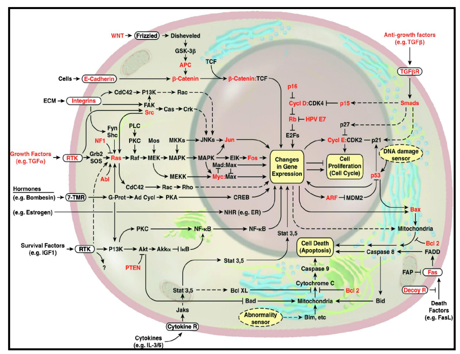
Modeling and Simulation in Computational Systems Biology

Lecture 1: Ordinary Differential Equations and the Applications in Modeling



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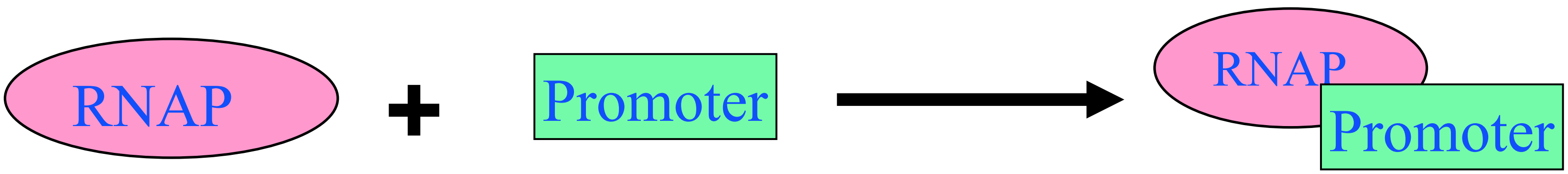
Summary

- General Introduction for ODEs
- Modeling with ODEs

A Chemically Reacting System

- Molecules of N chemical species $S_1, \ldots, S_N$
  - In a Volume Ω, at temperature T
  - Different conformation or excitation levels are considered different species if they behave differently

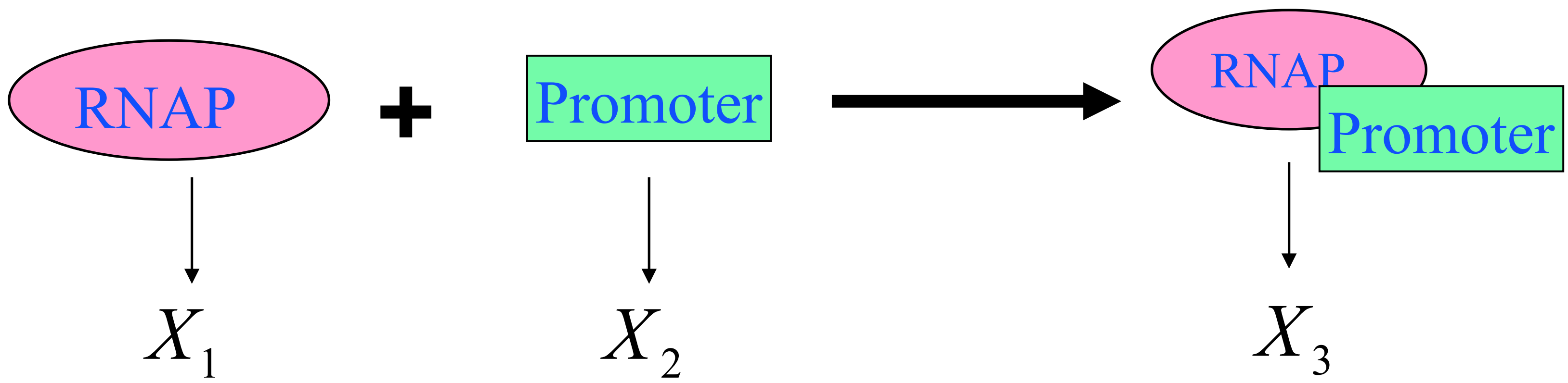


- M elemental reaction channels $R_1, \ldots, R_M$
  - Each R_j describes a single instantaneous physical event which changes the population of at least one species. For example,

$$
\begin{aligned}
&A \rightarrow S_i, \\
\text{or} \quad &S_i \rightarrow \text{something else}, \\
\text{or} \quad &S_i + S_j \rightarrow \text{something else.}
\end{aligned}
$$

Ordinary Differential Equation

For each species, assign a state variable, which describes its concentration or population.



Basic Deterministic Assumption:

The state change is proportional to the state of the reactants and time

$$\Delta X_1(t) = -kX_1(t)X_2(t)\Delta t$$

$$X_1'(t) = -kX_1(t)X_2(t)$$

Ordinary Differential Equations

Many scientific applications result in the following system of equations

$$\frac{dx}{dt} = f(t,x)$$

Example: Newton's Motion Law $F = m\ddot{x}$

which is called ordinary differential equations (ODEs).

Two types:

- Initial value problem (IVP)
- Boundary value problem (BVP)

Analytic Solution

There are a few types of ODEs for which we are able to obtain analytic solution and analyze their properties.

- Equation with separable variables

$$y' = f(x)g(y) \quad \Longrightarrow \quad \int \frac{dy}{g(y)} = \int f(x)dx + C$$

  – example

$$y' = \lambda y$$

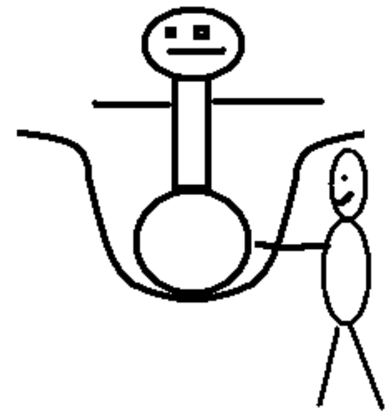
- Total differential equations

$$P(x,y) + Q(x,y)y' = 0$$

  – example

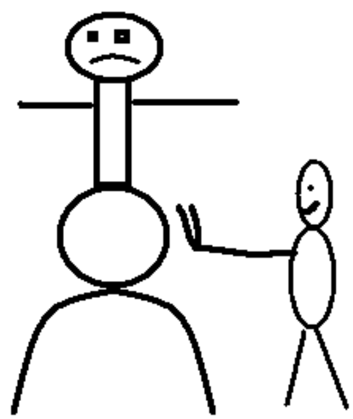
$$y' = \lambda y$$

When we cannot find analytic solution



- **Existence**
  - Continuous function
- **Uniqueness**
  - Lipschitz condition

$$\|f(t,y) - f(t,z)\| \le L\|y - z\|$$



- **Equilibrium State**
- **Stability**
  - Example: linear system $y' = Ay$
  - Lyapunov function

Numerical Solution

- **Multistep Methods**
  - Euler method
  - Adams method
  - BDF method

- **Runge-Kutta Methods**
  - Explicit RK
  - Implicit RK

Softwares for Numerical Solution

- DASSL (BDF method)
- CVODE (BDF method)
- RADAU5 (RK method)
- MATLAB functions

