A STUDY ON DYNAMIC MATHEMATICAL MODELLING IN BIOLOGY

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by

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CERTIFICATE

This is to certify that the dissertation entitled, **A STUDY ON DYNAMIC MATHEMATICAL MODELLING IN BIOLOGY** is a bonafide record of the work done by Ms. **MEERA JOSEPH** under my guidance as partial fulfillment of the award of the degree of **Master of Science in Mathematics** at Bharata Mata College, Thrikkakara affiliated to Mahatma Gandhi University, Kottayam. No part of this work has been submitted for any other degree elsewhere.

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DECLARATION

I hereby declare that the work presented in this project is based on the original work done by me under the guidance of Dr.Lakshmi C, Assistant Professor and Head, Department of Mathematics, Bharat Mata College, Thrikkakara and has not been included in any other project submitted previously for the award of any degree.

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Thrikkakara. MEERA JOSEPH

Date: 30/05/2024 **220011015803**

ABSTRACT

Dynamic mathematical modeling in biology offers a transformative approach to understanding the intricate dynamics of living systems. By translating biological processes into mathematical equations, this field enables the simulation and analysis of complex behaviors over time. From cellular signaling pathways to ecological interactions, dynamic models provide insights that deepen our comprehension of biological phenomena. Through this project, we embark on a journey to explore the principles, methodologies, and applications of dynamic mathematical modeling in biology, uncovering its role in advancing scientific understanding and addressing real-world challenges.

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Chapter 1

INTRODUCTION

Mathematical modelling is becoming an increasingly valuable tool for biology. More so is Dynamic mathematical modelling. Dynamic mathematical modeling in biology explores complex systems, using equations to simulate and understand biological processes like growth and interactions. Such models capture the dynamics of populations, ecosystems, and cellular processes, contributing to breakthroughs in fields like medicine and ecology. A Dynamic mathematical model accounts for time-dependent changes in the state of the system.
In this study we aim for learning the methods to develop a model based on ODE and also to analyse it.
Before diving into how to create a model it will be essential to skim through some basic concept in molecular biology as we will be studying mathematical modelling in molecular biology as well. We will also be studying mathematical modelling in macro biology which does not require the prerequisite of studying the molecular biology.

The rest of the sections in this chapter contains some essential concepts we need to know for creating a mathematical model.

1.1 Some Basic Concepts

Before we begin, we should know that every model that we create will only be a simplification of the real phenomenon; Thus it might not an-

swer all the problems related to that event.
The first step in creating a model is to collecting information; this is mainly through existing literature, old models etc.,
The second step we need to make is to simplify the model using assumptions.
The third step is to create a graphical model; which will serve as a visual representation of complex processes.
The final step is to create the model and analyze it.
This study is restricted to creating models using ODEs. So, in regards to ODE, we will always have to make some key assumptions such as,

- The system is homogenous (well mixed)
- Size of the system is large

We will have to make the first assumption since we are employing ODEs, our only independent variable will be time and not space; thus our system must be identical through out so that the system will not change depending on space.
We make the second assumption so that the dependent variable changes continuously.(So that Calculus may be applied.)

1.1.1 Law of Mass Action & Rate Constants

We will be creating models based on Law of Mass Action: *the rate of a chemical reaction is proportional to the product of the concentration of the reactants.*
The Law of mass action has an intuitive basis: it states that the probability of of a reaction occurring is proportional to the probability of the reactants colliding with one another.

Reaction	Rate of reaction
X$\longrightarrow$ P	k_1[X]
A+B$\longrightarrow$ C	k_2[A][B]
D+D$\longrightarrow$ E	$k_3[D]^2$

The exponent to which each reactant appears in the rate law is called

the *kinetic order* of the reactant in the reaction. For example, reactant A has kinetic order 1 in the second reaction listed above, while D has order 2 in the third reaction. If a reaction describes uptake from the outside environment, it can be written with no explicit reactant (e.g. $\longrightarrow$A). The rate of such a reaction is constant. Because these reactions satisfy a rate law with a reactant concentration raised to the power zero($k[S]^0 = k$), they are called *zero-order* reactions.
If you have observed the rate of reactions, given in the table, you will notice that there are constants like k_1, k_2 etc., they are nothing but the constant of proportionality and is called *rate constant* of a reaction and can be indicated in the reaction formula like this:

$$\mathbf{A} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

The dimensions of the rate constant depend on the number of reactants. The rate constant for a single-reactant reaction has dimension of $time^{-1}$.
If a reaction has two reactants, the rate constant has dimension of $concentration^{-1} \cdot time^{-1}$.
For a zero-order reaction, the rate constant is equal to the reaction rate which has dimension of $concentration \cdot time^{-1}$.

1.1.2 Transient & Steady-state

A system is said to be at steady state when it has achieved dynamic equilibrium; i.e.,when the rates of change of various quantities are balanced, resulting in a constant state of the system.
Thus, to find the concentration of substrates or product during steady state, we may equate the ODE or the system of ODEs to zero to obtain the value or ratio.
Note that in steady state there is a non-zero flux through the network.

Transient is the state of the system before it achieves steady state. So we could say that the transient state occurs while the concentration relaxes to its steady state value.

1.1.3 Analytic method Vs. Numerical simulation

Analytic method is the method in which we find solutions to an ODE analytically(i.e, with paper and pen),whereas Numerical simulations produce approximate values of the solution at a specified collection of time-points using computational method.
Numerical simulation of differential equation models are not as useful as analytic solution formulas, for two reasons. Firstly, an analytic formula is valid for all initial conditions. In contrast, each numerical must be generated from a particular initial condition. Secondly, the dependence on the model parameters can be easily discovered from an analytic solution formula; but no such insights are granted by the numerical simulation, in which the parameter values are fixed.
Nevertheless, we use numerical simulation in most of the models since finding solution analytically to complex ODEs are quite hard.

1.1.4 Basic Principle of Numerical Simulation

We normally use computational software to simulate ODE models. In this section we will learn about the algorithms used by those computational soft-wares to generate simulations.
The simplest form of such an algorithm is *Euler's method.* which is

based on the following approximation:

Given a differential equation of the form
$\frac{d}{dt}a(t) = f(a(t))$
the derivative $\frac{d}{dt}a(t)$ **can be approximated by a difference quotient:**
$\frac{d}{dt}a(t) \approx \frac{a(t+h) - a(t)}{h}$, **for** h **small.**
Substituting this approximation into the differential equation gives
$\frac{a(t+h) - a(t)}{h} \approx f(a(t))$.

Treating this as an equality yields an update formula that can be used to determine the approximate value of $a(t+h)$ **given the value of** $a(t)$**:**

$$a(t+h) = a(t) + hf(a(t)). \tag{1.1}$$

Euler's Method consists of applying this update formula repeatedly. To implement Euler's method, we choose a step-size h**. This yields a mesh of time-points** $t = 0, h, 2h, 3h, ..., nh,$ **for some fixed number of steps n. Given the initial value of a(0), we then use formula (1.1) to approximate values at the other points on the grid:**

$$\begin{aligned}
a(0) &= a(0) \qquad \textbf{(given)} \\
a(h) &= a(0) + hf(a(0)) \\
a(2h) &= a(h) + hf(a(h)) \\
a(3h) &= a(2h) + hf(a(2h)) \\
&\vdots \\
a(nh) &= a((n-1)h) + hf(a(n-1)h)
\end{aligned}$$

Because the computer can carry out these repeated calculations rapidly, the step-size h **is often chosen so small that the set of points generated**

by this algorithm appears as a continuous curve.

