi(I,C))\, C(1 - (C/K_c)^{\alpha}) \quad (3)$$

Here μ and α are parameters that describes the growth and sensitivity of cancer cells to environmental regulatory signals, and Ψ is the function that can describe both immune inhibition or simulation of cancer growth. C(t) the growth of cancer cells over time, t and immune cells I(t).

And the inhibitory functional form is given by:

$$\Psi(I,C) = -\theta(I^{\beta}/\varphi C^{\beta} + I^{\beta} + \varepsilon \log_{10}(1 + I)) \quad (4)$$

Where θ,β and φ and ε are immune predation parameters.

The immune population is also describe by a modified logistic growth formulation,

$$dI/dt = \lambda(I = rC)\, (1 - I/K_1) \quad (5)$$

Where λ is the growth rate and r is a recruitment parameter.

2.3 Index Reduction Of Differential Algebraic Equations

1) Here we applied the inductive method described above to a non - linear system that describes the concentration of a drug with a first – order input and Michaelis - Menten output. i.e.

$$V\, dC/dt = k_a D e^{-k_{\alpha} t} - V_{max} C/ km + C\,, \; C(t_0) = 0 \quad (6)$$

Where $C(t_0)$ is the initial concentration of drug in the blood (at time 0) with units of mg/L, *D* is dose (1 mg) and the parameters, k_a (first order absorption rate constant), V_{max} (maximum velocity of the enzyme) and *km* (Michaelis – Menten constant – defined as the concentration for which the enzyme is at half – maximal rate). The parameters and their values are given in table 1.

This system can obviously be written in the form in the form of eqn (2) by letting

$y(t) = C(t)$ and

$$A(t,C) = - V_{max} C/ km + C\,, \; f(t,C) = k_a D e^{-k_1 t}/V, \quad (7)$$

And hence, according to the inductive scheme above and stating with the naïve initial estimate $C^{[0]}(t) = 0$ (for all t)

We can now generate successive approximation inductively which converge to the solution of eqn (6) i.e.

$$dC^{[n]}/dt = K_{\alpha} D e^{-K_{\alpha} t} - (V_{max}/V\ ) C^{[n]}(t)\,; \; C^{[n]}(0) = 0 \quad (8)$$

$$V \qquad Km + C^{[n-1]}(t)$$

For n=1,2,3,……..using the integrating factor formula we get the solution for n^{th} iterate expressed in integral form:

$$C^{[n]}(t) = {}_0\int^t e^{\int_\tau^t V_{Max}/V} \frac{K_\alpha D e^{-K_\alpha \tau}}{Km + C^{[n-1]}(s)} \frac{d\tau}{V}$$

We see that for n=1, this can be evaluated exactly to give the linear approximation i.e.

$$C^{[1]}(t) = \frac{K_\alpha D((e^{-V_{max} t} / VKm) - e^{-K_\alpha t})}{(V_{max}/ Km) - VK_\alpha)} \qquad (10)$$

Subsequently iterates can be estimate using Gauss – Legendre quadrature i.e.

$$C^{[1]}(t) \approx K_\alpha Dt \sum_{J=1}^{N_1} w_{1j} e^{-K_\alpha \frac{t(x_{1j}+1) - t(1-x_{1j})}{2}} \sum_{k=1}^{N_2} \frac{w_{2k} V_{max}/V}{Km + C^{[n-1]}_{(t(xij+3 + x2k(x1j+1))/4)}}$$

Where x_{ij}, w_{ij} are N_i- point abscissas and weights for i=1,2.

Table 1: Parameters and their values for the equations above

Parameter	Description	value/units
V_{max}	Maximum elimination rate	0.0734 mg/h
Km	Michael – Menten constant	0.3672 mg/L
V	volume of distribution	1L
k_α	Absorption rate constant	l/h

2) The equations (5) and (6) can also extends as

$dK_c/dt = pC(t) - qK_c(t)C(t)^{2/3}$,

Which allows the cancer cells to modify its own carrying capacity .Where p and q are growth stimulation and inhibition constants respectively. We may further this model to allow carrying capacities to depend on both populations and generally describe them by:

$dK_c/dt = f(I,C)$ and $dK_I/dt = g(I,C)$. (11)

Parameters values should be determined by fitting the model to experimental or clinical data.

Literature Review

Introduction to the Reduction approaches

The purpose of this paper is to explain the real life applications of calculus (ODEs) especially in medicine when considering drug dosages, blood flow ad tumor growth. This is important because ordinary differential equations can be used not only to solve and analyze in medical procedures more efficient and beneficially.

According to Bunker Hill Community College, Calculus is often used in medicine to determine the best dosage of a drug to administer to a patient. This is important when taking into consideration drug sensitivity, rate of dissolution and blood pressure. Specifically, the scope of this theme issue is to give a general view of the current research in the field of mathematical methods to medicine, as well as to show how mathematics can help in such important aspects as understanding, prediction, treatment and data processing.