Simple Chemical Reaction

- Degradation

This process can be modeled as

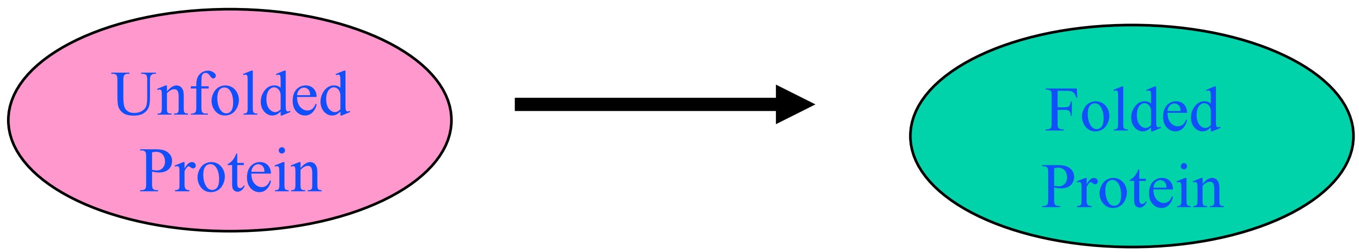
$$S \xrightarrow{k} \varnothing$$

which can be further formulated into reaction rate equations (RREs)

$$\frac{dx}{dt} = -kx$$

Simple Chemical Reaction

- Isomerization



This process can be modeled as

$$S_1 \xrightarrow{k} S_2$$

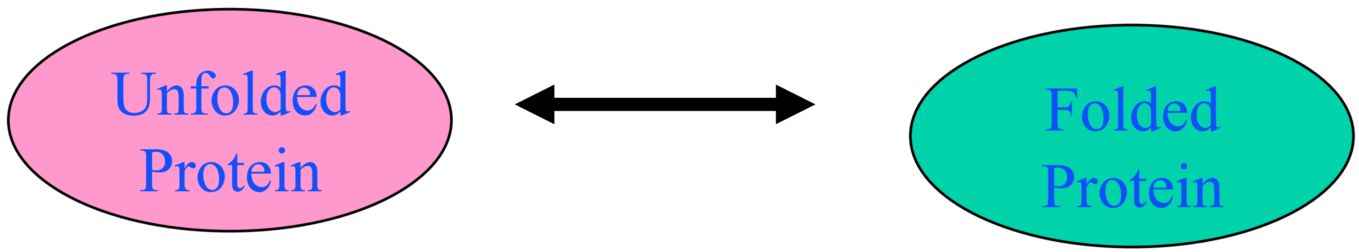
which can be further formulated into RREs

$$\frac{dx_1}{dt} = -kx_1$$

$$\frac{dx_2}{dt} = kx_1$$

Simple Chemical Reaction

- Reversible Isomerization



This process can be modeled as

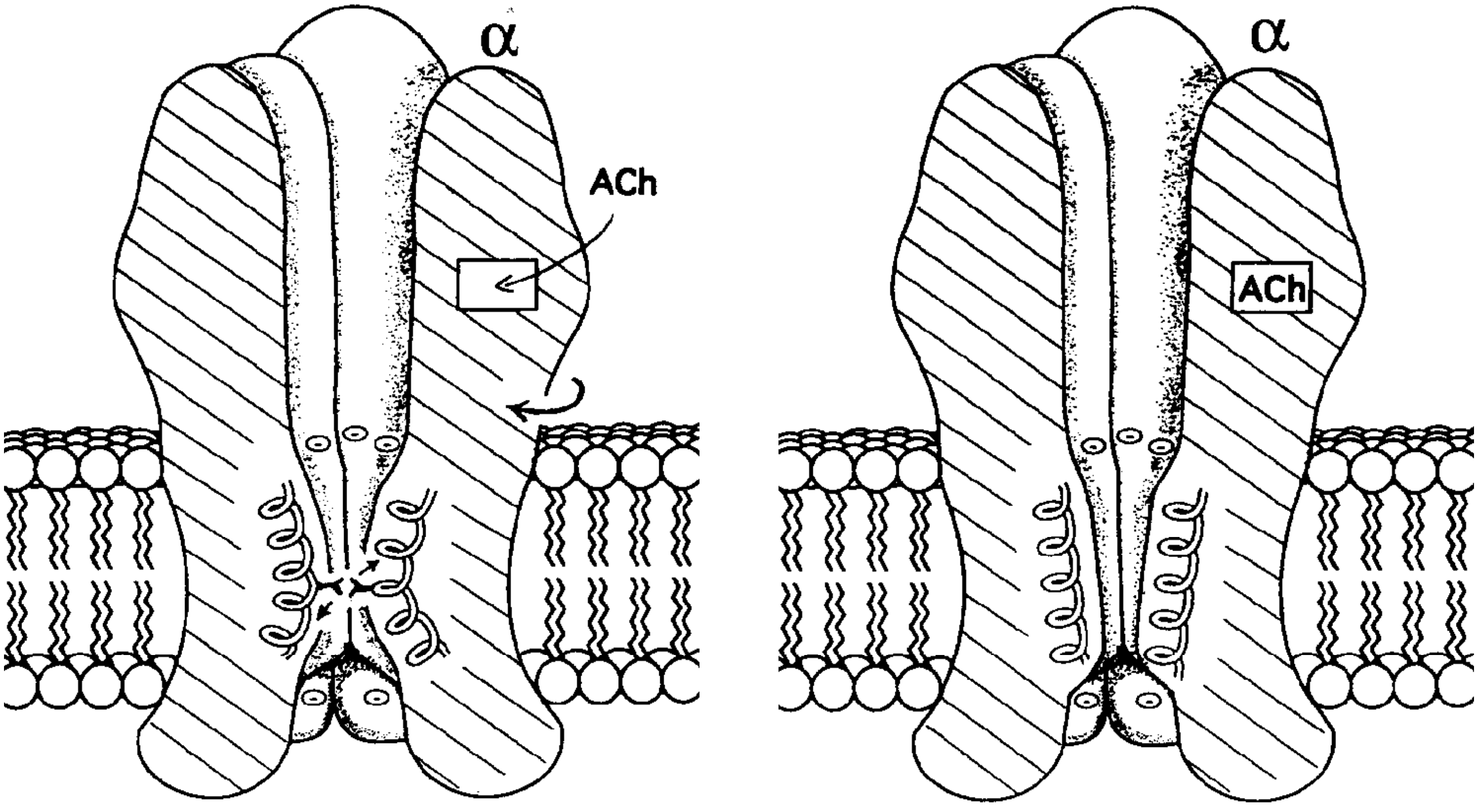
$$S_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S_2$$

which can be further formulated into RREs

$$\frac{dx_1}{dt} = -k_1 x_1 + k_{-1} x_2$$

$$\frac{dx_2}{dt} = k_1 x_1 - k_{-1} x_2$$

AChR: Proposed gating mechanism (Unwin, 1995)



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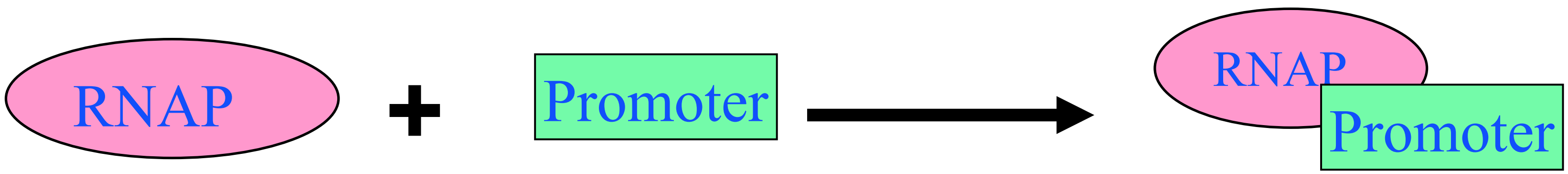
Simple Chemical Reaction

- Dimerization (Bi-molecular Reaction)