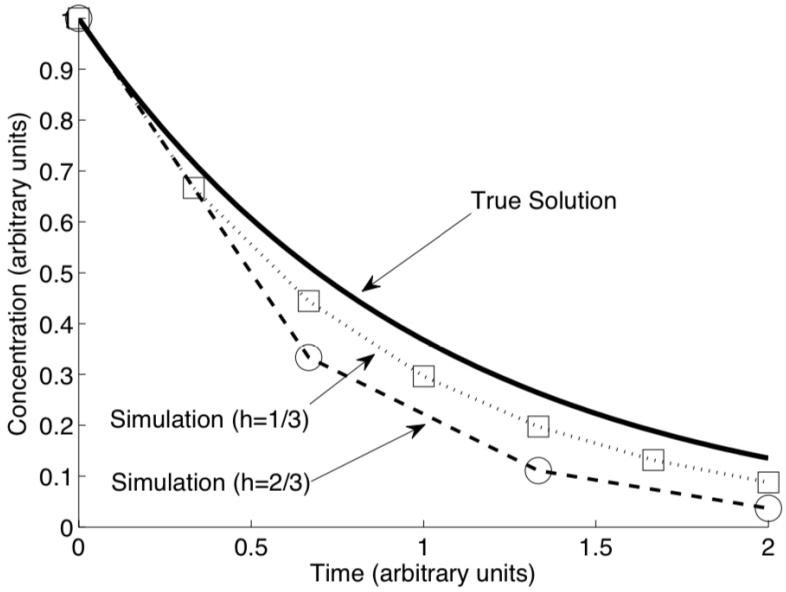


Figure 1.1: Numerical simulation of the model $\frac{d}{dt}a(t) = -a(t)$. The initial condition is a(0)=1.

Figure 1.1 shows simulations generated for two different step sizes. The simulation is more accurate/closer to the true solution when the step size h is chosen to be smaller.

Computational software packages that implement numerical simulation make use of algorithms that improve on Euler's Method. Some examples of such soft-wares are MATLAB, XPPAUT, JSIM etc,.

1.1.5 Simulating a model using Matlab

In order to simulate a model using Matlab, first, we have to enter the code in the editor tab and save it with a suitable name, say, *Model1.m* (MATLAB files end with the file extension .m. They are referred to as m-files). Then, to simulate the model, we need to enter the name in the command line without the extension '.m'.

Given below is the code to simulate an enzymatic reaction model. (given in section 2.2.1 of Chapter 2)

```
function simulateODEs()
    % Define constants
    k2 = 0.1;   % Example value, replace with your actual value
    k3 = 0.2;   % Example value, replace with your actual value
    KM = 300;   % Example value, replace with your actual value
    ET = 3;   % Example value, replace with your actual value

    % Define time span for simulation
    tspan = [0 10000];  % Time span from 0 to 10 (example), adjust as needed

    % Initial conditions
    S0 = 1000.0;   % Example initial condition for S
    P0 = 0.0;   % Example initial condition for P
    y0 = [S0; P0]; % Initial condition vector

    % Solve ODEs
    [t, y] = ode45(@ode_system, tspan, y0);

    % Plot results
    plot(t, y(:,1), 'b-', t, y(:,2), '--');
    xlabel('Time');
    ylabel('Concentration');
    legend('S', 'P');
    title('Simulation of ODEs');
    grid on;

    % Define the ODE system
    function dydt = ode_system(t, y)
        S = y(1);
        P = y(2);

        dSdt = -k3*ET*S/(KM+S);
        dPdt = k3*ET*S/(KM+S);

        dydt = [dSdt; dPdt];
    end
end
```

This m-file makes use of the command ode45 to generate the simulation. This is one of many simulation routines that are available in MATLAB.

Note that lines in the code that begin with % are comments that are ignored by the program. MATLAB is case-sensitive. The end of a command is indicated with a semicolon.

1.2 Some Basic Concepts for Modelling in Molecular biology

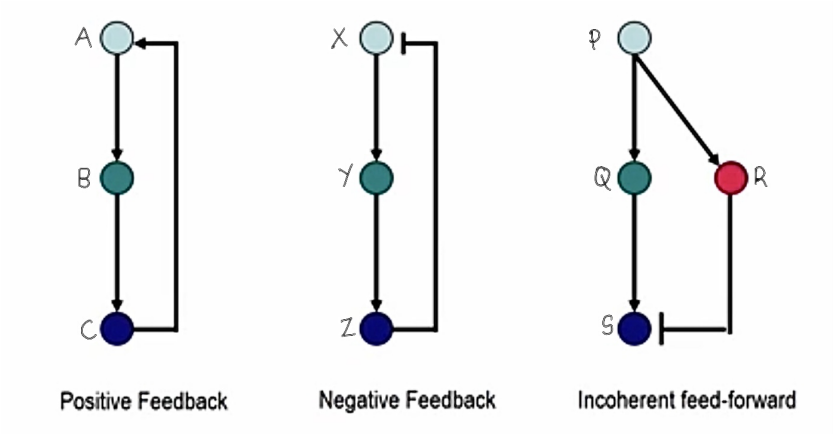
A large molecular network controlling a cellular process involves large number of molecules and processes. So, it is often difficult to study such large network as it is.

So, in order to model a molecular network we will have to break it down into recurring small sub-networks with specific dynamics and functions

called network motifs.

A network motif is made up of a few *elementary processes* like Ligand-receptor interaction, Enzymatic reaction, Transcription and Translation etc,.

There are many types of motifs. Some of the most common motifs are Positive feedback motif, Negative feedback motif and Incoherent feed-forward.



As you can observe in the figure given above, the positive feedback motif is a process in which an entity A induces the production of B which in-turn induces the production of C which in-turn induces the production of A, resulting in the amplification of concentration of A.

Whereas in negative feedback motif, an entity X induces the production of Y which in-turn induces the production of Z which inhibits the production of X resulting in the depletion of concentration of X.

In Incoherent feed forward lets say P is a transcriptional factor which induces the production of two other transcriptional factors Q and R in which Q induces the production of S whereas R inhibits the production of S, resulting in a controlled expression of S.

1.2.1 Quasi-Steady State Assumption(QSSA)

When constructing a dynamic model, one must decide which time-scale to address. This choice is typically dictated by the time-scale of the relevant reactions and processes.

Biological processes take place over a wide range of time-scales. Con-

sider, for example, a genetic network that generates a circadian rhythm. A model of this network will describe oscillatory behaviour with a period of roughly 24 hours, and so will incorporate processes acting on the time-scale of hours. However, the network is based on gene expression, which involves the binding of proteins to DNA; these chemical processes happen on the scale of seconds. Moreover, the circadian oscillator is entrained to seasonal changes in the light-dark cycle-changes that occur on the order of months. It would not be possible to resolve all of these time-scales in a single model.

To model a system that involves processes acting on different time-scales, a primary time-scale must be chosen. Other time-scales are then treated as follows:

- processes occurring on slower time-scales are approximated as frozen in time;
- processes occurring on faster time-scales are presumed to occur instantaneously.

Thus we will have to reduce a model by separation of time-scales.

This model reduction process approximates the original model with a model of reduced complexity.

We next present techniques for model reduction by separation of time-scales.

Elimination of slow variables is straightforward-we simply assign a constant value to each slow variable and treat it as fixed parameter. The treatment of fast variables requires more care. There are mainly two approaches that allow processes to be treated as instantaneous: The Rapid Equilibrium Assumption and the Quasi-Steady State Assumption.

The rapid equilibrium approximation is reached by treating individual reaction processes as instantaneous. Whereas the QSSA focuses on individual species. Evermore, the rapid equilibrium assumption may sometime produce error whereas the QSSA is guaranteed to be accurate at steady state.

