UNIVERSITY of WASHINGTON

BIOE 498 / BIOE 599: Computational Systems Biology for Medical Applications

CSE 599V: Advancing Biomedical Models

Lecture 2: Modeling Essentials

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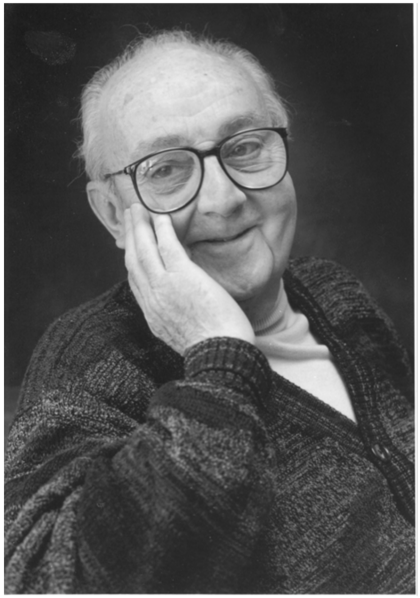
G.P.E. Box (Famous Statistician)



All models are wrong.
But some models are useful.

Agenda

- Conceptual models
  - Variables and relationships
- Dimensional analysis
- Modeling Workflow
- Example: Modeling the lac operon
- Technical models with differential equations
- Technical models with Markov Models
- Review

Lecture Notes

https://github.com/ModelEngineering/advancing-biomedical-models/tree/master/Lectures

A Motivating Example: Modeling Water Flows and Levels for a Reservoir

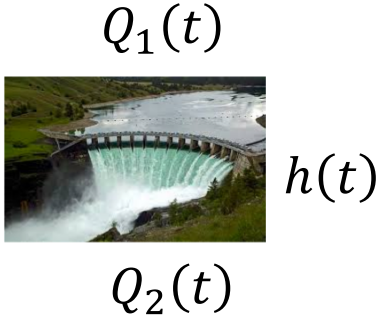
$Q_1(t)$= flow in *(m^3s^{-1})*

$h(t)$= water height *(m)*

$Q_2(t)$= flow out *(m^3s^{-1})*

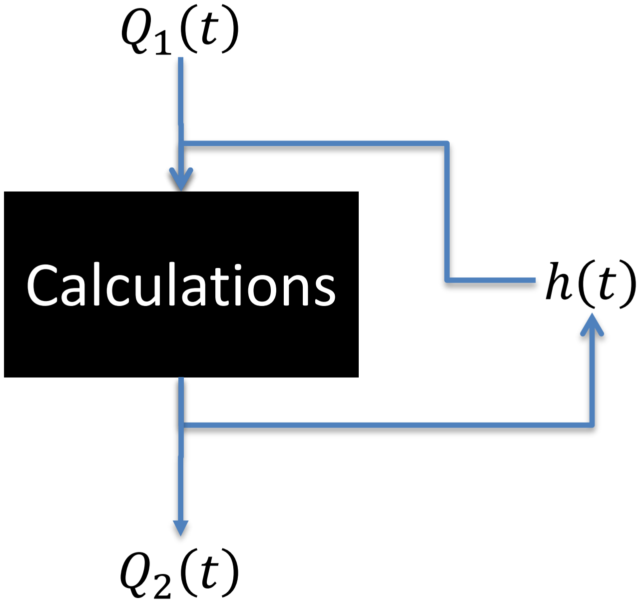
m = meters
s = seconds

A conceptual model specifies variables and their roles.



Variable Roles

- *Input*. Exogenous variable that does not depend on the model.
- *Output*. Computed variable of interest to the modeler.
- *State*: Computed variable used to calculate output variables and/or other state variables.



Technical models detail calculations.

$Q_1(t)$

$h(t)$

$Q_2(t)$

Initial Technical Model

$$\frac{dh(t)}{dt} = a(Q_2(t) - Q_1(t)), \qquad h(t) > 0$$

Issues

- What if *h(t)* exceeds the height of the dam?
- How is a obtained?

Estimating $\boldsymbol{a}$

- *If* the reservoir is a cylinder with radius *r*, then $a = \frac{1}{\pi r^2}$

Technical Model with cylinder assumption when $\boldsymbol{h(u) > 0}$

$$h(t) = \int \frac{Q_2(u) - Q_1(u)}{\pi r^2} du$$

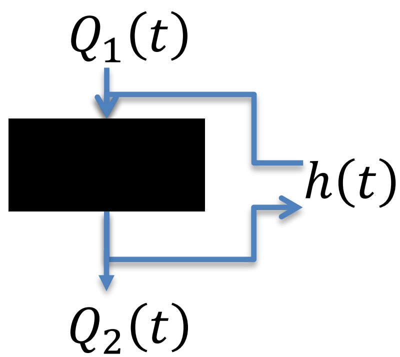
~~The reservoir is a cylinder?~~

The model is wrong.
But the model *may* be useful.

Modeling Workflow

System Diagram

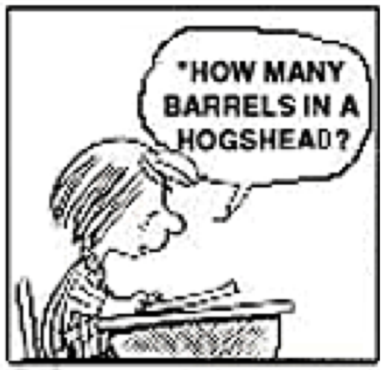
Conceptual Model



Technical Model

$$h(t) = \int \frac{Q_2(u) - Q_1(u)}{\pi r^2} du$$

Dimensional Analysis



Why dimensional analysis?