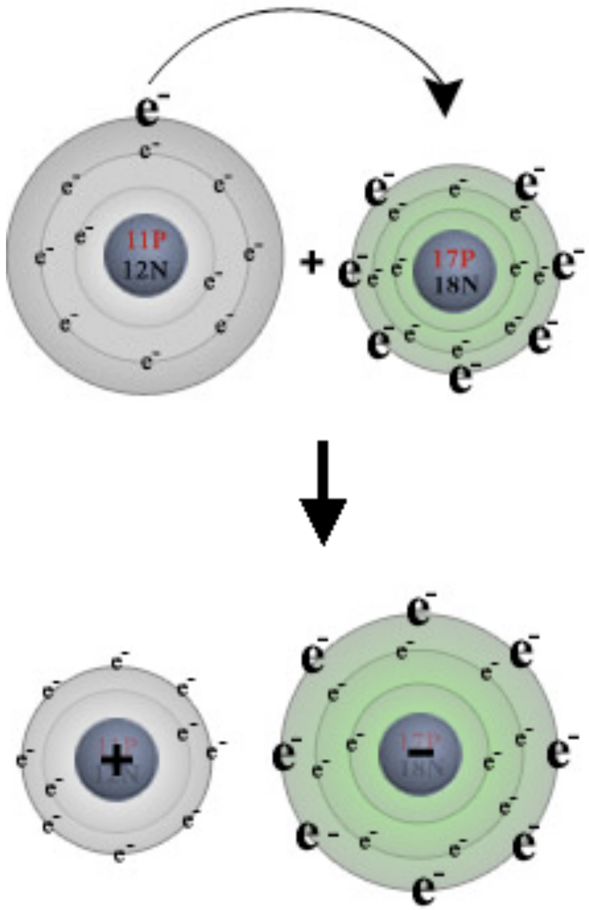
This process can be modeled as

$$S_1 + S_2 \xrightarrow{k} S_3$$

which can be further formulated into RREs

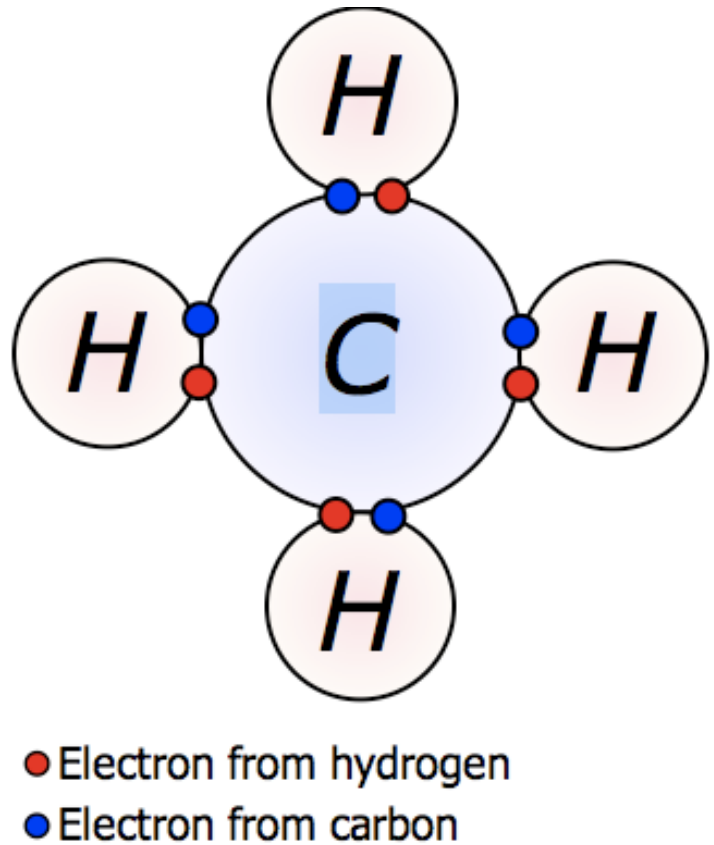
$$\frac{dx_1}{dt} = -kx_1x_2$$
$$\frac{dx_2}{dt} = -kx_1x_2$$
$$\frac{dx_3}{dt} = kx_1x_2$$

Bi-molecular Reaction



Na + Cl = Na Cl

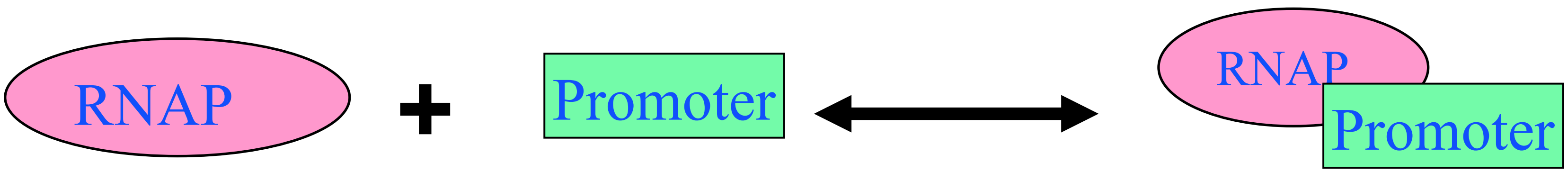
Ionic bond



Covalent bond

Simple Chemical Reaction

- Reversible Dimerization



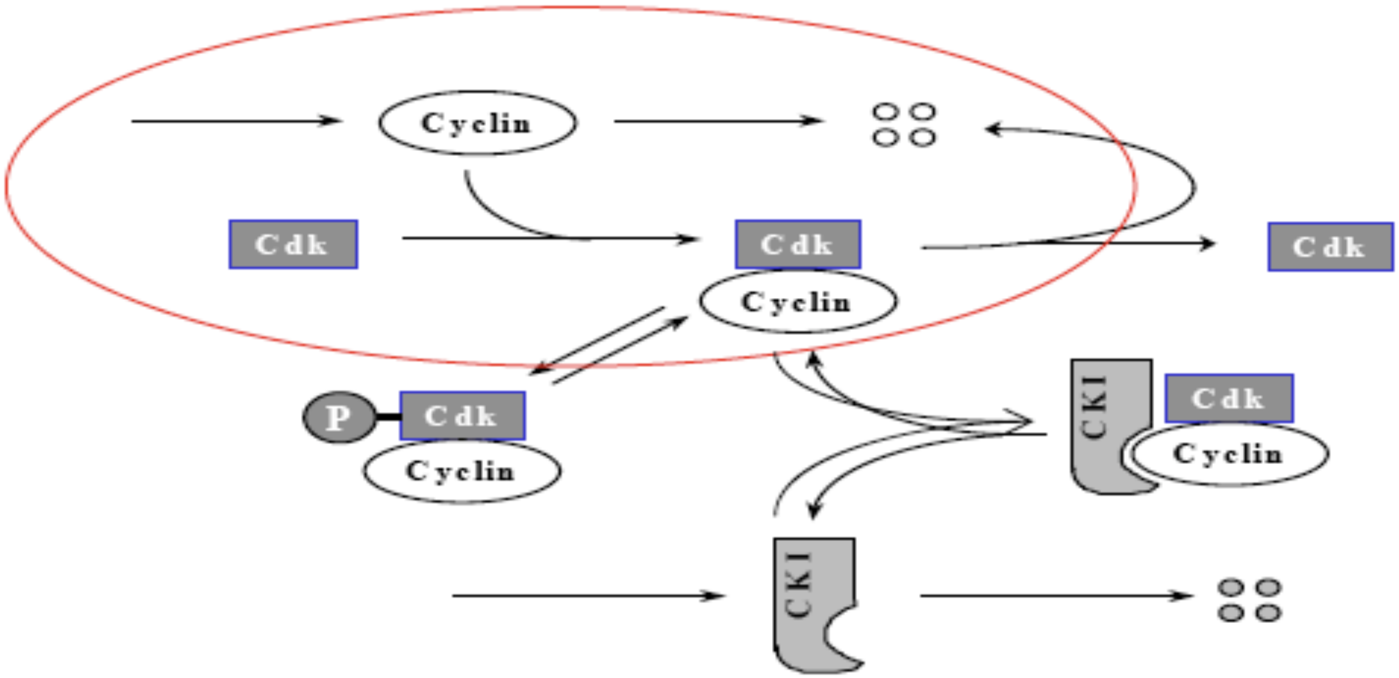
This process can be modeled as

$$S_1 + S_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S_3$$

which can be further formulated into RRE

$$\frac{dx_1}{dt} = -k_1 x_1 x_2 + k_{-1} x_3$$
$$\frac{dx_2}{dt} = -k_1 x_1 x_2 + k_{-1} x_3$$
$$\frac{dx_3}{dt} = k_1 x_1 x_2 - k_{-1} x_3$$

Example of a Simple System



Each icon represents a chemical species. Each arrow represents a chemical reaction that occurs at a certain rate.