We will be only considering the QSSA model reduction method. Consider the network:

$$\xrightarrow{k_0} \quad \mathbf{A} \quad \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad \mathbf{B} \quad \xrightarrow{k_2}$$

So, our model will look like (will be explained how in Chapter 2):

$$\frac{d[A]}{dt} = k_0 - k_1[A] + k_{-1}[B]$$

$$\frac{d[B]}{dt} = k_1[A] - k_{-1}[B] - k_2[B]$$

suppose $k_1 + k_{-1} \gg k_2$

we observe that all dynamic reactions involving species A occur on the fast time-scale, so that, compared to the dynamics of B, species A comes rapidly to its steady state concentration. Following this idea, we replace our original differential equation-based description of the behaviour of [A] (that is, $\frac{d[A]}{dt} = k_0 - k_1[A] + k_{-1}[B]$ **) with an algebraic description indicating that concentration [A] is in steady state with respect to the other variables in the model.**

For each time instant t, the quasi-steady state $[A]^{qss}$ **satisfies:**

$$0 = k_0 + k_{-1}[B] - k_1[A]^{qss}$$

or equivalently

$$[A]^{qss} = \frac{k_0 + k_{-1}[B]}{k_1} \tag{1.2}$$

Here,we are replacing the differential description of [A] with an algebraic description that says: [A] instantaneously reaches the steady state it would attain if all other variables were constant.(Because it equilibrates rapidly, the other variables are essentially constant from A's point of view.)

The reduced model, called the quasi-steady state approximation (QSSA), follows by replacing [A] with $[A]^{qss}$ **in the original model.**

To emphasize that the model reduction leads to an approximate model that is different from the original, we introduce the notation [$\tilde{B}$] for the concentrations in the reduced model, we get:

$$\begin{aligned}\frac{d[\tilde{B}]}{dt} &= k_1[A]^{qss} - (k_{-1} + k_2)[\tilde{B}] \\ &= k_1\frac{k_0 + k_{-1}[\tilde{B}]}{k_1} - (k_{-1} + k_2)[\tilde{B}] \\ &= k_0 + k_{-1}[\tilde{B}] - (k_{-1} + k_2)[\tilde{B}] \\ &= k_0 - k_2[\tilde{B}]\end{aligned}$$

Thus our reduced model will look like:

$$[A]^{qss} = \frac{k_0 + k_{-1}[\tilde{B}]}{k_1}$$
$$\frac{d[\tilde{B}]}{dt} = k_0 - k_2[\tilde{B}]$$

The quasi-steady state approximation is illustrated in Figure 1.2.

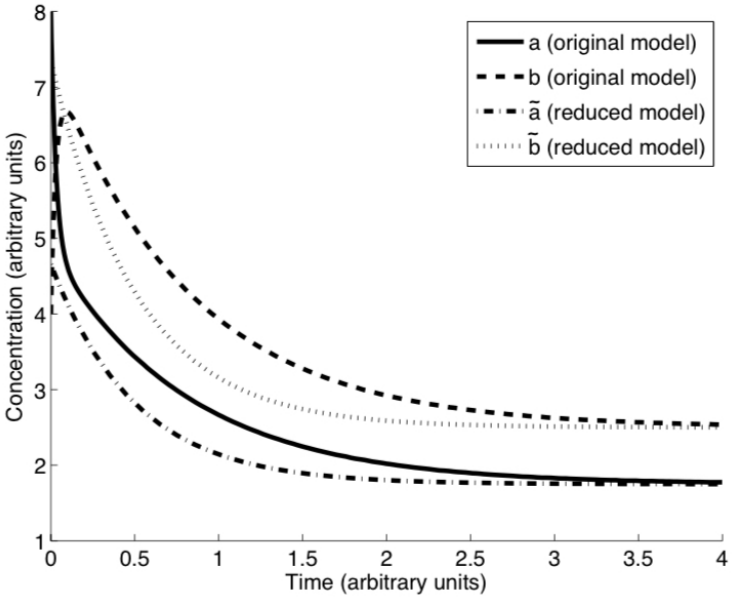


Figure 1.2: Parameter values are (in $time^{-1}$) $k_0 = 5, k_1 = 20, k_{-1} = 12, and k_2 = 2$ .The approximation exhibits an error over the transient, but converges to the original model in steady state. Initial conditions are a(0)=8, b(0)=4, and $\tilde{b}$(0)=235/32

A significant error occurs during the transient, but diminishes as the steady state is approached.

Chapter 2

HOW TO CREATE A MODEL

Let's learn how to create some mathematical models in biology from these examples

2.1 Modelling Macroscopic Processes

2.1.1 Modelling Spread of Infectious Disease

Here we are discussing a simple model on spread of infectious disease. so in order to simplify it we make some assumptions

- The disease spreads only when an infected person comes in contact with an uninfected one.
- Everybody should come in contact with everyone
- The Total population is very large
- The total population. remains constant over time(no death or birth)
- No one gets cured

The second and third assumptions are made since we are creating an ODE based model. We have seen in Chapter 1 that when creating ODE based models we will need to assume that the system is Homogenous and the size of the system is large.
The rest of the assumptions are made so as to simplify the model.
Now we need to create a simple representation of our model:

$$Infected + Normal \xrightarrow{\mathbf{r}} 2 \cdot Infected$$

let

x=fraction of the population that is infected

(1-x)=fraction of the population uninfected

r=rate constant for the spread of the infection

Then our model will look like:

$$\frac{dx}{dt} = r(1-x)x \tag{2.1}$$

This is because the rate of change of fraction of people getting infected is directly proportional to the fraction of people infected as well as the fraction of people uninfected.

Now using this model we will be able to answer some questions like

- **Let at time=0, fraction of population infected be x_0.What will be the fraction of the infected population at time t?**
- **Create time vs x plot to show the dynamics of spread of infection.**

In order to answer these questions we need to find the solution for (2.1) (In this example we are using analytic method which is often not feasible for complex models)

So we need to integrate (2.1)

$$\begin{aligned} & \int_{x_0}^{x} \frac{dx}{x(1-x)} = r\int_0^t dt \\ \implies & \int_{x_0}^{x} \frac{dx}{x} + \int_{x_0}^{x} \frac{dx}{(1-x)} = r\int_0^t dt \\ \implies & [lnx]_{x_0}^{x} - [ln(1-x)]_{x_0}^{x} = rt \end{aligned}$$

$$\implies ln\frac{x}{x_0} - ln\frac{(1-x)}{(1-x_0)} = rt$$
$$\implies \frac{x(1-x_0)}{x_0(1-x)} = \epsilon^{rt}$$

$$\implies x = \frac{1}{1+(\frac{1}{x_0}-1)\epsilon^{rt}} \tag{2.2}$$

Equation (2.2) gives the fraction of infected population at time t.Thus this is the answer for the first question
In order to answer the second question, all we need to do is plot x i.e., equation (2.2) with respect to time.
The Graph will look like this:

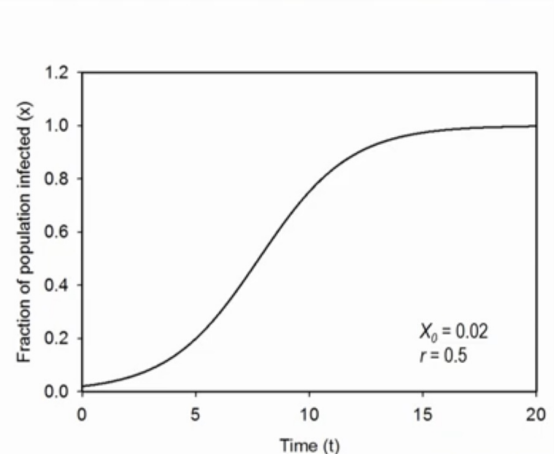


Figure 2.1: Time vs x plot with initial parameter x_0=0.02 and r=0.5

As we can see the behaviour of the function is not Linear but rather Sigmoidal. It is also evident from the graph that the entire population gets infected between 15 to 20 days given the initial parameters.