- Ensure consistent units.
- Validate mathematical models.
- Derive mathematical models.

$$\underbrace{dh(t)}_{m} = \underbrace{a}_{\color{red}{x}}(\underbrace{Q_2(t)}_{m^3 s^{-1}} - \underbrace{Q_1(t)}_{m^3 s^{-1}})\underbrace{dt}_{s}$$

Height model

Units

Rules for Dimensional Analysis

1. The units for a variable expression are that expression applied to the units of the variables.
2. Multiplying (dividing) units creates a compound unit.
3. Adding (subtracting) the same units gives the same units. Adding different units is undefined.
4. The units must be the same on both sides of an equals sign.
5. The arguments of transcendental functions (e.g., natural log) must be unitless.

Solving for the units of a

$$\underbrace{dh(t)}_{m} = \underbrace{a}_{x}(\underbrace{Q_2(t)}_{m^3s^{-1}} - \underbrace{Q_1(t)}_{m^3s^{-1}})\underbrace{dt}_{s}$$

By Rules 1 & 4:

$$m = x(m^3s^{-1} - m^3s^{-1})s$$

By Rule 3:

$$m = x(m^3s^{-1})s$$

By multiplication:

$$m = xm^3$$

By division:

$$x = m^{-2}$$

Rules

1. The units for a variable expression are that expression applied to the units of the variables.
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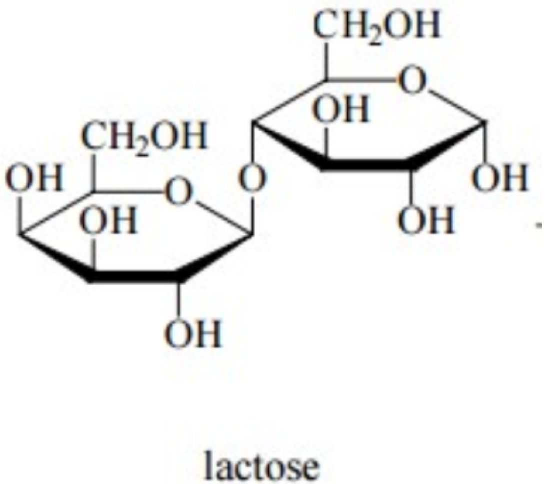
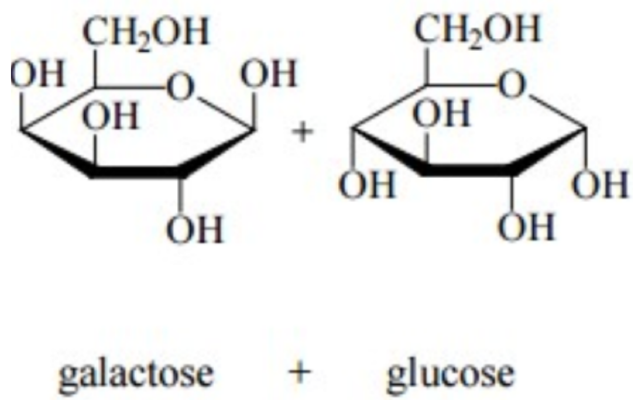
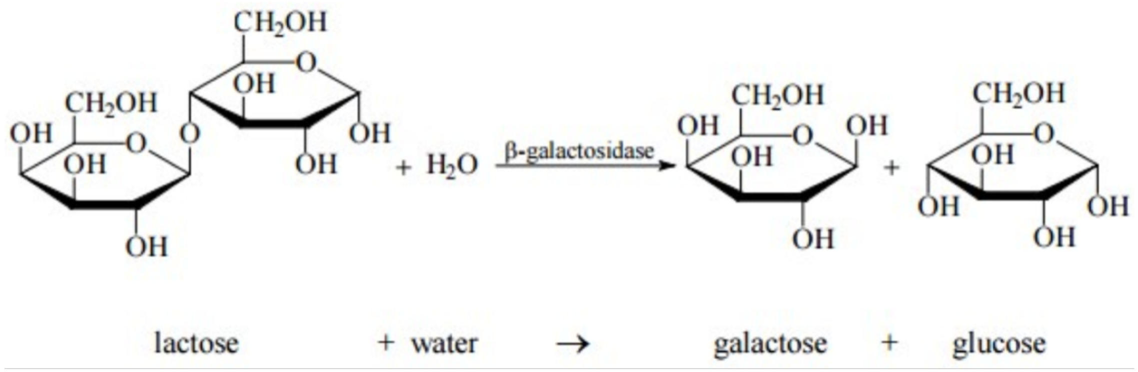
Modeling Example: lac Operon

Problem: yeast prefer glucose but sometimes only have access to lactose.