The brief description about the Michaelis – Menten Equation:

$$v = \frac{V_{max}[S]}{Km + [S]} \qquad (12)$$

v = velocity of reaction

Here, V_{max} represents the maximum velocity achieved by the system, at maximum substrate concentrations. *Km* is the substrate concentration at which the reaction velocity is at 50% of the V_{max}. [S] is the concentration of the substrate S.

This equation is the rate equation for a one – substrate enzyme – catalyzed reaction. This equation relates the initial reaction rate (V_0), the maximum reaction rate (V_{max}), and the initial substrate concentration [S] through the Michaelis constant *Km* – a measure of the substrate – binding affinity.

Three assumptions are implicit in Michael-Menten equation, the rapid equilibrium approximation, the steady-state approximation and the free ligand approximation.

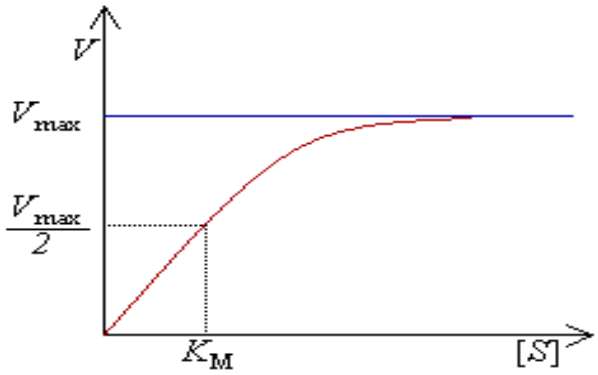

Fig:1 Graphical representation of Michaelis – Menten equation.

This is a plot of the Michaelis – Menten equation's predicted reaction velocity as a function of substrate concentration, with the significance of the kinetic parameters V_{max} *and Km* graphically depicted.

3.2 An Inductive Approximation to the Solutions of Systems of nonlinear ordinary differential equations in Pharmacokinetics – Pharmacodynamics:

The study of the time course of medication absorption, distribution, metabolism, and excretion is known as pharmacokinetics. The application of pharmacokinetic concepts to the safe and effective therapeutic management of medications in a single patient is known as clinical pharmacokinetics. Pharmacodynamics, on the other hand, is the study of the biochemical, physiologic, and molecular effects of medications on the body, including receptor binding, post-receptor effects, and chemical interactions. Pharmacokinetics is the study of how the body interacts with the medicine, whereas pharmacodynamics is the study of how the drug interacts with the body. The convergence of inductive estimates $C^{[n]}(t)$ is depicted in the diagram..... the bottom dashed line represents the linear approximation $C^{[n]}(t)$ (t). The inductive approximations approach the solution supplied by equation (5) solve in MATLAB as the number of iterations increases. Figure 1 shows the convergence of the inductive estimates $C^{[n]}(t)$ (using $N_1=N_2=5$ in the Gaussian quadratures). The number of iterations is variable and can be changed to fit the accuracy requirements of the model's intended application. The linear approximation C[1] is shown by the lower dashed line (t). The inductive approximations approach the solution supplied by the ODE45 saver in MATLAB as the number of interactions increases (MATrix LABoratories R2014a, The Works INc).

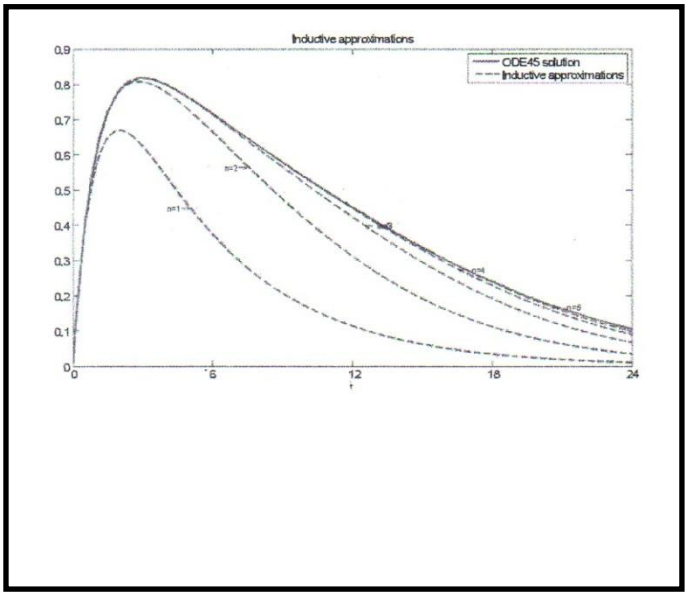

Fig2: convergence of the inductive estimates $C^{[n]}(t)$ to solutions of equation 5 for the parameter in