2.1.2 Modelling Population Growth of Bacteria in a Petri dish

Now we are going to model a simple growth model. We assume that there is no death of bacteria in the petri dish. Since the petri dish is the environment we provide for the bacteria's growth, we know that it only provides limited resources. As a result, the bacteria will cease growing after the resources are fully consumed. We call this maximum capacity, the carrying capacity; we denote it as k. thus our Growth model will look like this:

$$\frac{dx}{dt} = r(1 - \frac{x}{k})x \tag{2.3}$$

Where
x=population at time t
r=rate constant for growth
k=carrying capacity

This is because the rate of change of population at time t is proportional to the current population x, and the term$(1 - \frac{x}{k})$tends to one when $x \ll k$ and tends to zero when $x \approx k$

Now lets try answering some questions based on this model.

- **At time=0, the population is x_0.What will be the population at time t?**
- **Plot the population dynamics**

To answer the first question all we need to do is to fin the solution for (2.3) for this we need to integrate (2.3) within the limits x from x_0 to x and t from 0 to t

$$
\begin{aligned}
& \frac{dx}{dt} = r(1 - \frac{x}{k})x \\
\implies & k\frac{dx}{dt} = r(k-x)x \\
\implies & \frac{k}{(k-x)x}dx = rdt \\
\implies & \frac{dx}{x} + \frac{dx}{k-x} = rdt \\
\implies & \int_{x_0}^{x} \frac{dx}{x} + \int_{x_0}^{x} \frac{dx}{k-x} = r\int_0^t dt \\
\implies & [lnx]_{x_0}^{x} - [ln(k-x)]_{x_0}^{x} = r[t]_0^t \\
\implies & ln(x) - ln(x_0) - ln(k-x) + l(k-x_0) = rt \\
\implies & ln(\frac{x(k-x_0)}{x_0(k-x)}) = rt \\
\implies & \frac{x(k-x_0)}{x_0(k-x)}) = e^{rt}
\end{aligned}
$$

$$
\implies x = \frac{k}{1 + (\frac{k}{x_0} - 1)e^{-rt}} \tag{2.4}
$$

Thus, (2.4) gives the answer to the first question.

To answer the second question, we need to plot x with respect to time t. So the Graph will look like this:

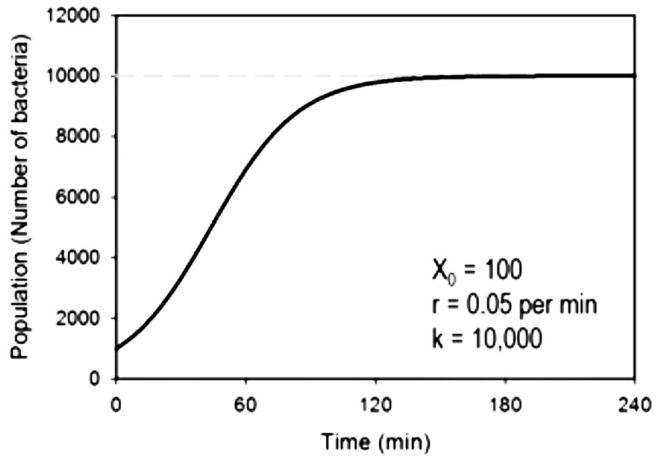


Figure 2.2: Time vs x plot with initial parameter x_0=100, r=0.05 per min and k=10,000

2.2 Modelling Molecular Process in Cell

In this section we will model some basic molecular processes.
As we have seen in Chapter 1, to model any complex biological process(Circuit) we need to break it up into smaller units called motifs which even further must be broken down into elementary processes. In this Section, we will model a basic elementary process, and a motif.

2.2.1 Modelling Enzymatic Reaction

As we know, most of the biochemical processes involves enzyme. An important thing to note is that while an enzyme helps to convert a substrate to a product it does not get used up.
Let us now model this reaction:

$$\mathbf{S} \xrightarrow[k_1]{\mathbf{E}} \mathbf{P}$$

It is is easy to model this reaction using Law of mass action. And thus it would look like this:

$$\frac{d[P]}{dt} = k_1[E][S]$$
$$\frac{d[S]}{dt} = -k_1[E][S]$$

Where [E],[S],[P] denotes concentration of Enzyme, Substrate and Product at time t respectively.

As we can see the rate of change of [P] increases by the forward reaction thus it is proportional to [E]and[S]. Similarly the rate of change of [S] decreases as the forward reaction keeps happening, thus it is the negative of $\frac{d[P]}{dt}$.

We can easily figure out the concentration of P at time t either by using Analytic method or Numerical Simulation.

We have thus modelled the simplest Scheme of the enzymatic reaction. But this model may sometimes produce errors as it avoids the mechanics of the reaction. We are now going to model the detailed scheme(which contains the mechanics) of the enzymatic reaction.
Detailed scheme:

$$\mathbf{S} + \mathbf{E} \rightleftharpoons \mathbf{S\text{-}E} \rightleftharpoons \mathbf{P\text{-}E} \rightleftharpoons \mathbf{P} + \mathbf{E}$$

To simplify the model we are making some assumption:

- **The inter-conversion between substrate-enzyme(S-E) and product-enzyme(P-E) complexes is very fast (compared to the timescale of the association and disassociation events). Consider them as a single entity, C.**
- **the product formed does not bind to the enzyme.(this assumption is motivated by the fact that laboratory measurements of reaction rates are typically carried out in the absence of product.)**

So, our simplified model will look like this:

$$\mathbf{S} + \mathbf{E} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathbf{C} \xrightarrow{k_3} \mathbf{P} + \mathbf{E}$$

Now let us model this reaction:

$$\begin{aligned}
\frac{d[S]}{dt} &= -k_1[E][S] + k_2[C] \\
\frac{d[E]}{dt} &= -k_1[S][E] + k_2[C] + k_3[C] \\
\frac{d[C]}{dt} &= k_1[E][S] - k_2[C] - k_3[C] \\
\frac{d[P]}{dt} &= k_3[C]
\end{aligned}$$

Since this model is a system of differential equations, it will be quite hard to compute the concentration of [P] at any given time t.

Thus we need to further simplify it to one or two ODEs using some simple algebraic equations and assumptions.

We know that the enzyme does not get used up. Thus by conservation of enzyme, we get:
$[E]_T = [E] + [C]$
Where $[E]_T$ remains a constant.
Assumptions to simplify:

- $[S] \gg [E]$
- **The complex, C, remains Quasi-steady state.**

Since C is in quasi-steady state,

$$\begin{aligned}
&\frac{d[C]}{dt} = 0 \\
\implies\ & k_1[E][S] - k_2[C] - k_3[C] = 0 \\
\implies\ & k_1[E][S] - (k_2 + k_3)[C] = 0 \\
\implies\ & k_1([E]_T - [C])[S] - (k_2 + k_3)[C] = 0 \\
\implies\ & k_1([E]_T - [C])[S] = (k_2 + k_3)[C] \\
\implies\ & ([E]_T - [C])[S] = \frac{(k_2 + k_3)}{k_1}[C] \\
\implies\ & [E]_T[S] = \frac{(k_2 + k_3)}{k_1}[C] + [C][S]
\end{aligned}$$

$$\implies [C] = \frac{[E]_T[S]}{\frac{(k_2 + k_3)}{k_1} + [S]}$$

Now we can substitute the equation for [C] in $\frac{d[P]}{dt}$
Thus,

$$\begin{aligned}
\frac{d[P]}{dt} &= k_3[C] \\
&= k_3 \cdot \frac{[E]_T[S]}{\frac{(k_2 + k_3)}{k_1} + [S]} \\
&= \frac{k_3[E]_T[S]}{K_M + [S]}
\end{aligned}$$

This reduced model describes $S \longrightarrow P$ as a single (non-elementary) reaction. The reaction rate is called a *Michaelis-Menten rate law.* Where $K_M = \dfrac{(k_2 + k_3)}{k_1}$ is the Michaelis-Menten Constant.