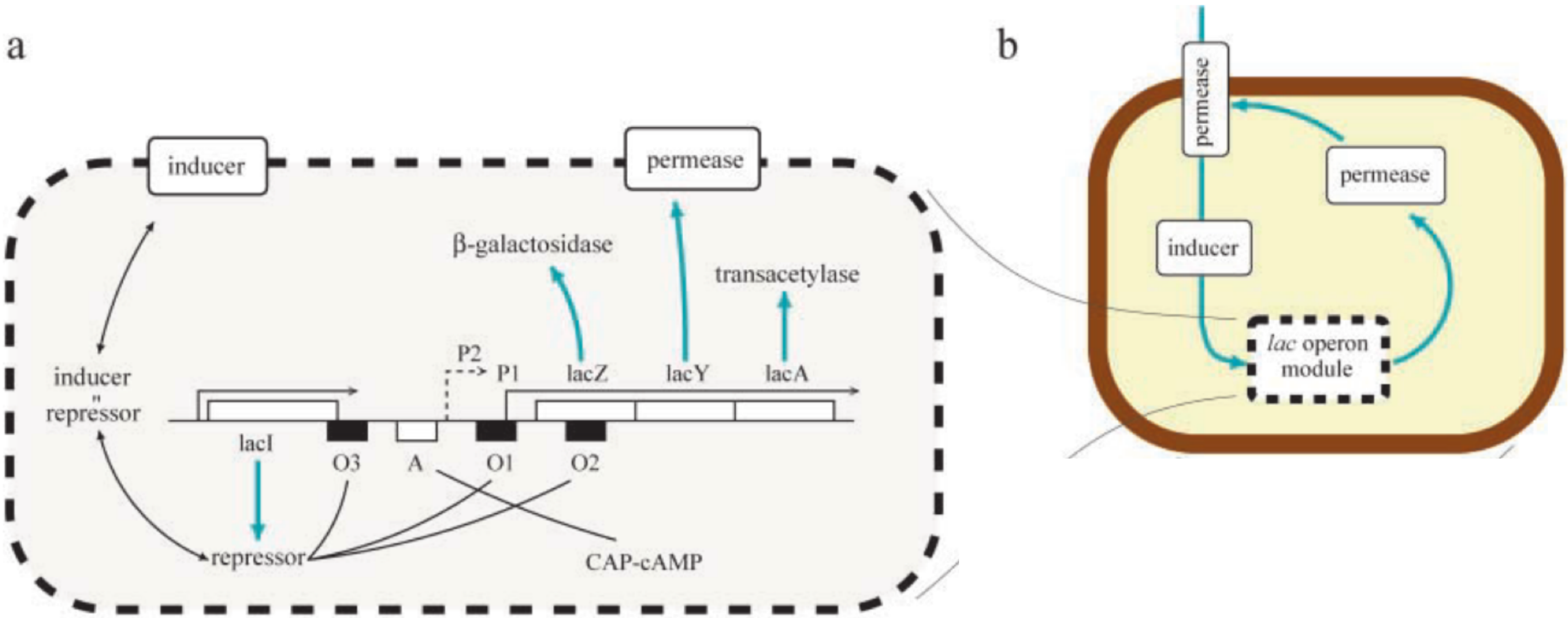
When Should Yeast Adapt?



Glucose	Lactose
+	–
+	+
–	–
–	+

How Yeast Adapts: lac operon

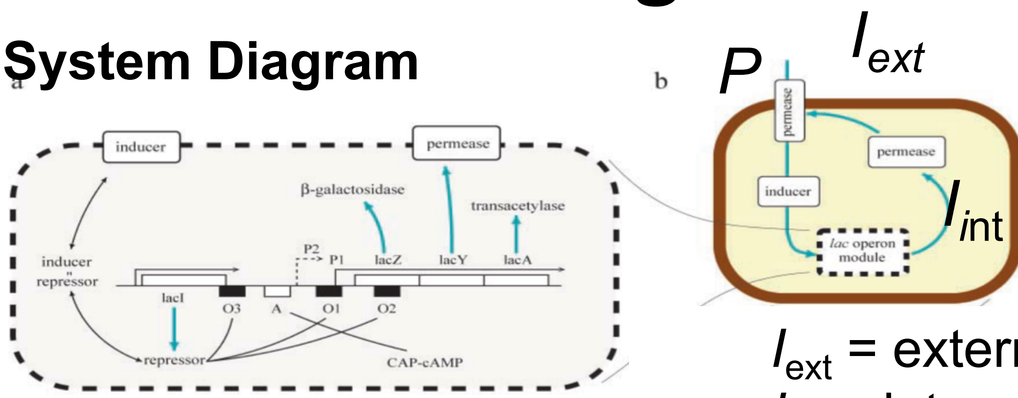
Adaptations
- Allow lactose into the cell
- Convert lactose to galactose and glucose



*Vilar et al., 2003. Journal of Cell Biology.

Modeling the lac Operon

System Diagram



*Vilar et al., 2003. Journal of Cel

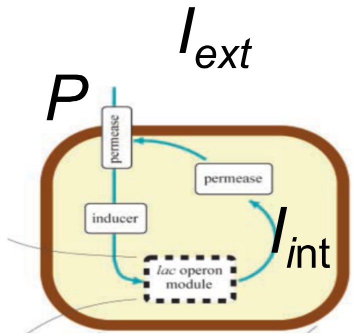
I_{ext} = external inducer (lactose)
I_{int} = internal inducer
P = permease

- I_{ext}, I_{int}, P are concentrations
  - count in moles (mol)
  - divided by volume in liters (l)

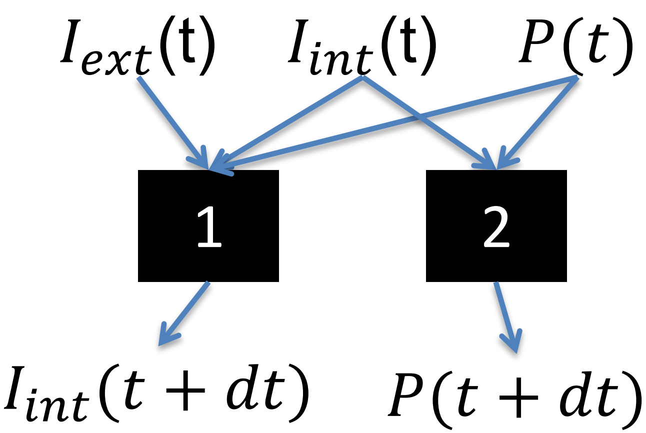
  mol l^{-1}

Modeling the lac Operon

Simplified System Diagram



Conceptual Model



Technical Model

$$dx = x(t+dt) - x(t)$$

1: $$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

2: $$\frac{dP}{dt} = cI_{int} - eP$$

Questions

- What are the units of *dP/dt?*
- What are the units of *c*?
- What are the units of *a*?