For each species, we can write a rate equation, for example:

d[Cyclin]/dt = synthesis – degradation – binding + dissociation

Example of a Simple System

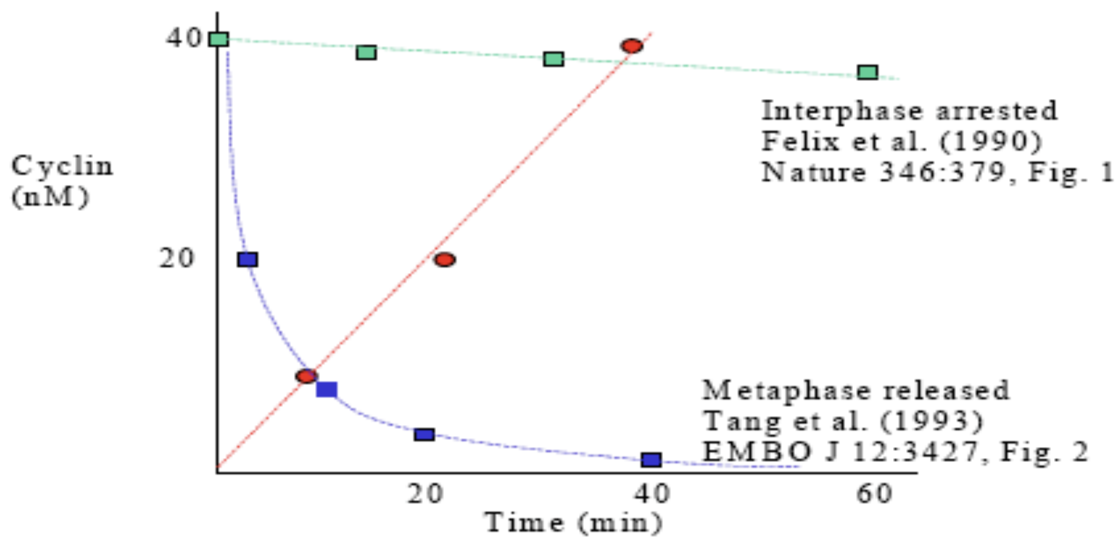
1. Synthesis

$$X(t) = [\text{cyclin}]$$

$$\frac{dX}{dt} = k_1, \quad X(0) = X_0$$

$$X(t) = X_0 + k_1 t$$

Estimate k_1 from the "red" data:



Example of a Simple System

2. Degradation

$$\frac{dX}{dt} = -k_2 X, \quad X(0) = X_0$$

$$X(t) = X_0 e^{-k_2 t}$$

$$X(t_{1/2}) = \frac{1}{2} X_0 = X_0 e^{-k_2 t_{1/2}} = \frac{1}{e^{k_2 t_{1/2}}} X_0$$

$$2 = e^{k_2 t_{1/2}}, \quad \text{or} \quad t_{1/2} = \frac{\ln 2}{k_2} \cong \frac{0.7}{k_2}$$

Estimate k_2 from the "blue" and "green" data above. How can it be that cyclin has different half-lives in different phases of the cell cycle?

Example of a Simple System

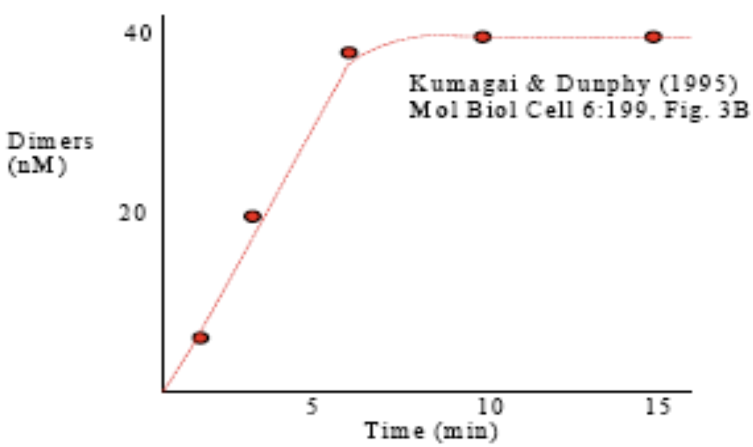
3. Dimerization

$X(t) = [\text{cyclin}]$, $C(t) = [\text{Cdc2}]$, $M(t) = [\text{dimer}]$,

$$\frac{dM}{dt} = k_3 C(t) X(t) = k_3 (C_0 - M)(X_0 - M), \quad M(0) = 0$$

$$M(t) = \frac{C_0 X_0 (1 - e^{-\alpha t})}{C_0 - X_0 e^{-\alpha t}}, \quad \text{where} \quad \alpha = k_3 (C_0 - X_0)$$

Estimate k_3 from the data below, given that $C_0 = 100$ nM.



4. Synthesis and Degradation

$$\frac{dX}{dt} = k_1 - k_2 X, \quad X(0) = 0,$$

$$X(t) = \frac{k_1}{k_2}\left(1 - e^{-k_2 t}\right)$$

$$\text{Note: as } t \to \infty, \quad X(t) \to \frac{k_1}{k_2} \quad \text{(stable steady state)}$$

From your previous estimates of k_1 and k_2, estimate the steady state concentrations of cyclin in interphase and late anaphase (end of mitosis).

Phase	k_1	k_2	X_{ss}
Interphase			
Anaphase			

- General Introduction for ODEs

- Modeling with ODEs

Thomas Malthus

An Essay on the Principle of Population

An Essay on the Principle of Population, as it Affects the Future Improvement of Society with Remarks on the Speculations of Mr. Godwin, M. Condorcet, and Other Writers.

LONDON, PRINTED FOR J. JOHNSON, IN ST. PAUL'S CHURCH-YARD, 1798.

"I SAID that population, when unchecked, increased in a geometrical ratio, and subsistence for man in an arithmetical ratio. "

---- Thomas Malthus

Malthus Model:

Assumption: the reproduction rate is proportional to the size of the population

$$\frac{dP}{dt} = kP, \quad k = \text{growth rate per capita}$$

Solution: $P(t) = P(0)e^{kt}$

$k > 0$: exponential growth, $\quad k < 0$: exponential decay

Malthus Model

Computational Science and Engineering

The reproduction rate is proportional to the population

$$P(t+\Delta t) = P(t) + kP(t)\Delta t$$

Solve it we have

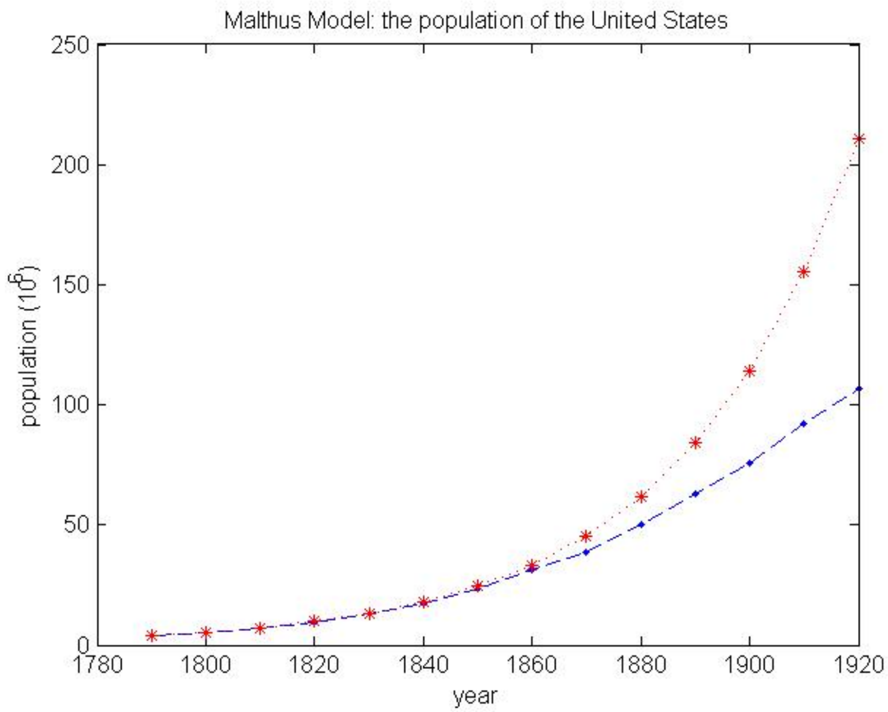
$$P(t) = P_0 e^{k(t-t_0)}$$

The population in the United States in year 1790 is 3.9×10^6 .

