Math for Biology - An Introduction

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Differential Equations - Our Goal

- We will *NOT* be solving differential equations
- The tools - Rule Bender and BioNetGen - will do that for us
- This lecture is designed to give some background about what the programs are doing

Differential Equations - An Overview

- Differential Equations contain the derivatives of (possibly) unknown functions.
- Represent how a function is changing.
- We work with first-order differential equations - only include first derivatives
- Generally real-world differential equations are not directly solvable.
- Often we use numerical approximations to get an idea of the unknown function's shape.

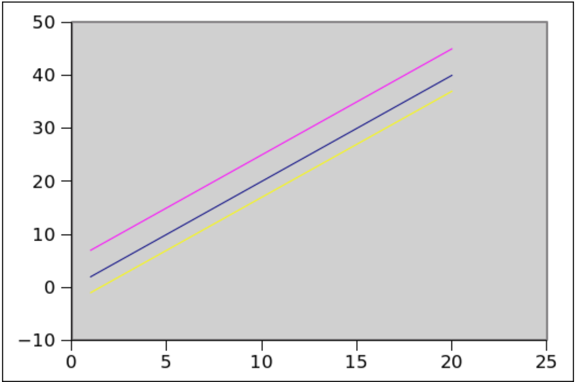
Differential Equations - Starting from the solution

- A differential equation: $f'(x) = C$

Differential Equations - Starting from the solution

- A differential equation: $f'(x) = C$
- A few solutions.

Figure: Some solutions to $f'(x) = 2$



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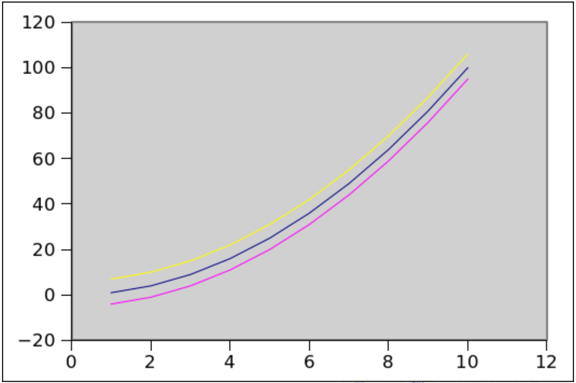

Differential Equations - Initial Conditions

- How do we know which is the correct solution?
- Need to know the value for a point - the initial conditions.
- Only one necessary for these types of problems. Need an initial condition for each variable in the equation.

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- $f(x) = x^2 + 6$.

Differential Equations - A Slightly More Complex Example

- The Logistic Curve
- Models population growth
- Differential equation:
- $\frac{d}{dt}P(t) = P(t)(1 - P(t))$
- When does $P(t)$ not change? In other words, when is the derivative equal to 0?
- Under what conditions is the derivative positive? Negative?

Differential Equations - A Slightly More Complex Example

- The Logistic Curve - Solution
- What more do we need before we find a solution?

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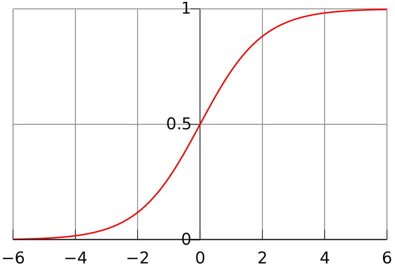
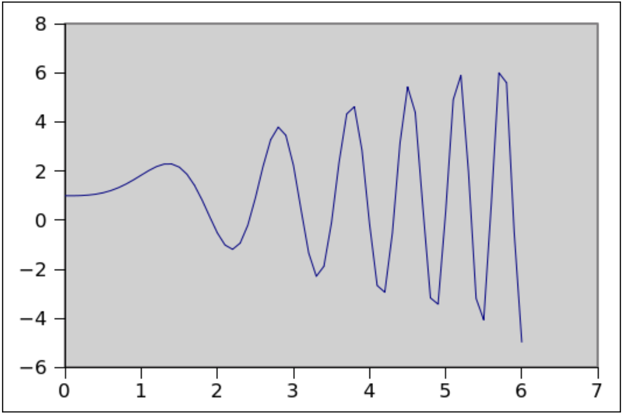
- What more do we need before we find a solution?
- $P(0) = .5$
- $P(t) = \dfrac{1}{1 + e^{-t}}$
-



Differential Equations - How about this one?