Similarly by simplifying $\dfrac{d[S]}{dt}$ using enzyme conservation equation and concentration of C, we get:

$$\frac{d[S]}{dt} = -k_3 \cdot \frac{[E]_T[S]}{K_M + [S]}$$

Thus we have simplified our model to just two ODEs;

$$\frac{d[S]}{dt} = \frac{-k_3[E]_T[S]}{K_M + [S]}$$
$$\frac{d[P]}{dt} = \frac{k_3[E]_T[S]}{K_M + [S]}$$

Now by using numerical simulation or Analytic method we can easily figure out the concentration [P] at any time t.

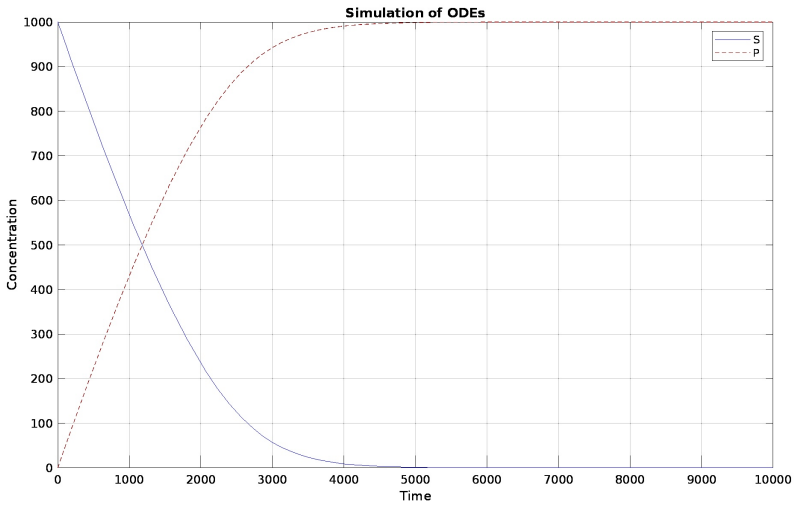
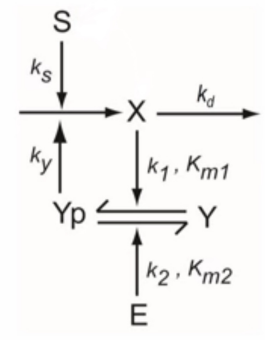


Figure 2.3: Numerical simulation of the given model with initial concentration S(0)=1000M, and $[E]_T = 3M, k_3 = 0.2persec, K_M = 300M$

2.2.2 Modelling Positive Feedback Motif

In this section we will be modelling the given positive feedback motif:



In this motif, an external signal S activates X which in fact is an enzyme kinase, which phosphorylates Y to become Yp. As usual, the phosphorylation is a reversible reaction, thus in this case, an enzyme, a phosphatase E, de-phosphorylates Yp to create Y. Yp on the other hand, activates X, which further induces the production of Yp and thus forming a positive feedback loop.
It is to be noted that, in this particuar motif, the enzymatic reaction follows Michaelis-Menten Kinetics.
To model this reaction we essentially need to find the dynamics of X and Yp.

We could model them in this way,

$$\frac{d[X]}{dt} = k_s S + k_y[Yp] - k_d[X]$$
$$\frac{d[Yp]}{dt} = \frac{k_1[X][Y]}{K_{m1} + [Y]} - \frac{k_2[E][Yp]}{K_{m2} + [Yp]} - k_y[Yp]$$

This is an incomplete model since $\frac{d[Yp]}{dt}$ depends upon [Y] whose ODE we have not formulated. But including the ODE of [Y] will further complicate the model. So in order to simplify the model, we will use a conservation equation:

$$[Y]_T = [Y] + [Yp]$$

Now we could substitute for $[Y]$, and thus we will obtain:

$$\frac{d[X]}{dt} = k_s S + k_y[Yp] - k_d[X]$$
$$\frac{d[Yp]}{dt} = \frac{k_1[X]([Y]_T - [Yp])}{K_{m1} + ([Y]_T - [Yp])} - \frac{k_2[E][Yp]}{K_{m2} + [Yp]} - k_y[Yp]$$

Which gives us the model for this positive feedback motif.

2.3 Online Resources for Mathematical modelling in Biology

In order to create a model, collecting data is the first step.
We would certainly need Pathway/Molecular information if we are modeling in molecular biology. One of the basic ways to get such information is through existing literature. Some best places to search for them will be:

- **PubMed : Repository of Abstracts of Publications over ages**
- **Google Scholar**

Another way to collect information regarding the pathways is through Databases; The information in these Databases are manually collected and distilled from the existing literature. Some Databases are:

- **KEGG : http://www.genome.jp/kegg/pathway.html**
- **Reactome**
- **Panther**
- **WikiPathways**

A best place to get information to create models is by learning from old models.One could even recycle an old model by making some tweaks in an existing model.

Some important repositories and databases from which we could get old models are:

- **BioModels Database: http://www.ebi.ac.uk/biomodels.main/**
- **CellML Model Repository: http:// models.cellml.org/cellml**
- **JSim Model Archives: http://www.physiome.org/jsim/models/index.html**

An Important information to collect while modelling is the numerical values of Parameters involved(The constants involved in the ODEs). We could get such information through existing literature, old models through databases and even by performing experiment and by doing parameter estimation by fitting. To do this we need to first collect the experimental data. Then we will have to create a model and try different parameter values and simulate the model. The parameter set for which the simulated data is closer to the experimental data will be the best fit. Parameter Estimation will not give us the exact value but rather a satisfactory value.
Some of the many tools which helps one to estimate parameter values are *JSim, COPASI, and D2D*

Here are some important databases to collect parameter values:

- **BioNumbers**
- **SABIO-RK**
- **BRENDA**

Chapter 3

HOW TO ANALYZE A MODEL

3.1 Steady State Analysis for a single ODE

As we know, to find the steady state of a single ODE, all we need to do is, to equate the rate to zero, and so we could get the values of the dependant variable at which the system is at steady state.
That is,
for the ODE, $\frac{dx}{dt} = f(x,t)$
x is at steady state, when $\frac{dx}{dt} = 0$
that is when $f(x,t) = 0$
we will only need to solve this equation to fin d the steady state values.