The corresponding population in year 1800 is 5.3×10^6 .

With a data fitting, we obtain:

$$P(t) = 3.9\times10^6 e^{0.0307(t-1790)}$$



Logistic Population Model

- **Developed by Belgian mathematician Pierre Verhulst (1838) in 1838**
- **The rate of population increase may be limited, i.e., it may depend on population density**

$$P(t+\Delta t) = P(t) + k(P(t))\Delta t$$

where

$$k(P(t)) = k_0\left(1 - \frac{P(t)}{P_m}\right)P(t)$$

The solution is

$$P(t) = P_0 e^{k_0(t-t_0)} \frac{P_m}{P_0 e^{k_0(t-t_0)} + (P_m - P_0)} = \frac{P_m}{1 + (\frac{P_m}{P_0} - 1)e^{-k_0(t-t_0)}}$$

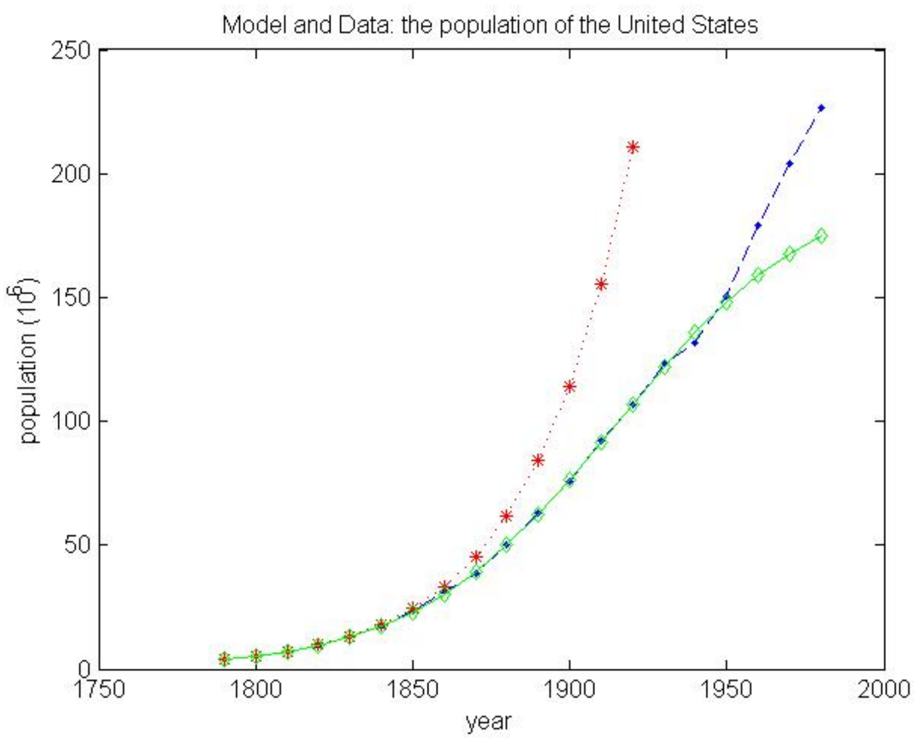
Logistic Population Model

The solution of the Logistic model

$$P(t) = P_0 e^{k_0(t-t_0)} \frac{P_m}{P_0 e^{k_0(t-t_0)} + (P_m - P_0)} = \frac{P_m}{1 + (\frac{P_m}{P_0} - 1)e^{-k_0(t-t_0)}}$$

With a data fitting

$$P_m = 197 \times 10^6, \qquad k_0 = 0.03134$$



Model of two species (Competition)

Let the population of two species be $x(t)$ and $y(t)$, and they compete in the same environment. If there is no competition, the population of X will satisfy

$$\dot{x}(t) = r_1 x(t)(1 - \frac{x}{N_1})$$

With the competition,

$$\dot{x}(t) = r_1 x(t)(1 - \frac{x + \alpha y}{N_1})$$

For another species, there is a similar equation

$$\dot{y}(t) = r_2 y(t)(1 - \frac{y + \beta x}{N_2})$$

The physical meaning of α and β can be understood as:

$$\alpha = \frac{\text{the resource each X species consume}}{\text{the resource each Y species consume}}.$$

Thus we have

$$\alpha\beta = 1$$

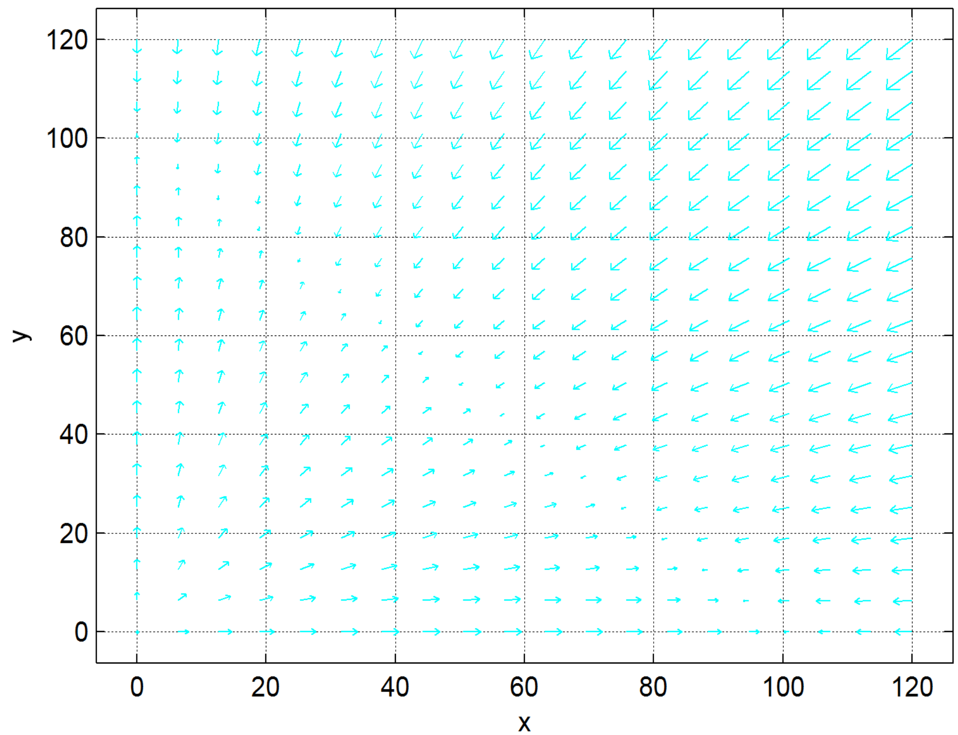
State Dynamics Plot vs Phase Plot

State Dynamics Plot: state vs time,

Phase Plot: the state space, use arrow to represent the tangent vector

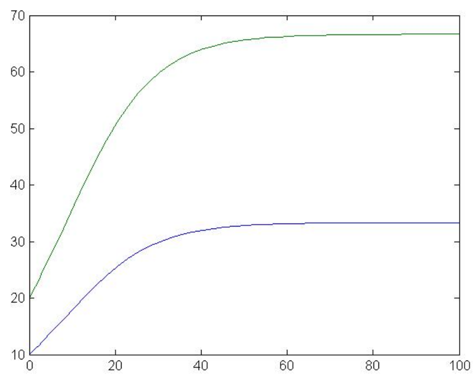
The phase plot reveals the geometric property of a dynamic system represented by a pair of ODEs.