mol $l^{-1}\ s^{-1}$

s^{-1}

mol $l^{-1}\ s^{-1}$

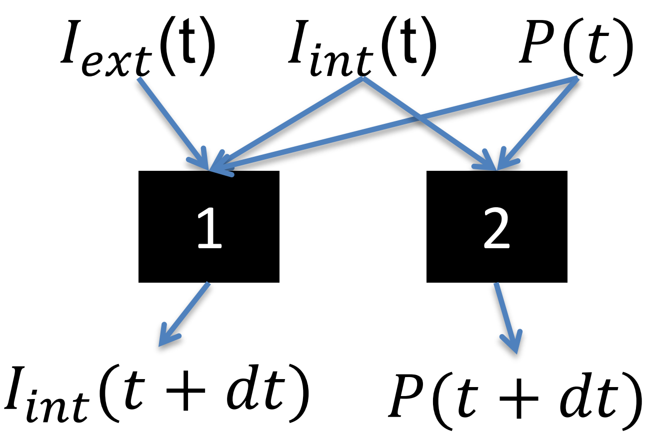
Technical Models With Differential Equations

- Differential equations describe how variables change, typically with respect to time.
- A differential is a small change

  dt is a small change in t

  $dx(t)$ is the change from $x(t)$ to $x(t + dt)$

Lac operon: Concentration of inducer and permease



$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

$$\frac{dP}{dt} = cI_{int} - eP$$

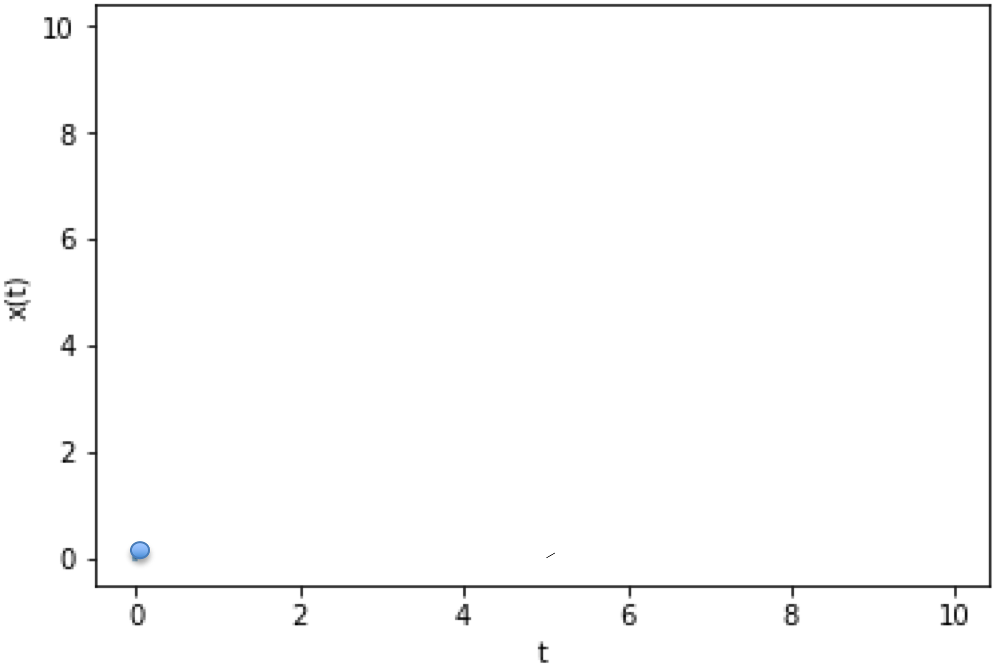
What We Assume Using a Model Based on Differential Equations

- The system is deterministic
  - Repeated experiments produce essentially the same results
  - Counter example: Individual chemical reactions
- Variables are continuous
  - Counter example: Small number of molecules

Solving Differential Equations
Initial Value Problem (IVP)

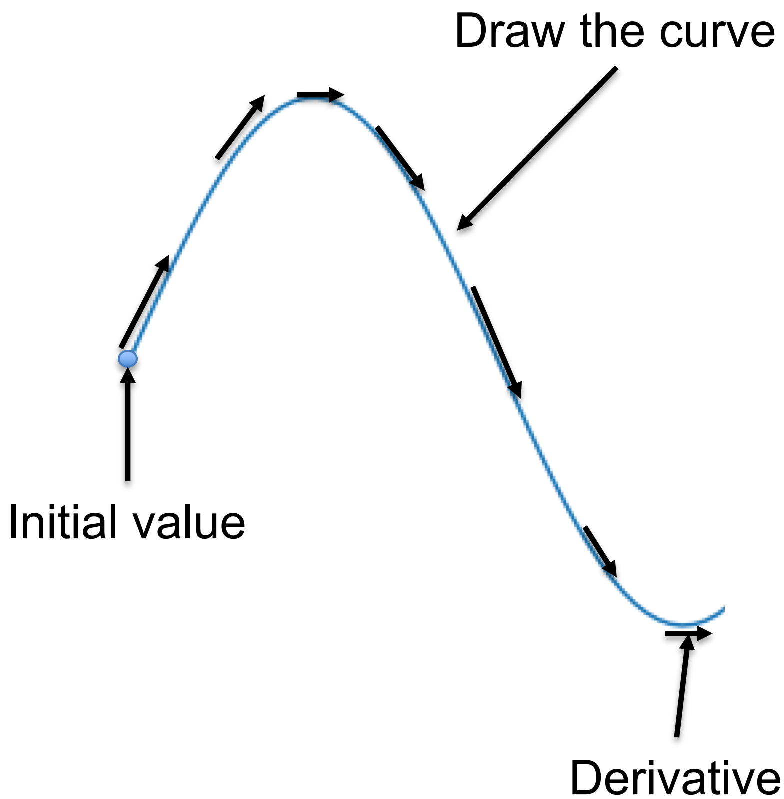
Given derivative of variables and their initial values.
Find values of variables over time.