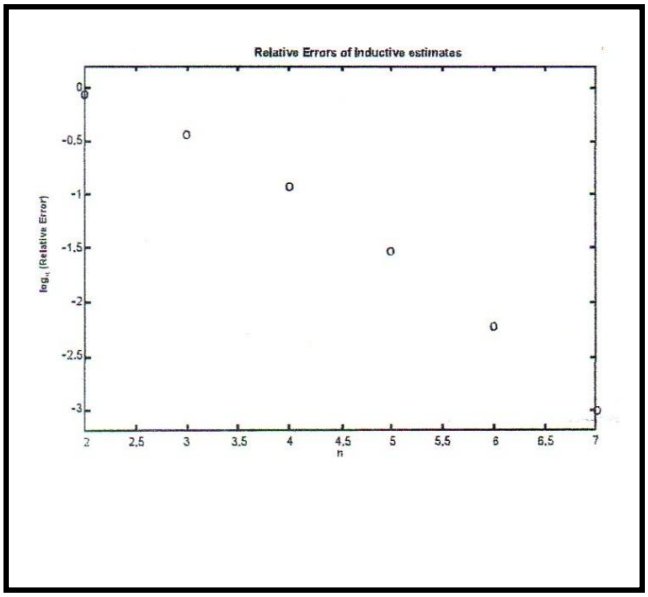

Fig3: Relative errors of successive inductive

3.3 Simple ODE Models of tumor Growth :

The interactions of cancer cells with the environment, which includes a variety of functionally distinct immune cells, determine tumor progression within a host. Immune-induced tumor dormancy is a stage of cancer growth in which the aberrant cells and microenvironment change over time, but the tumor mass stays the same. Immunotherapy tries to increase the cytotoxic immune response in order to eradicate the disease, yet it might have unpredictable and non-intuitive response dynamics.

The associated ODEs to mathematical modeling of tumor growth, where the growth is proportional to the tumor population, are shown in this section. We begin with a simple exponential tumor growth model. This model depicts the relationship between tumor site and time.

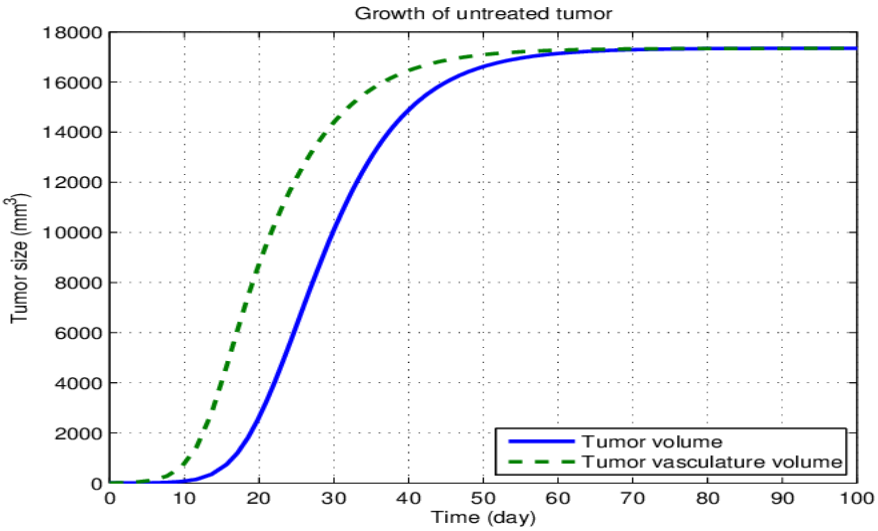

Figure: 4 logistic graph on tumor size and growth untreated tumor.

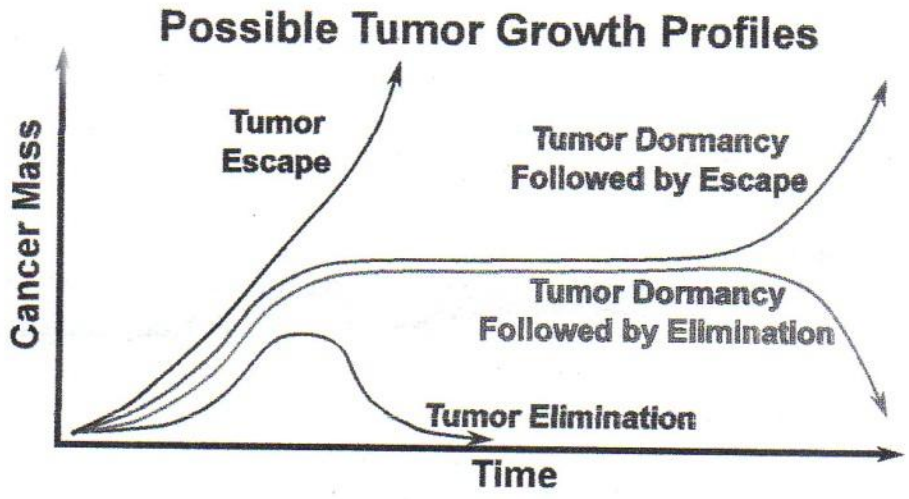

Fig 5: Possible tumor growth profiles including elimination, escape, and transient periods of tumor dormancy.

Tumor Dynamics Modelling:

Ordinary Differential Equations:

Basic growth model:

The bulk of the research used ordinary differential equations (ODE) to characterize variations in tumor load. In table 2, the natural growth of a tumor without treatment is often described by numerous fundamental functions, including linear, exponential, logistic, Gompertz, and a combination of exponential and linear models:

Figure 5 depicts the time curves of various models that were simulated. RxODE packets developed in R software were used to solve differential equations (version 3.4.1; R foundation for statistical computing, Vienna, Austria).