Biochemical Reactions - An Application of Differential Equations

- How can we represent the concentrations of molecules in solution?
- We can represent how much the concentrations change over time as differential equations.
- A set of differential equations that closely describe how a system develops is a model of the system.

Biochemical Reactions - Terminology Review

- *Chemical Reaction* A process that changes a set of chemical species into another
- *Reactants* The initial set of chemical species
- *Products* The new set of chemical species
- *A basic synthesis reaction* $\mathrm{A} + \mathrm{B} \rightarrow \mathrm{C}$
- *An equilibrium reaction* $\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C}$
- *Conservation of Mass* The mass of the products has to equal that of the reactants (in a closed system)

Biochemical Reactions - Some Basic Questions

- How quickly does a biochemical reaction take place?
- How will different concentrations of the reactants affect the reaction rate?
- What will be the concentrations of the reactants and products at equilibrium?

The Law of Mass Action

- Describes the rate at which chemicals collide and form new compounds
- It's a model that describes molecular interactions
- Example: $A + B \rightarrow C$
- Concentration is represented as $[A]$, $[B]$ and $[C]$.
- The rate can be expressed as the change in the amount of compound C: $\frac{d[C]}{dt}$
- This rate is determined by the number of collisions between A and B and the probability that a collision will lead to the combination of the molecules.

The Law of Mass Action

- $\frac{d[C]}{dt} = k[A][B]$
- Called the Law of Mass Action
- k is the rate constant. Takes into account shapes, attraction and temperature.
- k is different for every reaction.

Equilibrium Constant

- $\mathrm{A} + \mathrm{B} \underset{k_-}{\overset{k_+}{\rightleftharpoons}} \mathrm{C}$
- A is consumed by forward reaction and produced by the reverse reaction, so
- $\dfrac{d[A]}{dt} = k_-[C] - k_+[A][B]$
- At equilibrium, the reactions cancel each other out and
- $\dfrac{k_-}{k_+} \equiv K_{eq} = \dfrac{[A]_{eq}[B]_{eq}}{[C]_{eq}}$
- Exercise: Show that this equation follows from the previous one

Equilibrium Constant - Exercise

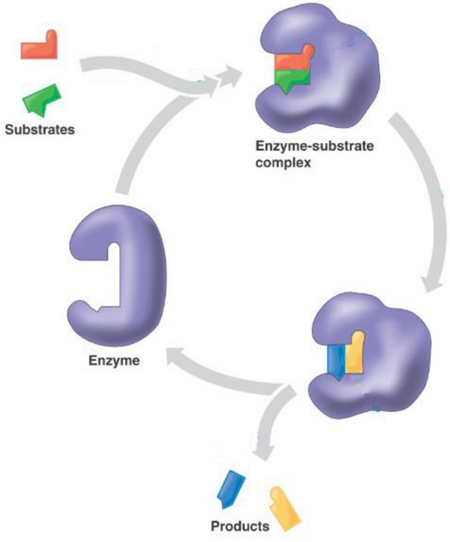
$$\frac{k_-}{k_+} \equiv K_{eq} = \frac{[A]_{eq}[B]_{eq}}{[C]_{eq}}$$

- What is the relationship between the equilibrium concentrations of A, B and C if K_{eq} is greater than 1?
- Less than 1?
- Almost equal to 1?

Enzyme Basics

- Enzymes help to convert *substrates* into *products*
- Catalysts - affect the rate of the reaction but are not changed by it
- Speed up biological reactions by up to 10 million times
- Very specific - usually one enzyme catalyzes one reaction
- Regulated by feedback loops - like those found in signalling pathways

How Enzymes Work - An example



Enzyme Kinetics - A Law Breaker

- Assume a model of an enzyme catalyzed reaction:
- $\mathrm{S} + \mathrm{E} \rightarrow \mathrm{P} + \mathrm{E}$
- If we increase the concentration of the substrate, what happens to the reaction rate?