3.1.1 Direction Field

Direction fields are very useful in analysing staedy staes in a single ODE based model.
In order to create a Direction field of an ODE $\frac{dx}{dt}$ **all we need to do is:**

- **Draw an X-T space.**
- **Divide X-T space in a grid to obtain equidistant points.**
- **At each grid point draw an arrow with slope= dx/dt**
- **Do it over the entire space.**

Here we can see that at the steady states of the model (i.e., when $\frac{dx}{dt} = 0$**) the arrows are at angle of** 0^o **with the horizontal axis, thus implying that**

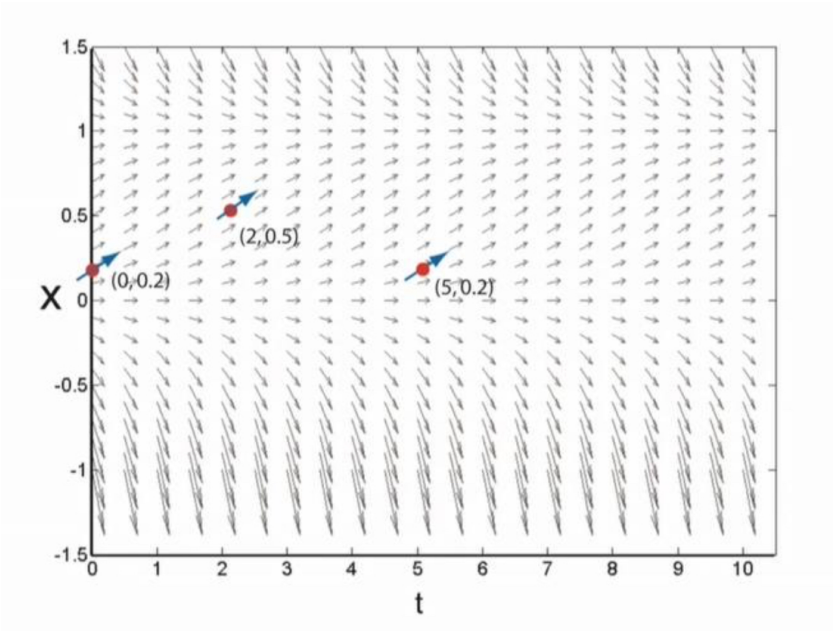


Figure 3.1: Direction field of the model $\frac{dx}{dt} = x(1-x)$

x=1 and x=0 are the steady states of the system.

3.1.2 Stability of steady state

Stability of a steady state is define by the time evolution of the dependant variable around the steady state. That is if x(dependant variable) is pertrubed from its steady stae value x_{ss},with time, whether it would return to x_{ss} or move away from x_{ss}.

3.1.3 Checking stability by analysis of Direction field

One of the best ways to check the stability of steady state is by analyzing the direction field.
Lets consider the direction field of $\frac{dx}{dt} = x(1-x)$ given in Figure 3.1.
There are two steady state for this model; they are x=1 and x=0
let us first consider the steady state x=1. If we perturb x to 1.1, we can see that over time it will collapse into x=1. If we perturb x to 0.7, it will also move toward x=1 over time. Thus, no matter in which direction the value of x is perturbed it will collapse into the steady state x=1.
Such a steady state is known as *Stable steady state*.
Now lets consider the steady state x=0.

if we perturb x to either x<0 or x>0, we can observe that it would move away from x=0 over time. Such a steady state is known as ***Unstable steady state.***

3.1.4 Types of Steady states in a single ODE based model

There are mainly 3 types of steady states in a single ODE based model. They are:

- Stable steady state
- Unstable steady state
- Semi-stable steady state

we have discussed earlier the characteristics of Stable and Unstable steady states. Now let see how a Semi-stable steady state behaves.

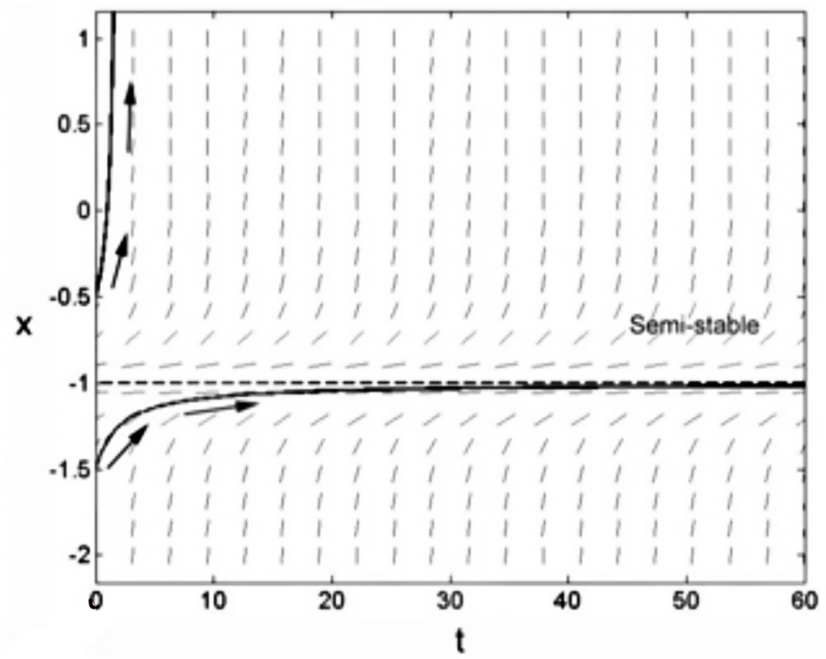


Figure 3.2: Direction field of $\frac{dx}{dt} = (x+1)^2$

Here, we can observe that x=-1 is the steady state of the system and if x is perturbed in a positive direction, it moves away from the steady state whereas if it is perturbed in the opposite direction, it will collapse into the steady state. If a steady state shows this type of behaviour it is called ***Semi-stable steady state.***

3.2 Steady state analysis for a system of ODEs

3.2.1 How to find steady state analytically

Lets consider this system of ODEs:

$$\frac{dx}{dt} = k_1 x - k_x 2y$$

$$\frac{dy}{dt} = k_2 xy - k_3 y$$

At steady state, both $\frac{dx}{dt} = 0$ **and** $\frac{dy}{dt} = 0$

$$\implies k_1 x - k_2 xy = 0 \tag{3.1}$$

$$k_2 xy - k_3 y = 0 \tag{3.2}$$

from equation (3.1),

$$x(k_1 - k_2 y) = 0$$

$$\implies x = 0 \text{ or } y = \frac{k_1}{k_2}$$

Now consider equation (3.2),

When:$x = 0$

$$k_2 \cdot 0 \cdot y - k_3 \cdot y = 0$$

$$\implies y = 0$$

When:$y = \frac{k_1}{k_2}$

$$k_2 \cdot x \cdot \frac{k_1}{k_2} - k_3 \cdot \frac{k_1}{k_2} = 0$$

$$\implies xk_1 - k_3 \frac{k_1}{k_2} = 0$$

$$\implies x = \frac{k_3}{k_2}$$

$\therefore$ The system has two steady states:

$$x = 0, y = 0$$

$$x = \frac{k_3}{k_2}, y = \frac{k_1}{k_2}$$

3.2.2 How to find steady state graphically

lets consider the same system of ODEs:

$$\frac{dx}{dt} = k_1 x - k_2 xy$$

$$\frac{dy}{dt} = k_2 xy - k_3 y$$

let $k_1 = k_2 = k_3 = 1$

then

$$\frac{dx}{dt} = x - xy$$

$$\frac{dy}{dt} = xy - y$$

at steady state:

$$\frac{dx}{dt} = 0$$

$$\implies x - xy = 0$$

$$\implies x(1 - y) = 0$$

$$\implies x = 0 \; or \; y = 1$$

By equating $\frac{dx}{dt}$ to 0 we have obtained two lines; When they are drawn in a phase plane(the graph which we are about to draw), these lines are called *x nullclines*

similarly at steady state:

$$\frac{dy}{dt} = 0$$

$$\implies xy - y = 0$$

$$\implies y(x - 1) = 0$$

$$\implies y = 0 \; or \; x = 1$$

Just like before, there lines are called *y nullclines*

The intersection of x and y nullclines gives us the steady states of the system. As we can see in the figure given above, intersection of the x and y nullclines gives us the points (0,0) and (1,1) which are the steady states of the given system of ODEs.