A constant zero-order growth rate is assumed in linear tumor growth. It has been used to describe the natural tumor progression of metastatic renail cell carcinoma 18 in patients based on measures of the target lesions' sum of longest diameter (SLD).

The exponential growth model assumes that a tumor's growth rate is proportionate to its size (first order growth; figure 6). It has been used to describe natural tumor growth in a commonly used tumor growth inhibition model developed by Claret et al.

A first order shrinkage term describing natural tumor death has been included to the linear and exponential growth models. For example, based on SLD measurements, a model with linear growth and first order shrinkage was used to describe natural tumor growth in patients with advanced solid malignancies. To represent the natural growth of pediatric neuroblastoma based on tumor volume data, an expoential growth with a first oreder shrinkage was also included as part of the model structure. For the description of variations in prostate cancer burden reflected by the amount of prostate-specific antigen, the same model structure was used.

When compared to linear and exponential growth models, the logistic and Gompertz growth models provide biologically realistic changes in the growth rate as the tumor burden grows (figure 6).

The logistic growth model posits that growth is constrained by a carrying capacity, whereas the Gompertz model assumes that the tumor's growth rate slows over time. The logistic and Gompertz moels, as well as simulation studies, have been used in several clinical research.

Finally, a model that combines exponential and linear growth models has been developed to describe tumor growth in patients, despite it was originally designed to characterize xenograph tumor dynamics. After reaching a threshold, this cimbine model structure assumes that exponential (first-order) growth shifts to linear (zero-order) growth (figure 6). It was commonly used to characterize the natural progression of vestibular schwannoma vlume in patients with neurofibromatosis type 2. Setting the power term to 20 increased the sharpness of the changes between the two growth patterns.

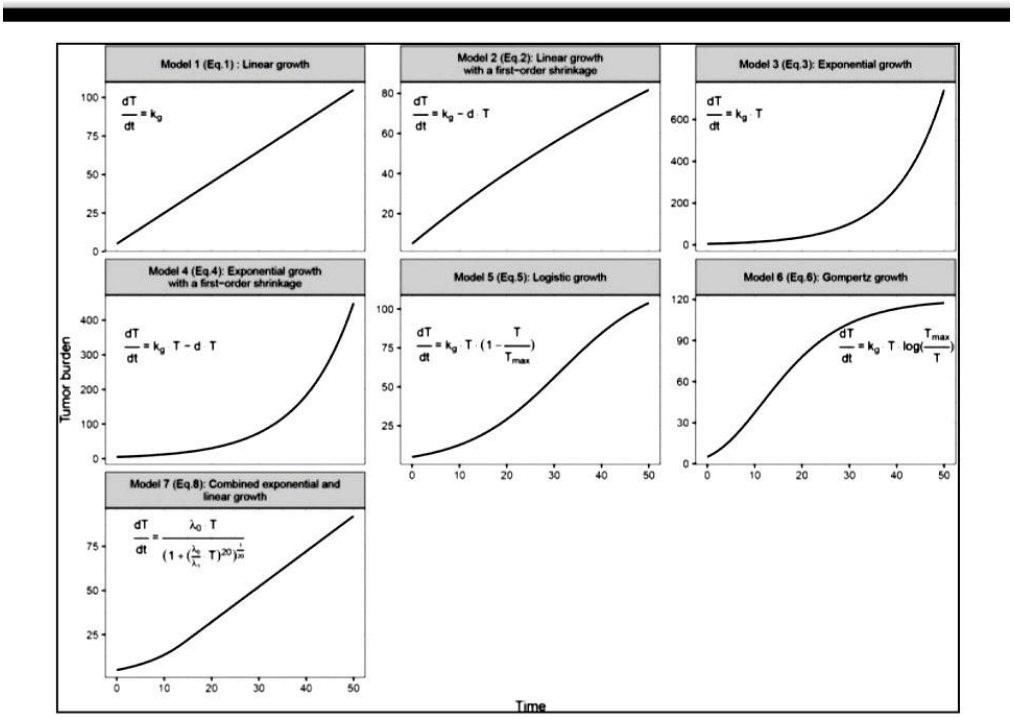

Figure 6: stimulated time curves of tumor burden(T) with tumor natural growth models displayed by the equations above**.**

3.4 The Generalized Logistic Equation

We know the general of exponential growth,

$$dN/dt = \lambda N, \qquad \lambda = \text{const.} \qquad (13)$$

One of the few near-universal observations about solid tumors is that almost all decelerate, i.e, reduce their specific growth rate ($\underline{dN}$)/N, a they grow larger [1,2].