Example: $\frac{dx}{dt} = 1, x(t_0) = 0$



Graphical solution
1. Place a point at initial value.
2. Draw a line with slope equal to the derivative.

A More Elaborate Initial Value Problem



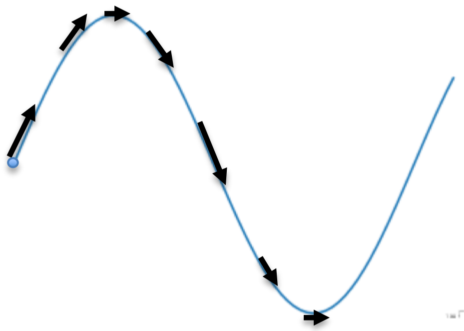
Euler Algorithm for IVP

Given: Differential equations and initial values for *n* variables

$$\frac{dx_n(t)}{dt} = f_n\big(x_1(t), \cdots, x_N(t)\big),\ x_n(0)$$

Find Values of variables at time T

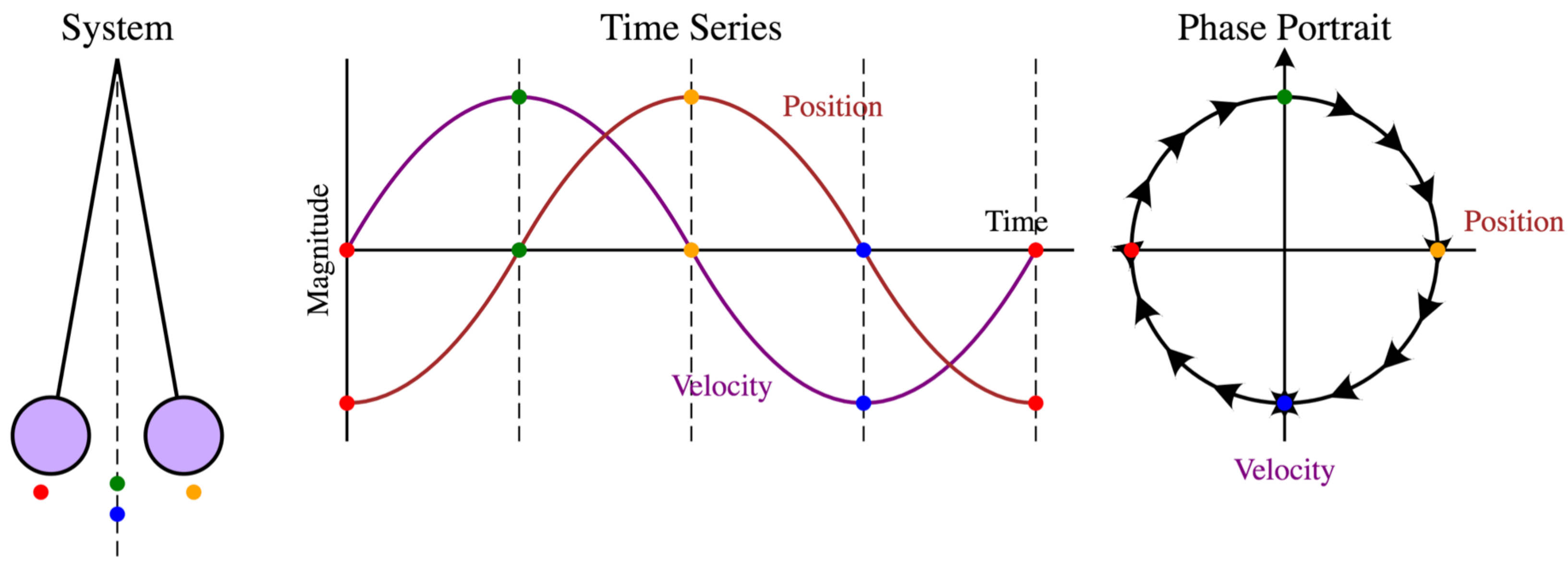
$$x_n(T)$$



1. For t = 0..T-1
   1. For n = 0..N
      1. delta = $f_n\big(x_1(t), \cdots, x_n(t)\big)dt$
      2. $x_n(t+1)$ = $x_n(t)$ + delta