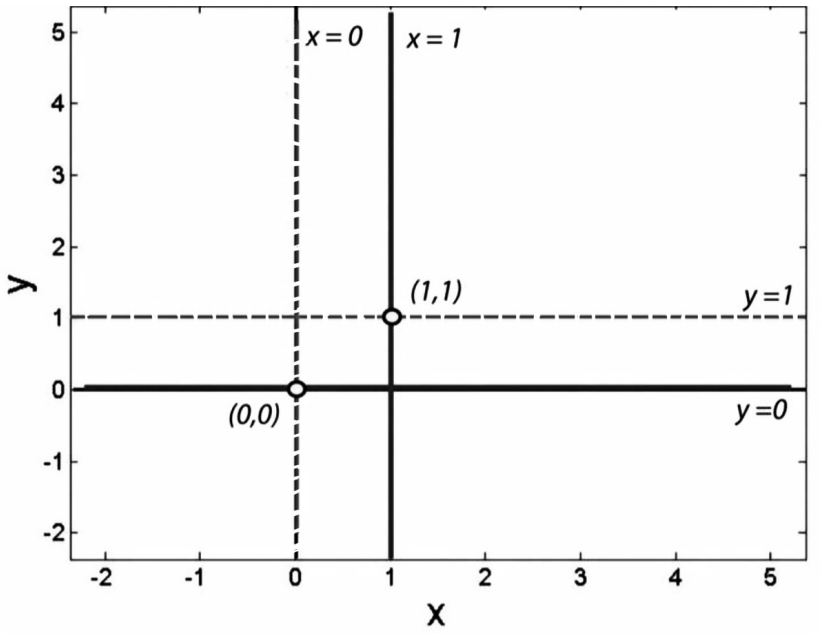


Figure 3.3: Phase plane and Phase plot of the given system.(The dashed lines represent the x-nullclines the black line represents the y-nullclines)

Here we have drawn a graph with two axes representing the two dependent variables. This type of graph is known as a *Phase Plane*.

3.2.3 Phase Plane and Phase Portrait

Just like we used a direction field to represent the dynamics of an ODE, for a system of ODEs, we use Phase Plane.
A Phase plane is nothing but a graph with two axe representing the two dependant variables.
Whereas a Phase Portrait is a geometric representation of the trajectories in the phase plane. It displays the time evolution of the two dependant variables in phase plane.

Given below are the steps to draw a phase portrait of a system of ODEs with two dependant variables x and y:

- **Draw an Y-X space.**
- **Divide Y-X space in a grid to obtain equidistant points.**
- **At each grid point draw a small line (leaving provision to draw an**

arrow head later) with slope = dy/dx (where dy/dx=$\frac{dy}{dt}/\frac{dx}{dt}$)

- **Do it over the entire space.**
- **Draw the arrow head over each line by following the steps below**
  - **when $\frac{dy}{dt}>0$ and $\frac{dx}{dt}>0$ draw:** ↗
  - **when $\frac{dy}{dt}>0$ and $\frac{dx}{dt}<0$ draw:** ↖
  - **when $\frac{dy}{dt}<0$ and $\frac{dx}{dt}<0$ draw:** ↙
  - **when $\frac{dy}{dt}<0$ and $\frac{dx}{dt}>0$ draw:** ↘

And thus, we will obtain a phase portrait.

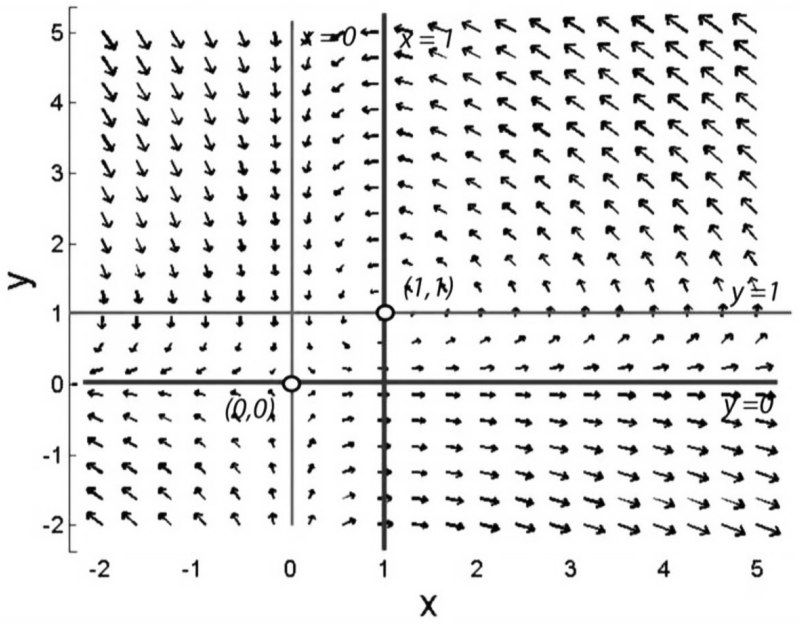
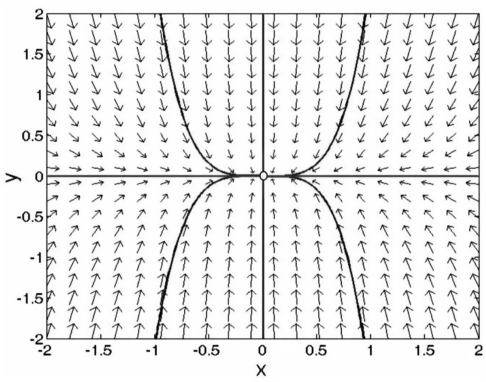


Figure 3.4: Phase Portrait of the system: $\frac{dx}{dt} = x - xy$ and $\frac{dy}{dt} = xy - y$

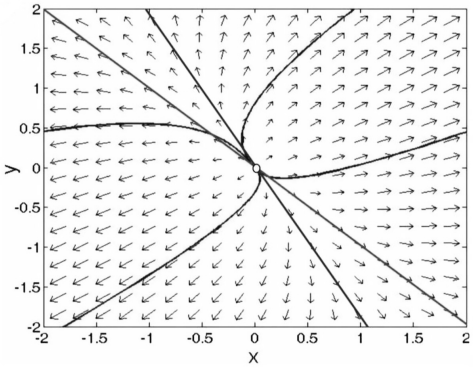
3.2.4 Types of Phase portrait of different steady states

There are different types of steady states let us try to under stand them by their phase portraits in the given figures:

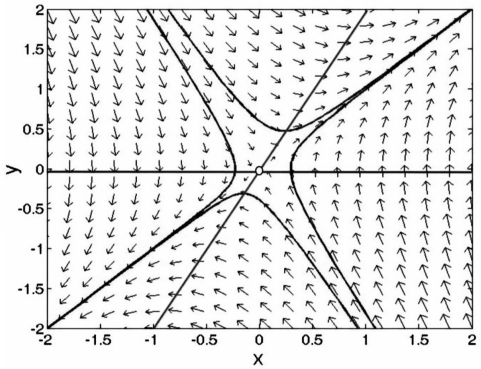
Sink node or Stable node



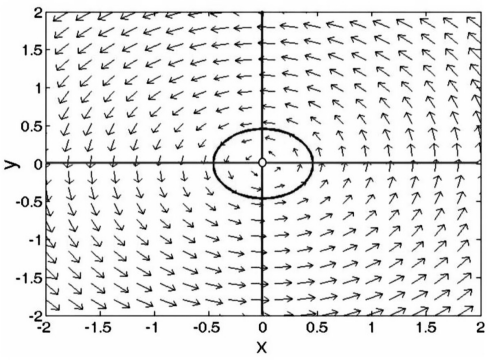
Source node or unstable node



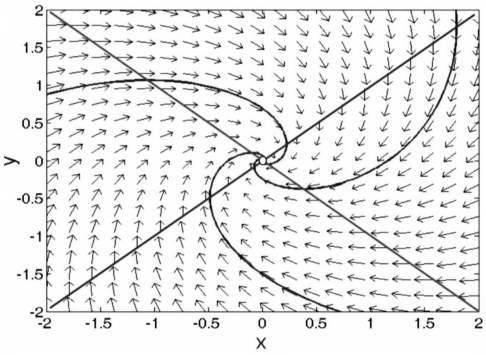
Saddle point



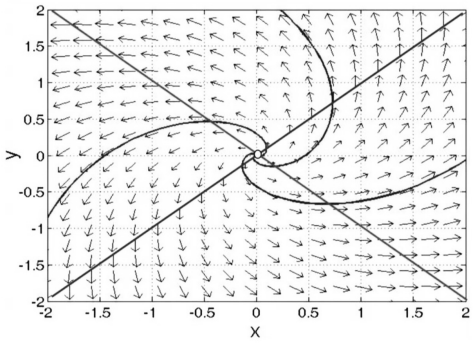
Center type



Stable Spiral or Spiral sink



Unstable spiral or Spiral source



We can observe that these phase portraits contain only one steady state. This is because the system of ODEs were linear, whereas the model we discussed before is non-linear and thus contains more than one steady state (0,0) and (1,1). By observing the phase portrait of that model given in figure(3.4), we can say that (1,1) is a center type steady state, whereas (0,0) is a saddle point.

3.3 Bifurcation

Bifurcation is defined as the change in qualitative behaviour of the system due to change in parameter values.
By qualitative behavior, we mean:

- **number of steady states**
- **stability of staedy states.**

Change in either of these two or both, will change the phase portrait. Therefore, bifurcation in a sense is change in phase portrait of the system with change in parameter.
Consider the ODE:

$$\frac{dx}{dt} = m - x^2$$

At steady state,

$$\frac{dx}{dt} = m - x^2 = 0$$

$$\implies x^2 = m$$

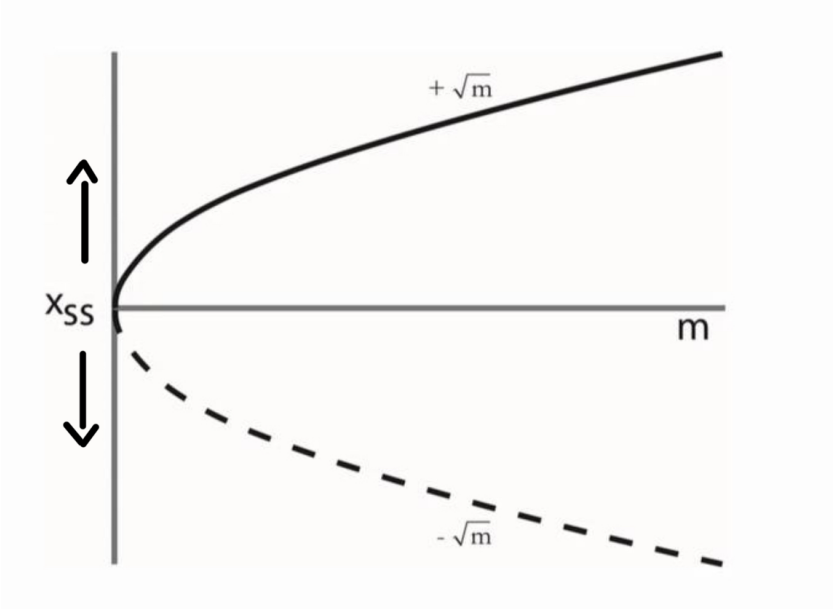
$$\implies x = \pm\sqrt{m}$$

When m>0,
x has two steady states, $x = +\sqrt{m}$ **and** $x = -\sqrt{m}$

When m=0
x has a single steady state,
x=0

When m<0,
x has no real steady states.

By plotting the steady state values along m we get the Bifurcation diagram:



If we observe the phase portrait of this model with different m values we can see the type of steady state that is formed with the change of parameter.

Bifurcation has great application in the field of Developmental biology and many other fields.

A great example is the Waddington's landscape which explains the embryonic development-in which a group of similar cell type differentiates into multiple cell types(cellular heterogeneity) due to bi-stable or multi-stable networks.(This multi-stability is caused by bifurcation)

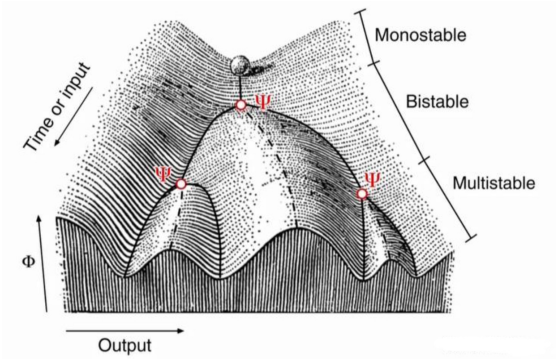
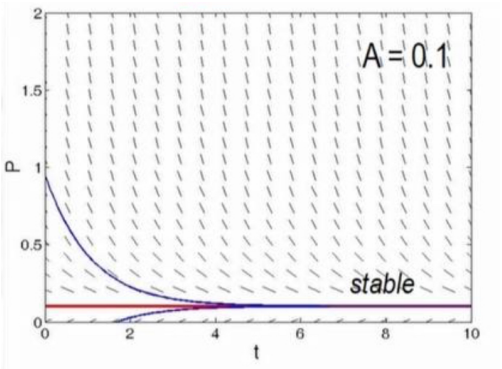
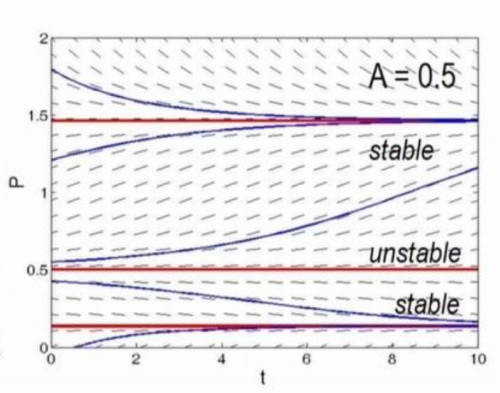


Figure 3.5: Waddington's landscape



(a) Direction field of the model at A=0.1



(b) Direction field of the model at A=0.5

Figure 3.6: A model of a protein P that exhibit uni-stability and bi-stability as the signal A(the parameter) changes

Chapter 4

CONCLUSION

In this study, we were able to learn some of the basic tools and concepts required to create a dynamic mathematical model in biology using ODE. This study might help mathematics students aspiring to do a project in mathematical biology.

Looking ahead, dynamical mathematical modeling holds immense promise for addressing pressing biological questions and addressing real-world challenges, such as disease dynamics, ecological sustainability, and biotechnological advancements. By leveraging the power of computational tools and mathematical abstraction, we can navigate the complexities of biological systems with greater precision and insight, ultimately paving the way for transformative discoveries and applications in the field of biology.

Furthermore, the interdisciplinary nature of mathematical biology encourages collaboration between mathematicians, biologists, and other scientists, leading to innovative approaches and breakthrough discoveries. As such, this study not only benefits mathematics students but also facilitates interdisciplinary interactions and promotes a deeper understanding of the interconnectedness of different scientific disciplines.

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