dt

Consequently, equation (13) is often generalized to a nonlinear first-order ODE which incorporates growth deceleration [1,3-56]

$$dN/dt = f(N) \qquad (14)$$

Where f(N) is an appropraite function. Observed tumor growth is consistent with the assumtion that the tumor would reach some given limiting cell number, the host carrying capacity K>0, if the treatment or death did not intervene. The most commonly used example of an ODE has one global attracter for the region N>0, at a point K, as follows:

$$F(N) = NF(N/K) = (\mu N/\nu)\,[1-(N/K)^{\nu}], \quad \mu>0 \qquad (15)$$

Here, ν is real and the value ν = 0 is to be understood as a limit; taking the limit gives the Gompertz equation

$$F(N/M) = -\mu \ln(N/M) \qquad (16)$$

Equation (13) can be obtained from equations (14) and (15) by restricting attention to the region N<K and then taking the limit μ, ν → infinity with μ/ν fixed at λ.
One other special case is ν = 1 , the logisteic equation which equation (15) generalises. Roughly speaking, μ/ν in equation replaces λ and ν governs how fast the tumor approaches the limiting number K.
one ODE models have frequently been applied to experimental clinical application of equation and found an optimal value of close to 0.25 for ν.
In analyzing tumor treatments or experiments on cell killing by external agents, a very common assumption is that treatment modifies equation (14) by adding an extra term as follow:

$$dN/dt = -\alpha c(t)\,N + f(N). \qquad (17)$$

c(t) is the agent concentration at the tumor location, regulated by treatment schedule and pharmacodynamic effects, and is a positive constant, the strength of the chemotherapeutic agent. The killing term's direct proportionality to c and N relates to mas – action chemical kinetics for a therapeutic substance and a cell reaction.
It has a long history of using mathematical models to simulate dynamic biological processes. Quantitative approaches have found their way into cancer research during the last couple of decades. With the ultimate goal of understanding the response of the cancer population to clinical intervention, an increasing variety of mathematical, physical computing, and engineering techniques have been used to various aspects of tumor growth. In silico trials, which predict individuals' specific responses to alternative dose schedules, treatment combinations, and sequencing, are on their way to becoming a vital tool for improving patient care. In this paper, we describe the fundamentals of mathematical modeling of tumor growth and tumor-host interactions, as well as summarize some of the most popular methodologies.

In the field of oncology, drug resistance is one of the most common causes of therapy failure.
• Increasing knowledge of inter-tumor and intra-tumor heterogeneity, which suggests that different cells exist in different or the same tumor, as well as cancer evolution, has improved understanding of anti-cancer treatment resistances, highlighting the need for precision medicine rather than one-size-fits-all approaches.
• The use of modeling and simulation, which can objectively characterize and anticipate the relationship between drug-exposure PK drug effects PD and disease development, is widely accepted to help drug decision making.
One important class of models used in cancer pharmacology is mathematical models that characterize the effect of anti-cancer medication treatment for solid tumors based on tumor size dynamics, which is often quantified with measurements of tumor diameter and volume. Various tumor growth modeling methodologies, such as agenty-based models, image-based models, multiscale models, and PK/PD models, have previously been reviewed.

To identify the challenges and opportunities of characterising tumor size changes and resistance evolution simmultaneously with a model based approaches that can facilitate ant-cancer treatment optimization and persolized medicine, an overview of the current available model structure is neeed. Thus, in the current review, we comprehenshiply smmarised mathematical models for the characterization of tumor growth,(inhibition) dynamics in solid tumor and the relevant clonal evolution of drug resistance by a systematic search an study of previous literature. The focus in this review lies particularly on models that are applicable for clinical data.

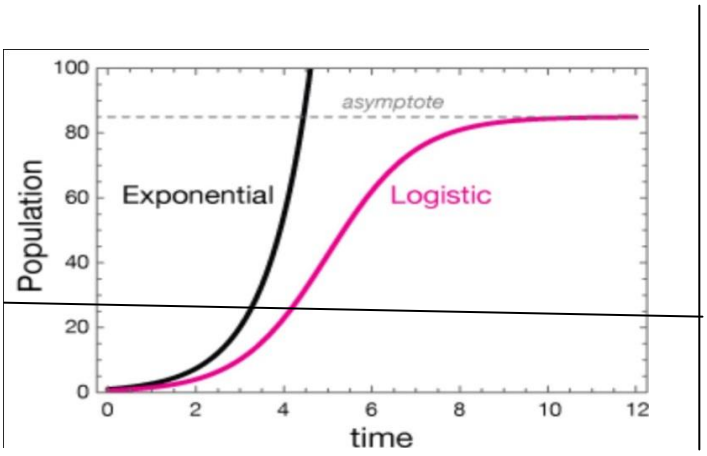

Fig 7: simple Logistic and Exponential graph

4 Parameter Identification Method:

4.1 General Iteration Process for Methods Implemented in this Project:

In computational mathematics, an iterative method is a mathematical procedure thatuses an initial value to generate a sequence of improving

approximate solutions for a class of problems, in which nth approximation is derived from the previous ones. The mathematical method that is used in this project or model is mostly calculus. The logistic equation (ODE) is often used to dtermine the required parameters.

4.2 General Description of Michaelis – Menten output:

The process described by the Micheal – Menten equation can be represented by a series of first order Differential Equations. These differential equations define the rate of change of each substance to be equal to the rate constant multiplied by the concentration of each molecule in the chemical reaction. But when there is a substrate inhibitation or activation due to the binding of a second substrate molecule, the Michaelis – Menten equation does not hold.