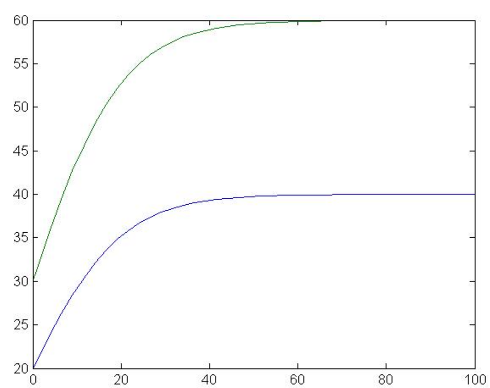
$$\begin{cases} \dot{x}(t) = 0.1x(1 - \dfrac{x+y}{100}) \\ \dot{y}(t) = 0.1y(1 - \dfrac{x+y}{100}) \end{cases}$$

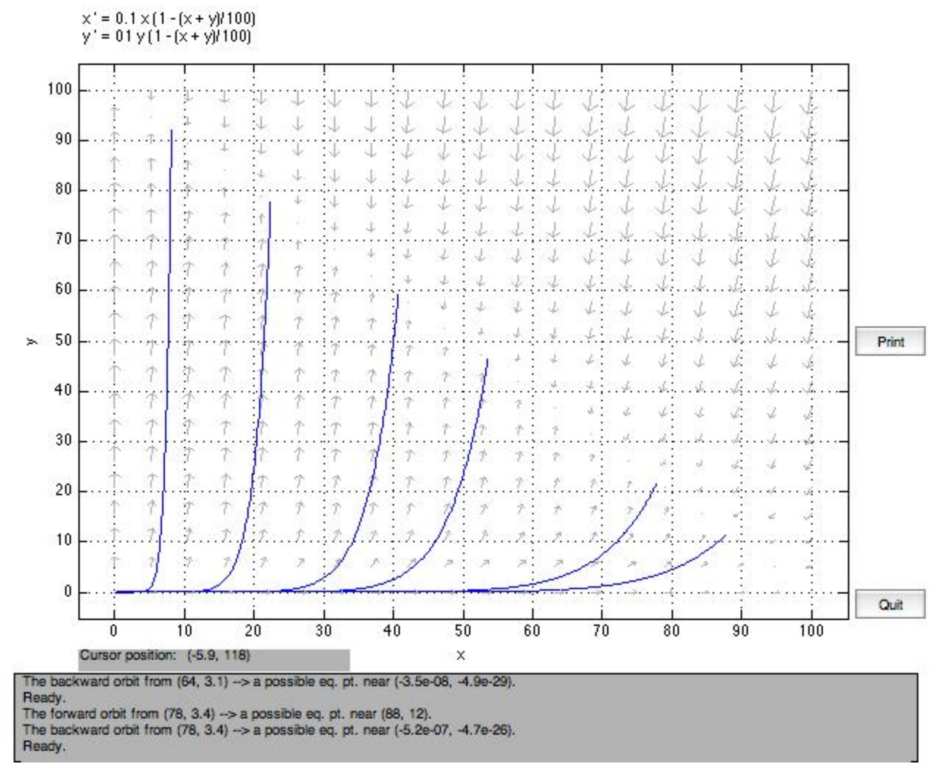


State Dynamics Plot vs Phase Plot

Example: from different initial value, the trajectory follow the direction of the arrows and reaches to its equilibrium state





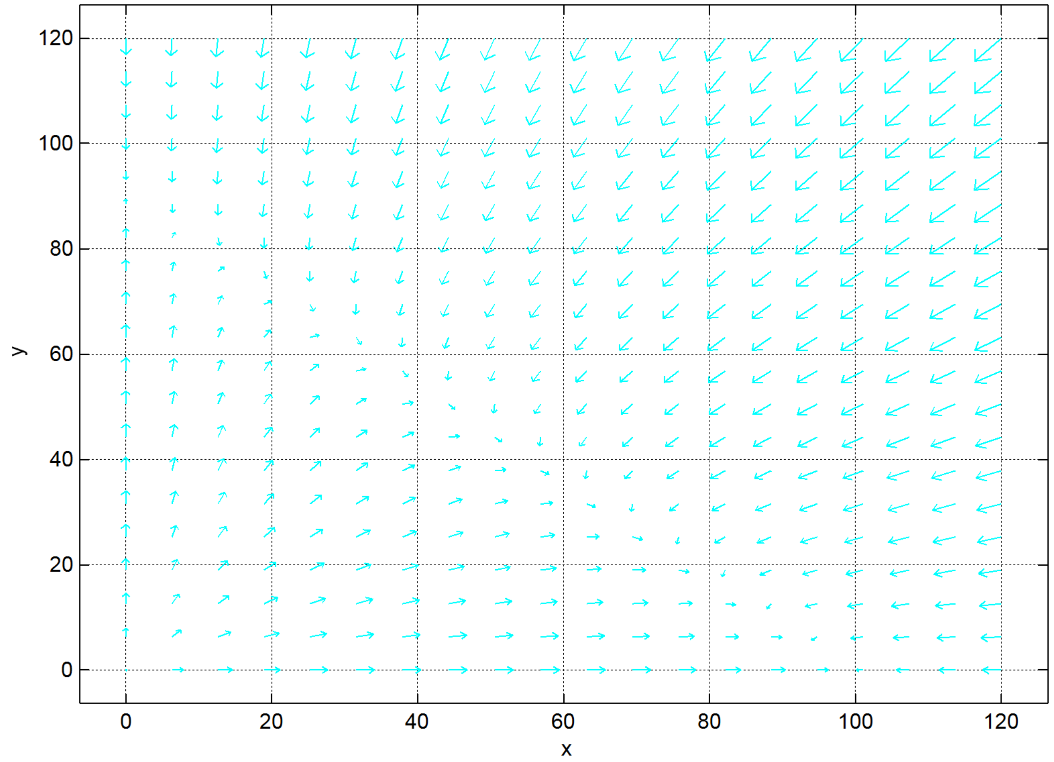


State Dynamics Plot vs Phase Plot

Computational Science and Engineering

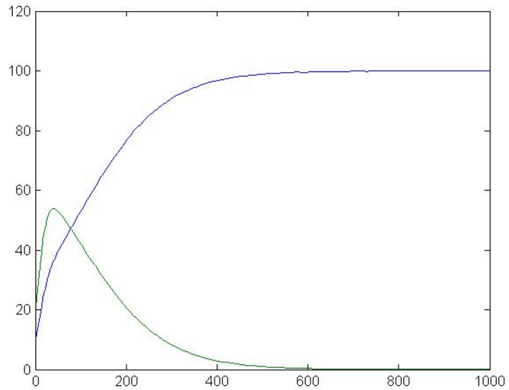
However, a slight change of parameters make a big difference in phase plot and lead to a different conclusion

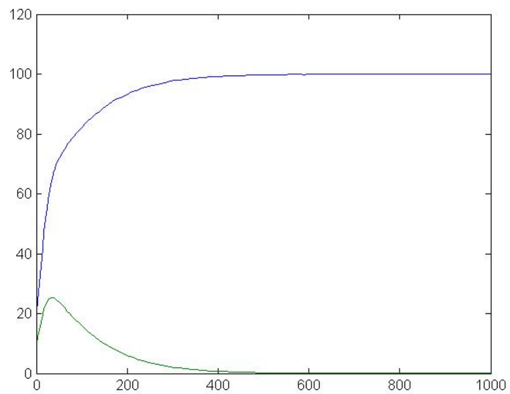
$$\begin{cases} \dot{x}(t) = 0.1x(1 - \dfrac{x+y}{100}) \\ \dot{y}(t) = 0.1y(1 - \dfrac{x+y}{90}) \end{cases}$$