Phase Portrait

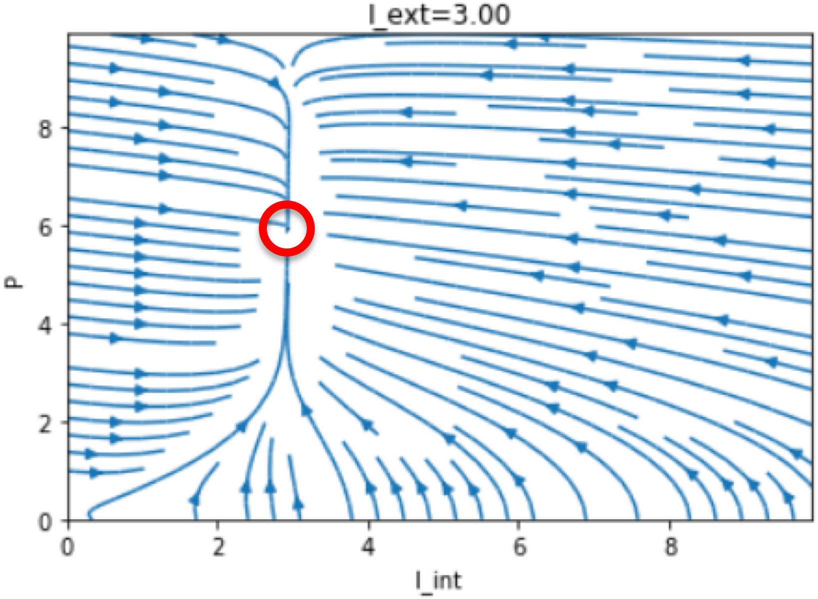
Geometric representation of how variables change.

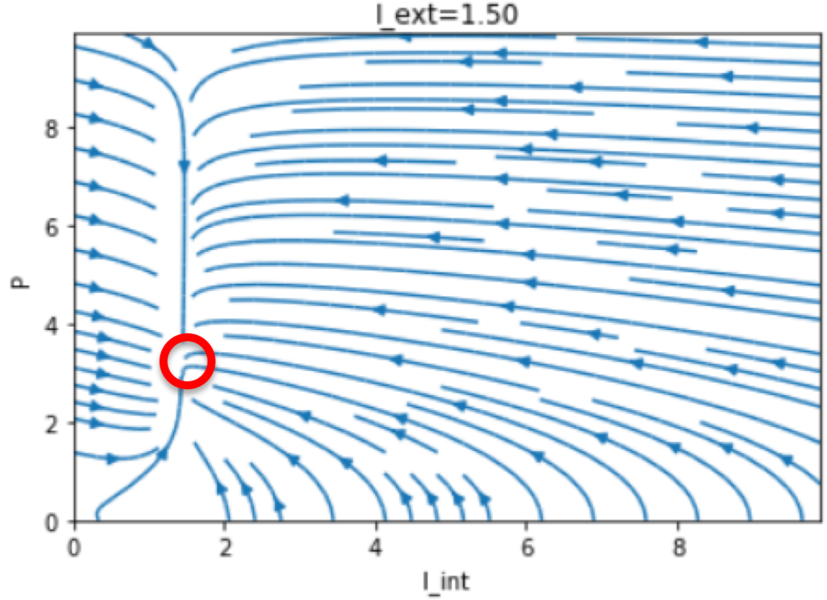


Phase Portrait For lac Operon Model

$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

$$\frac{dP}{dt} = cI_{int} - eP$$





Fixed point: All derivatives are 0.
Stable fixed point: Stays at fixed point.

$a = 1, b = 0.1, c = 1, e = 0.5$

Finding Fixed Points

Solve for variable values when derivatives are 0.

lac operon model

$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

$$0 = a(I_{ext} - I_{int})P - bI_{int}$$

$$\frac{dP}{dt} = cI_{int} - eP$$

$$0 = cI_{int} - eP$$

Solving:

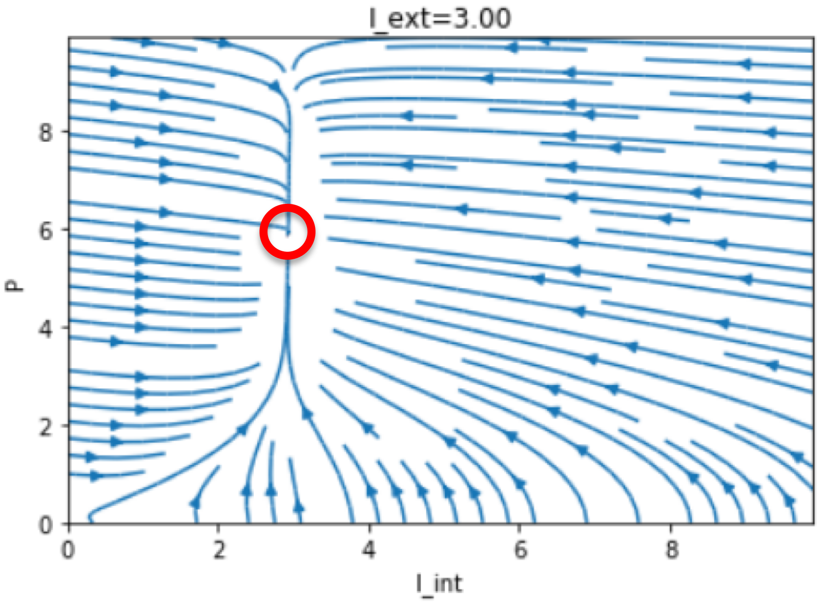
$$I_{int} = I_{ext} - \frac{be}{ac}$$

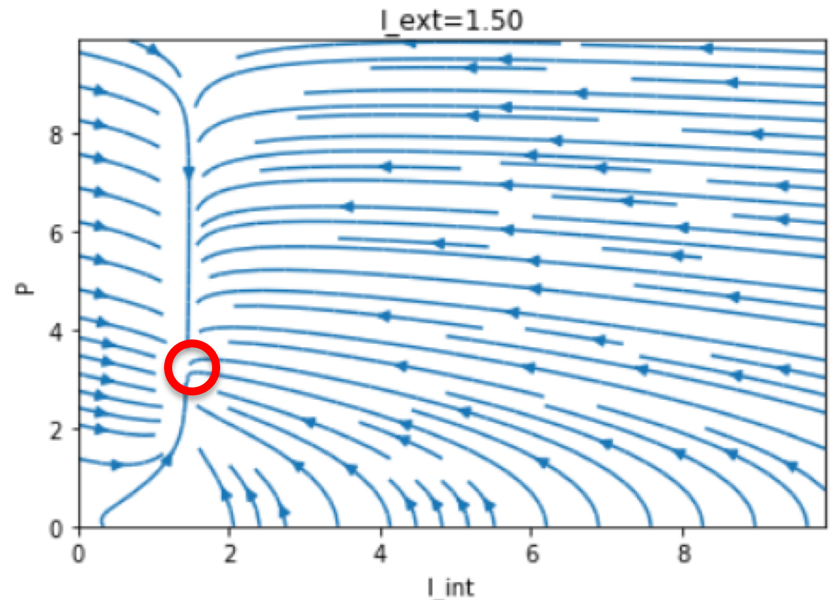
$$P = \frac{c}{e} I_{int}$$

For the values used:

$$I_{int} \approx I_{ext} \qquad P \approx 2I_{ext}$$

Relating Steady Calculations to Phase Portrait





$$I_{int} \approx I_{ext} = 3.0$$
$$P \approx 2I_{ext} = 6.0$$

$$I_{int} \approx I_{ext} = 1.5$$
$$P \approx 2I_{ext} = 3.0$$

Types of Differential Equations

- Ordinary differential equations
  - Only take derivative with respect to a single variable (e.g., time)
  - Partial differential equations have derivatives with respect to many variables
- Linear differential equations
  - No products (or other functions) of variables being differentiated
  - We mostly have non-linear, ordinary differential equations

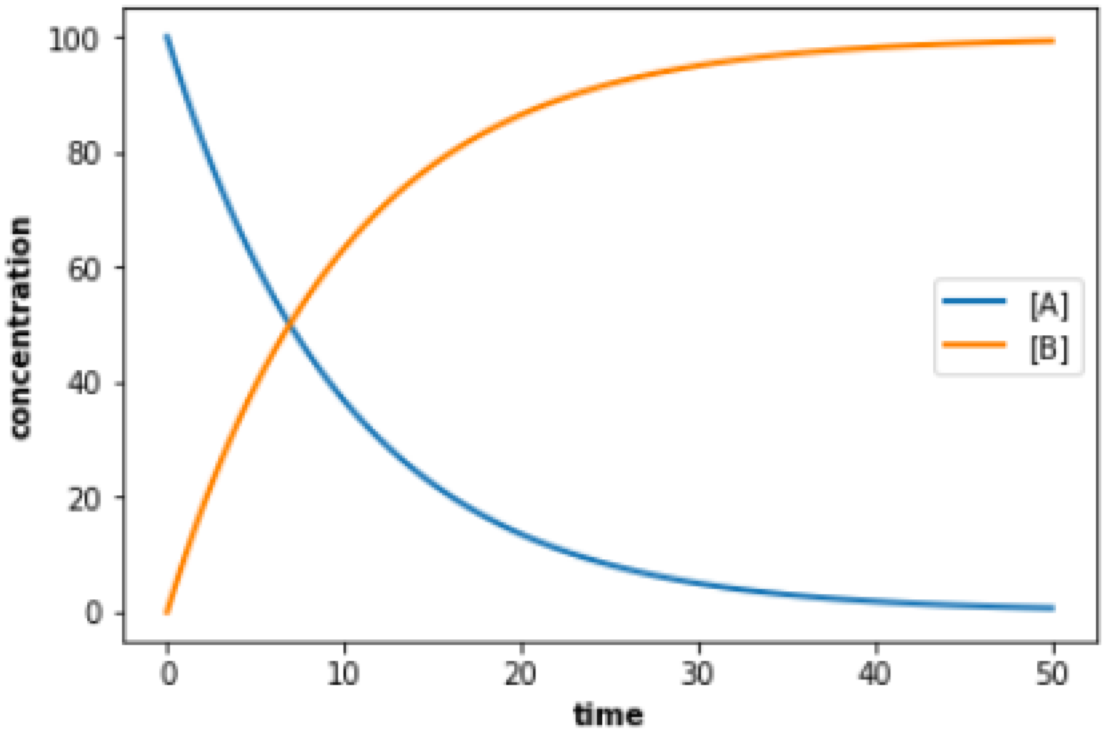
$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int} \qquad \frac{dP}{dt} = cI_{int} - eP$$

Differential Equations for Chemical Reactions

Reaction	Kinetics	Differential Equation
$A \rightarrow B$	kA	$\frac{dA}{dt} = -kA$
$A + B \rightarrow C$	kAB	$\frac{dA}{dt} = \frac{dB}{dt} = -kAB$
$A \rightarrow B + C$	kA	$\frac{dA}{dt} = -kA$
$A + B \rightarrow C + D$	kAB	$\frac{dA}{dt} = \frac{dB}{dt} = -kAB$

How Concentrations Change

Reaction	Kinetics	Differential Equation
$A \rightarrow B$	kA	$\frac{dA}{dt} = -kA$