In an enzyme catalyst reaction when there is large excess of substrate and the enzyme concentration is held constant, if substrate concentration is plotted against velocity or reaction rate , a hyperbolic curve is obtained (figure 7). This type of plot is also known as saturation plot.

In the beginning, there is approximately direct proportinality between substrate concentration and reaction rate untill the enzyme concentration becomes limiting and a steady state is obtained. In this situation addition of more substarte will not increase reaction rate because all the active sites of the enzyme are saturated with substrate molecules and the rate of reaction will increase only by addition of more enzyme.

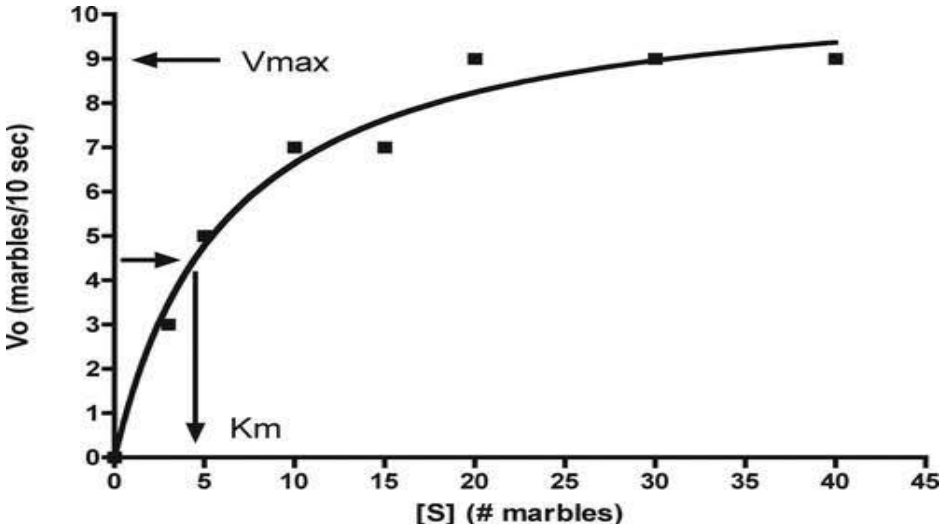

Figure 8: Michaelis – Menten graph

The concentratiopn of substrate required to half saturate the enzyme or in other words to cause half the maximal reaction rate(½ V_{max}) called as Michaelis – Menten constant and is denoted by K_m . Michaelis constant is a reflection of the affinity of enzyme for its substrare and its characteristic of a particular enzyme – subtrate system.

The smaller the value of K_m, the more stronly the enzyme binds the substrate. An enzyme that catalyses a reaction between two or more different substrate has different $K_m$value for each of the substrate.

Kinetics values of enzyme catalysed reaction are usually measure under steady state conditiopn and describe by a simple expression called Henry-Michealis-Menten, equation.

Signifance of Michaelis – Menten equation:

There are many advantages of knowing the K_M values of enzyme- substrate system:

- By knowing the K_m value of a particular enzyme – substrate system, one cn predict wehether the cell need more enzyme or more substrate to speed up the enzymatic reaction.
- If an enzyme can catalyst a reaction with two similar sunstrate (eg. Glucose and fructose) in the cell, it will prefer the substrate for which the enzyme has lower K_m value.
- K_m value gives an approximate measure of the concentration of substrate of the enzyme in the part of the cell where reaction is occuring. For instance, those enzyme which ctalyst reaction with relatively more concentrate substarte(such as sucrose) , usually have relatively high K_m value. On the other hand the enzyme that react with substrate which are present in very low concentration (such as hormones) have comparatively lower K_m value for the substrate.

4.3 Brief Translation on Cancer-Immune Interactions into Mathematical form:

We demonstrate how tumor dormacy is a transient state that necessarily ends in either tumor elimination or escape throught Logistic Equation. This method also determine the acccelerated repopulation and anomalous periods periods of growth prior to regression that have been observed post tumor

treatment. The method of applying ODEs to study cancer-immune dynamics requires, in the basic form, prescribing equations for the rate of change over time of the cancer cel and immune cell populations, thus creating a system of two ODEs that are solved simultaneiusly.

To conduct comparative effectiveness research on treatment options commonly used in community-base oncology practices, researchers need generalizable and accurate data about the entire treatment historyof patients diagnosed with cancer. Tumor registries generate extensive information about the first course of systemic therapy in patients, but they do not capture the full course of treatment, including the number of courses, discontinuation of therapy, or the use of multiple courses of therapy.

5 Dicussion:

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimixation of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral biovailability.

Recently many dicoveries regarding pharmacodynamics-pharmakinetics has disclose the possible strategies for optimising the clinical utility based upon the pharmacological studies throught computational mathematics. Therapeutic drug monitoring is increasingly giving way to dosing base on population based pharmakinetics values very quite a bit in individual patients. The FDA has approved a form of gene therapy. It uses some of our own mmune cells, called T cells, to treat the cancer.We have dicussed that the drug efficacy depends on multiple factors including absorption, distribution, metabolism and elimination and the effect of the drug to the body. Once the pharmacokinetics behaviour of a drug and its initial safety is confirmed in normal healthy volunteers in the early stage / phase 1 studies, additionally phase 12 studies are performed to determine if PK differs in various special populations. In phase 1 testing where safety is paramount and few prior data rare are available, the relatiuonship between drug dose aministered and patient exposure (C_{max} and AUC) is examined and PK parameters may be linked to toxic and therapeutic events.