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- $\mathrm{S} + \mathrm{E} \rightarrow \mathrm{P} + \mathrm{E}$
- If we increase the concentration of the substrate, what happens to the reaction rate?
- Should go up linearly
- That's not what happens
- The rate only increases to a maximum value

Enzyme Kinetics - A Better Model

- $\mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{P} + \mathrm{E}$
- Substrate combines with Enzyme to form Complex
- Complex breaks down into Product and Enzyme
- But the Product is mostly removed, so that reverse reaction doesn't really occur
- Can assume that reaction doesn't happen. The conventional form:
- $\mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \overset{k_2}{\to} \mathrm{P} + \mathrm{E}$
- Called the Michaelis-Menten Model of enzyme kinetics

Enzyme Kinetics - Rates of Change

$$\mathrm{S} + \mathrm{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \overset{k_2}{\rightarrow} \mathrm{P} + \mathrm{E}$$

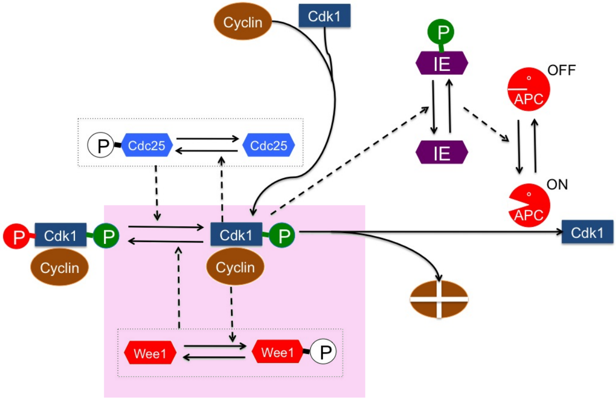
- For ease of writing, let $s = [\mathrm{S}]$, $c = [\mathrm{C}]$, $e = [\mathrm{E}]$, and $p = [\mathrm{P}]$.
- Using Law of Mass Action, can write four differential equations:
  - $\frac{ds}{dt} = k_{-1}c - k_1 se$
  - $\frac{de}{dt} = (k_{-1} + k_2)c - k_1 se$
  - $\frac{dc}{dt} = k_1 se - (k_2 + k_{-1})c$
  - $\frac{dp}{dt} = k_2 c$

Enzyme Kinetics - Michaelis-Menten Equation

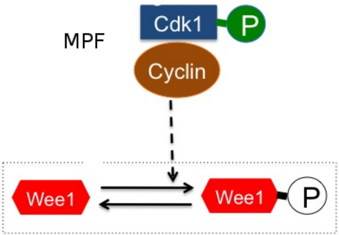
- Given the differential equations and some assumptions, it is possible to approximate the rate of product formation
- Definitions:
  - v the rate at which the product is formed
  - k_2 the rate constant for dissociation of the enzyme-product complex
  - $[E]_0$ the enzyme concentration
  - $[S]$ the substrate concentration
  - K_m the Michaelis constant which measures the affinity of the substrate for the enzyme.
- The Michaelis-Menten equation:

$$v = k_2[E]_0 \frac{[S]}{K_m + [S]}$$

Enzyme Kinetics - Application to the Frog Cell Cycle

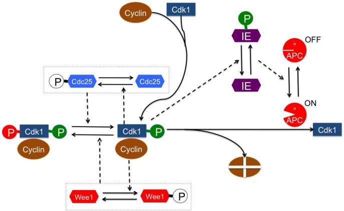


Enzyme Kinetics - Exercise 1



- Identify, substrate, enzyme and product
- Ignoring ATP, write the forward (phosphorylating) reaction following the Michaelis-Menten model
- What is the differential equation for the change in concentration of Wee1? Wee1-P?
- Use the Michaelis-Menten reaction to write a formula for the rate of product formation.

Enzyme Kinetics - Exercise 2



- With the people near you, choose a reaction from the cycle
- Identify, substrate, enzyme and product
- Ignoring ATP, write the reaction following the Michaelis-Menten model
- Use the Michaelis-Menten reaction to write a formula for the rate of product formation.
- Be ready to present to the group