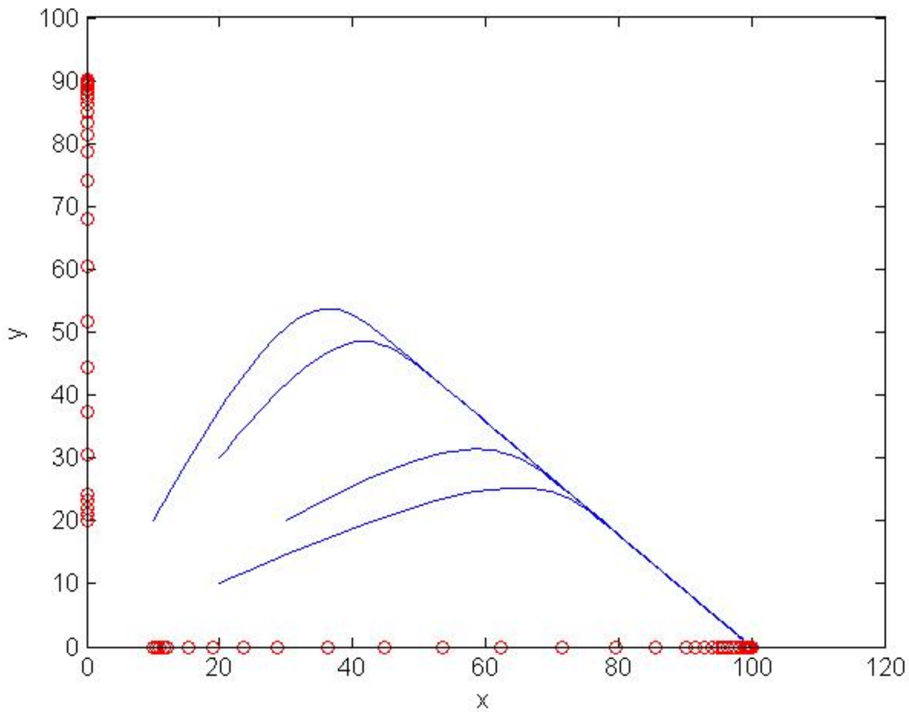


State Dynamics Plot vs Phase Plot

$$\begin{cases} \dot{x}(t) = 0.1x(1 - \frac{x+y}{100}) \\ \dot{y}(t) = 0.1y(1 - \frac{x+y}{90}) \end{cases}$$







State Dynamics Plot vs Phase Plot

A direct analysis through the phase plot

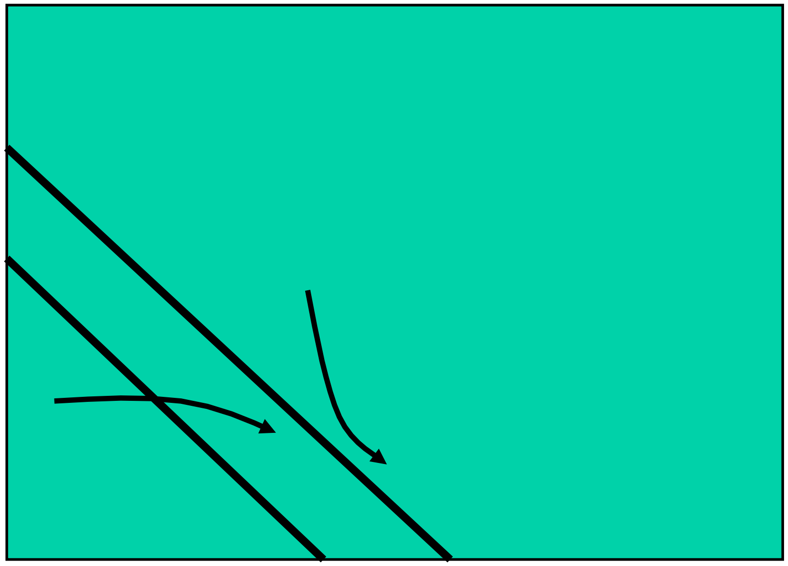
$$\begin{cases} \dot{x}(t) = r_1 x\left(1 - \dfrac{x + \alpha y}{N_1}\right) \\ \dot{y}(t) = r_2 y\left(1 - \dfrac{\beta x + y}{N_2}\right) \end{cases}$$

The sign of the derivatives are decided by two values

$N_1 - (x + \alpha y)$ **and** $\alpha N_2 - (x + \alpha y)$

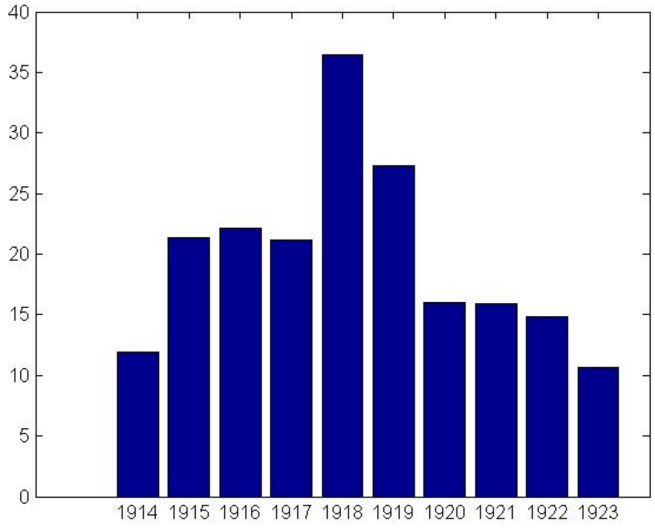
If $N_1 > \alpha N_2$ **, X species will win.**

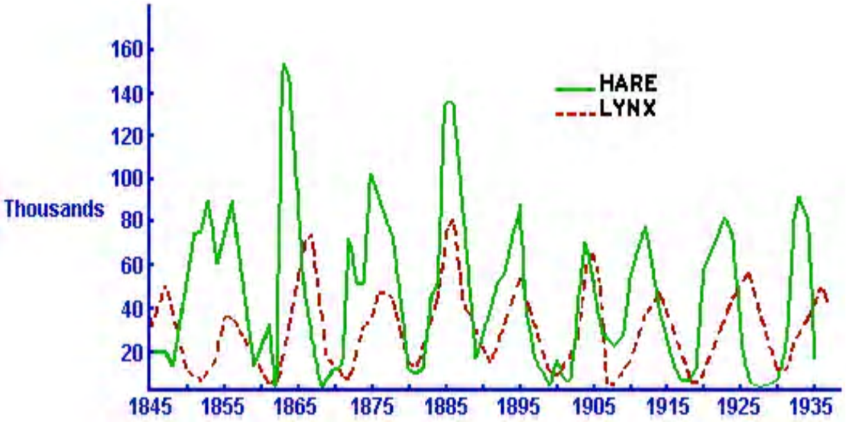
If $N_1 < \alpha N_2$ **, Y species will win.**



Model of two species (Predator and Prey)

- Lotka-Volterra Model
- The simplest model of predator-prey interactions developed independently by Lotka (1925) and Volterra (1926)
- Ancona's observation on Shark's population during world war I.





Model of two species (Predator and Prey)

Assumption:

- The predator species is totally dependent on a single prey species as its only food supply,
- The prey species has an unlimited food supply, and there is no threat to the prey other than the specific predator.