An essential part of the drug development plan is to establish that the compounds is safe and effective. Well – designed pharmacokinetics trials(which determine how the body affects the drug) measuring plasma levels of varying doses across time, provide the knowledge to plan well-controlled later phase triasls with different doses , or dosing regiments, to evaluate how the drug affectsnthe body (pharmacodynamics) and establish safety and efficacy. Pharmacodynamics – pharmacokinetics modelling and approaches have been a part of clinical research and development since the 1980s. pharmacokinetics – pharmacoynamics are two broadly devided of pharmacololy that provides a better understanding of drug efficacy and safety. Both pharmacokinetics and [phjarmacodynamics investigations are mandatory for the drug development process as both are fundamental requirements for the clinical usage of drugs. In other woprds, clinical pharmacokinetics is used for measuring the rate of a drug/ medicine's absorbtion , ,etabolism , excretion and distribution. The key object of harmacokinetics is to enhance efficiency and minimizing he harmfull effects of patients' drug therapy. Appication of pharmacokinetics principle is hightly beneficial for prescribers as it gos a long way towards helping them in ajusting drug dosage more accurately. Pharmacodynamics analyse the complex interactions between the boy and drug. While pharmacokinetics emphasizes the movement of a drug within the body. Pharmacodynamics refers to the molecular, physiological, and biochemicals affects by the drug to the body. It the interconnection t between the drug concentrarion t the site of drug action and the inter-effect, along with the timeframe and magnitude of curvature and adverse effect.

Importance of pharmacokinetics – Pharmacodynamics for drug companies and patients:

1. Without pharmacodynamics and pharmacokinetics investigation of the drug , regulation agencies would not approve its use.
2. PK-PD analyse help drug exposure: quntifying the inetnsityof drug exposure is necessaryfor identifying the ebst and safest way to make use of it in clinic.
3. Drug dosing requirements: PK-PD analyse help researchers deduce dosage requirements early in thye drug development procedure.
4. Evaluate modifications in dosing requirements: alterations in the formulatiopn of drugs are quite common in the early stage og drug development. Therefore, it is essential to dforecast the biologicasl impact of minor diiiiiiosage changes early in the drug development process.
5. Guesstimate the rate of absorption/elimination: PK-PD help researchers understand how quickly a body absorp and eliminate drugs so that they can make decisions pertaining to drug formulation and dosages requirements.
6. Determine safety margins: PK-PD modelling help analyze dosing threshold to determine the safety of the drug and identify maximum tolerated dosage.
7. Comprehend concentration – effect inter relationships: since the concentratin effect relationship is the foundation of PD, it is variables affecting the relationship to facilitate a successful drug development.

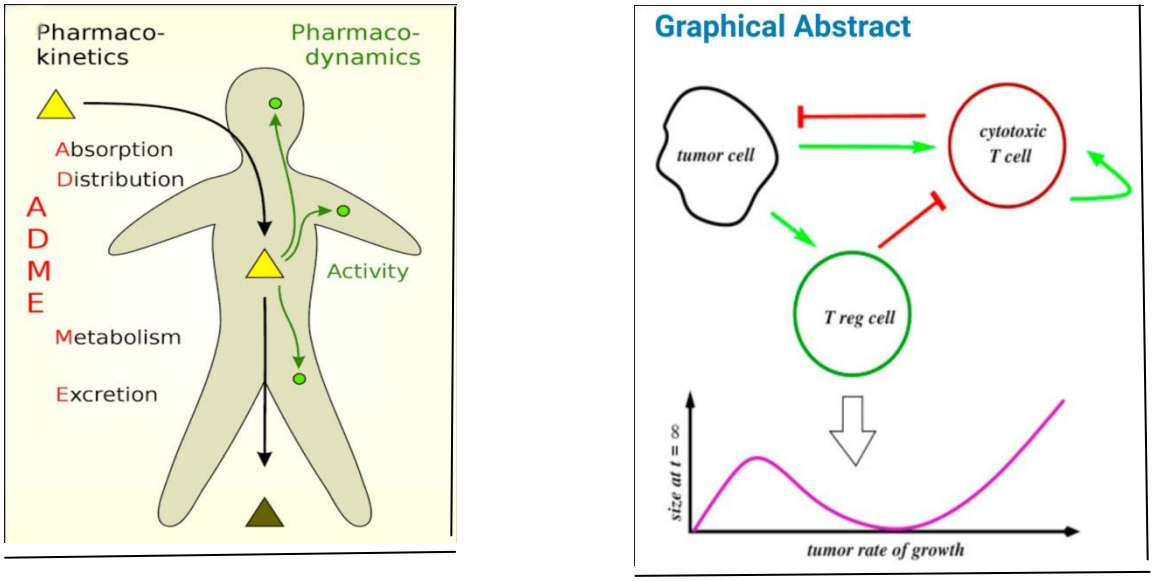

Figure 9: Inter-relationship of PK and PD and graphical abstract of tumor growth.

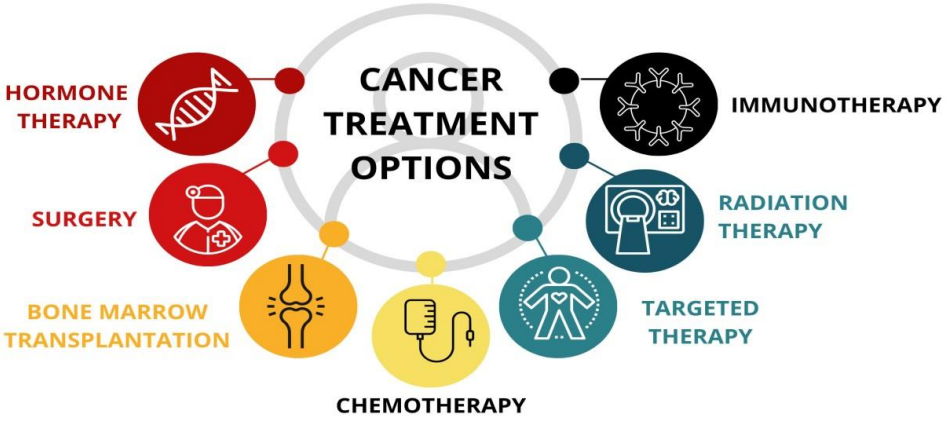

Figure 10: Types of cancer treatment

Why should we get Vaccination? What does vaccine efficacy mean?

Vaccine efficacy is a crucial marker to determine percentage reduction against illness amongst people during clinical trials. The efficacy rate determines the workability of given COVID 19 vaccine under clinical setting and showcases how potent itcould be, once approved. Now all four vaccines (COVASHIELD, COVAXIN, MODERNA and SPUTNIK V) that have passed the WHO nod for 50% efficacies against transmission. A vaccine shown to be highly effective in clinical trials with lasting protection and rare major side effects will command the public respect, paricularly if major public health organisations endorse it, as found by thr reserarchers. There won't be as many takers for vaccine that meets minimum U.S Food and Drug Administration standards, is approved under emergency use protocols. " The rolled of the vaccine and the public health effor to coomunicate to people the importance of getting vaccination".

Effectiveness would be the single most important factor in promoting the vaccine.

Following table shows the effecacy percent of COVID 19 vaccine in first and second vaccinaton:

Table 2: Efficacy of Covid vaccine

Vaccines	Covaxin	Covashield	Sputnik V	Moderna
First dose	77.8%	70.42%	78.6%	91%
Second dose	91%	83.1%	83.1%	100%

Covid 19 is a bigger risk than vaccine side effects but there are safety nets in place to monitor the covid 19 vaccines, and they are still working as they should. The covid 19 vaccines are proven to be overwhemimgly safe for most peple. The COvid 19 vaccine authorised are highly effective at preventing severe desease and death, including against the Delta variant. But they are not 100% effective and some fully vaccinated people will become infected (called at breakthrough infection) and experience illness.

6 Conclusion:

The main objective of my thesis project is to figure out how effective pharmaceutical doses are. Targeting the immune system to fight cancer/tumor cells is becoming a reality, as evidenced by the relative success of current immunotherapies, thanks to the development of new technical preclinical models and high-resolution equipment. This has opened up exciting new avenues, as exemplified by how targeting the immune system to fight cancer/tumor cells is becoming a reality, as evidenced by the relative success of current immunotherapies. This study also includes a brief overview of spatially homogenous mechanistic mathematical models that describe the interaction of a chemical with a cell or a tumor cell with the immune system. We start with the most basic models and work our way up to greater immuological detail. This method highlights the need to increase the complexity of models in order to capture the biological systems that we understand.

Finally, we'll go through some recent breakthroughs in cancer treatment and Phamacodynamics-Pharmakinetics. Finally, this project issue features a collection of excellent contributions at the junction of mathematics and medicine, not as an exercise in applied mathematics, but as a multidisciplinary research effort that cuts across both communities and our society as a whole.

Pharmacokinetics is a fundamental aspect of drug development and a vital part of early drug development, as indicated in the above article overview. Pharmacokinetics is a method utilized throughout the drug development program to link exposure to efficacy and safety, and it aids in the calculation of dosges of marketed medications; as a result, PK data are an important part of the information offered to clinicals.

A growing number of research involving the gene sequencing of tumor biopsies from various cancer types have revealed the dynamics of cancer progression. Intra-tumor heterogeneity, which results from cancer evolution and is evolving adaptability of heterogeneous tumors to treatment, is also becoming more well recognized as a significant element in the establishment of resistance. Mathematical models that included tumor evolution have been proposed to better characterize this process and account for tumor heterogeneity. Such evolution models, in combination with tumor growth models, may be useful in interpreting both tumor size changes and changing tumor progression throughout therapy, resulting in more rationalised appropriate treatments for individual patients and the eventual elimination of treatment resistance.

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