Let X represent the prey and Y represent the predator, without the predator, the Malthus model can be applied

$$\dot{x} = ax$$

However, because of the predator, r has to be modified

$$\dot{x} = (a - by)x$$

For the predator, the situation is just the opposite.

$$\dot{y} = (-c + dx)y$$

Thus we get the ODEs for this model

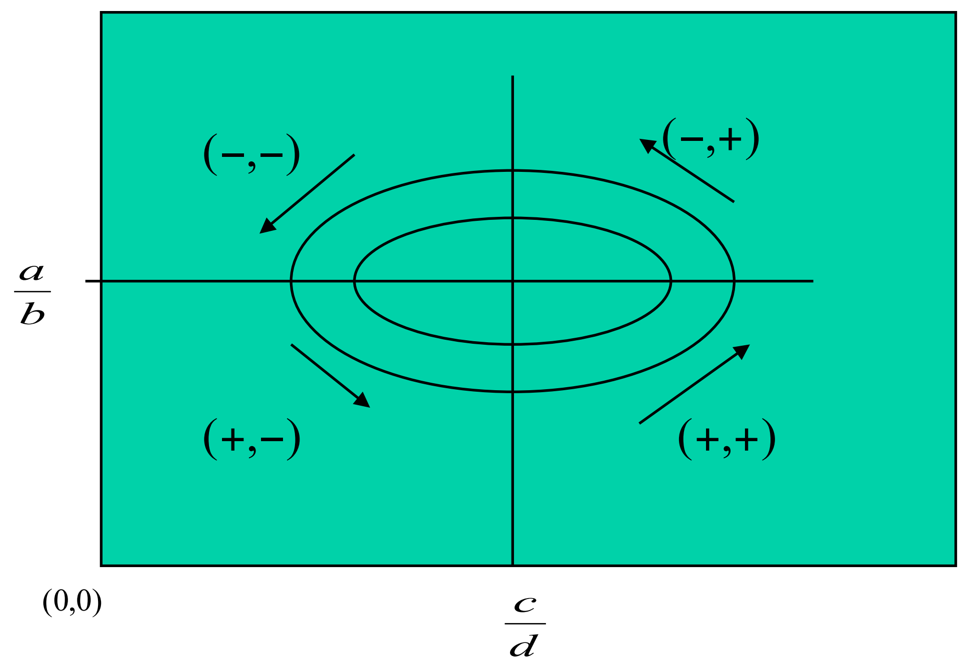
$$\begin{cases} \dot{x} = (a - by)x \\ \dot{y} = (-c + dx)y \end{cases}$$

Phase Plot Analysis

$$\begin{cases} \dot{x} = (a - by)x \\ \dot{y} = (-c + dx)y \end{cases}$$

There are two corresponding equilibrium points:

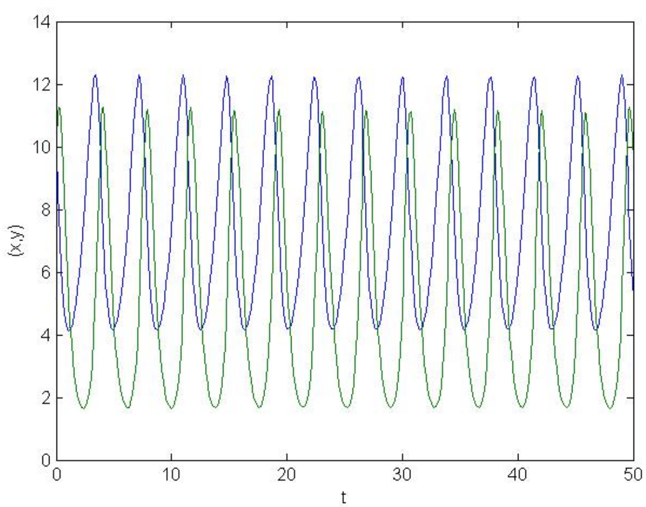
$(0,0)$ **or** $(\frac{c}{d}, \frac{a}{b})$

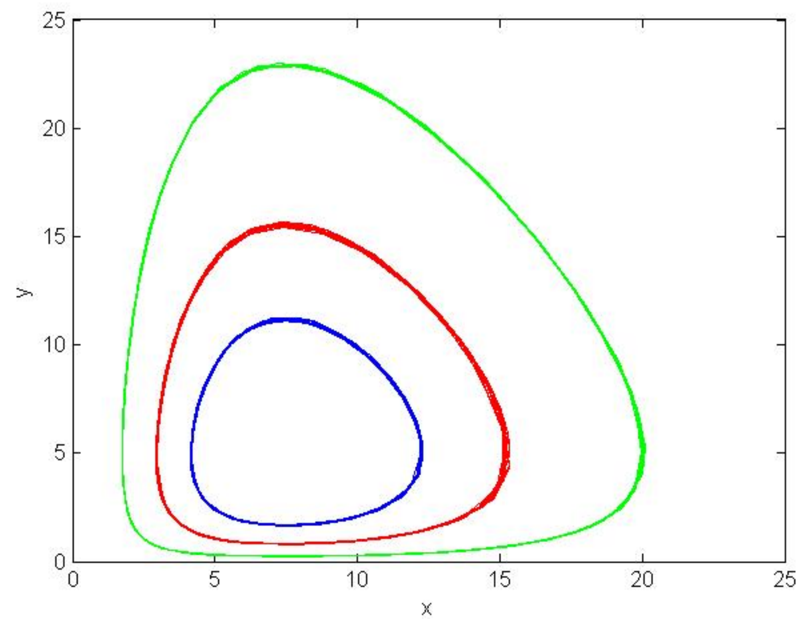


Matlab Simulation Result

Based on example:

$$\begin{cases} \dot{x} = (1-0.2y)x \\ \dot{y} = (-3+0.4x)y \end{cases}$$





Effect of Parameters

The solution of the LV predator-prey model is

$$x = \frac{c}{d}, \qquad y = \frac{a}{b}$$

where

a : the natural reproduction rate for the prey

b : the killing rate because of the predator

c : the natural death rate for the predator

d : the reproduction rate because of the prey

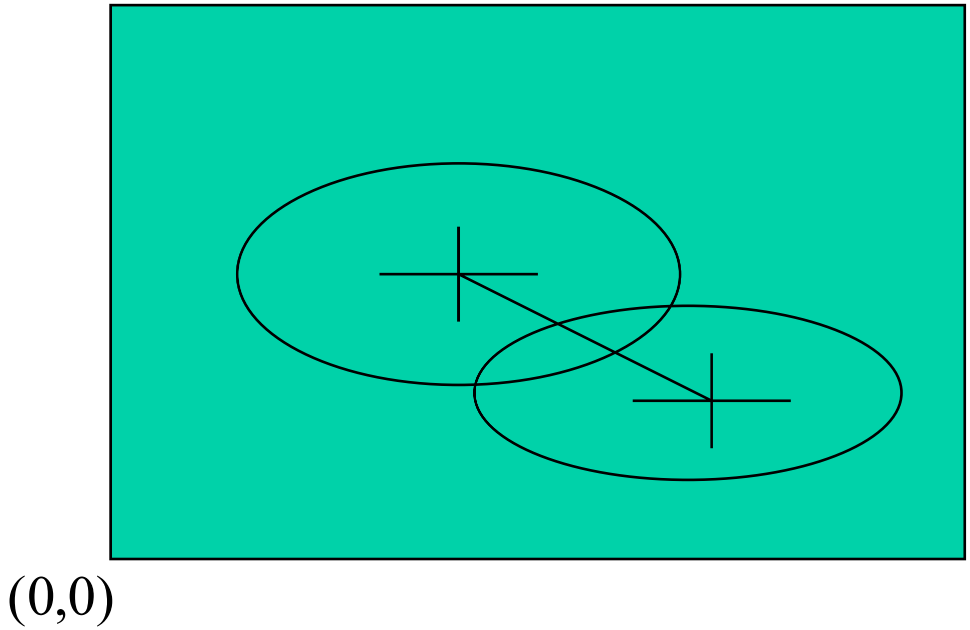
Question: Why the shark ratio increases during world war I?

Parameter Analysis

$$x^* = \frac{c}{d}, \qquad y^* = \frac{a}{b}$$

When fishing is introduced in the model, their effect will be increase the death rate of the predator and decrease the reproduction rate for the prey. Thus

$$c \rightarrow c + e, \qquad a \rightarrow a - e$$



SIR Model (Kermak – McKendrick Model)

S: Susceptible

I: Infected

R: Recovered/Removed

$$\frac{dS}{dt} = -\beta S(t)I(t)$$

$$\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t)$$

$$\frac{dR}{dt} = -\gamma I(t)$$

$$S(t)+I(t)+R(t) = \mathrm{N} = \text{the total population}$$

SIR Model

From the original model, we have

$$\frac{dS}{dt} = -\beta S(t)I(t)$$

$$\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t) = [\beta S(t) - \gamma]I(t)$$

Note that this type of equations is similar to what we've seen before.