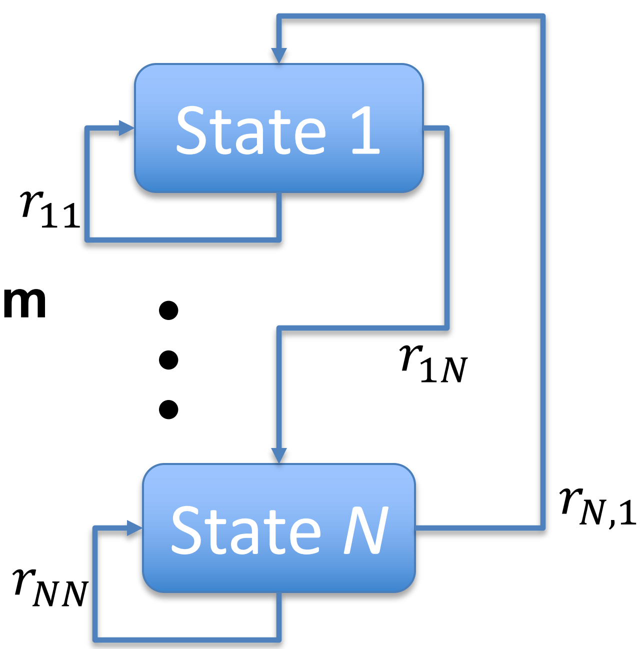
Technical Models With Markov Models

- Motivation
  - Address situations where there are few molecules (e.g., low expression rates)

Markov Model Core Concepts

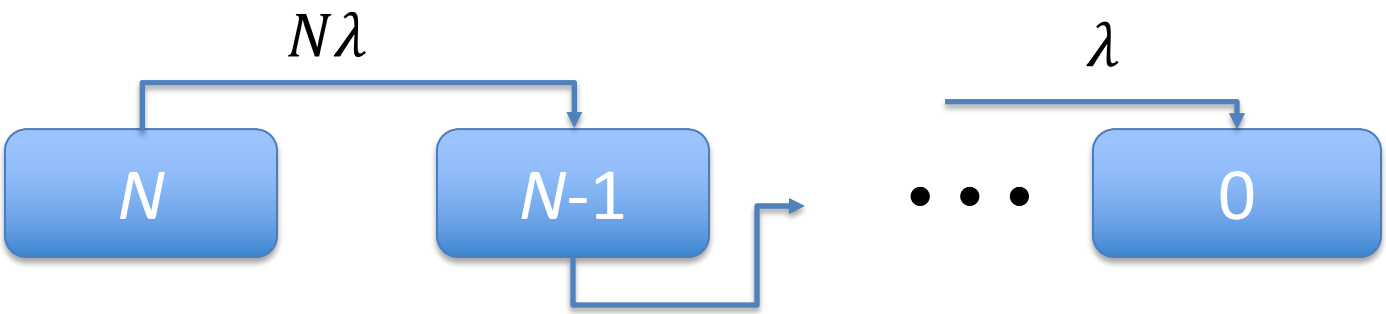
- **States**: Specifies variable values that completely characterize how the system behaves
- **Transition rates**: Probability per time unit of the system moving from state to state

State Diagram



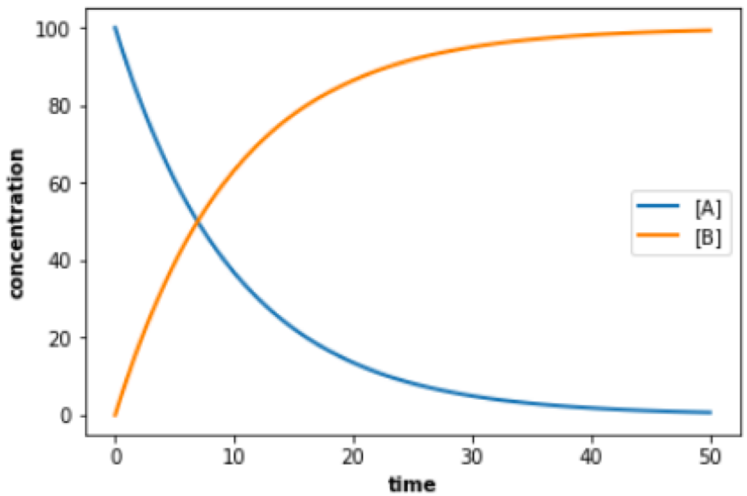
Markov Model Example: $A \rightarrow B$

- State: Number of molecules of *A* (or *B*)
- Transition: Change in the number of molecules of *A* as a result of a reaction
  - Each molecule of *A* reacts at a constant rate λ

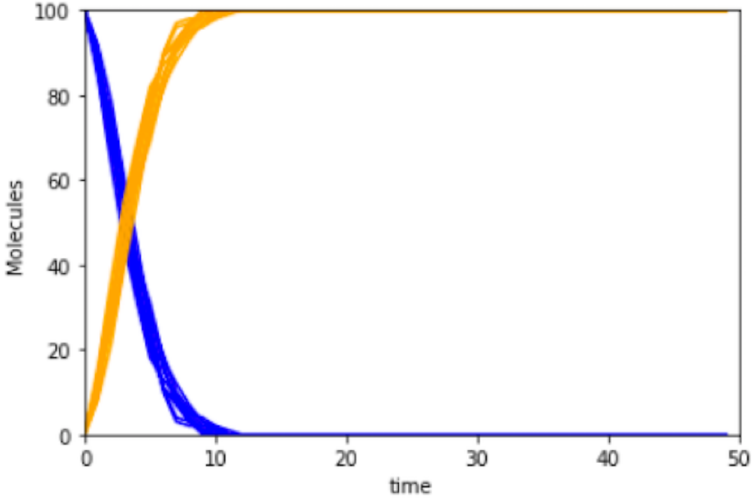


Deterministic vs. Stochastic Model

Deterministic
(Differential Equation)

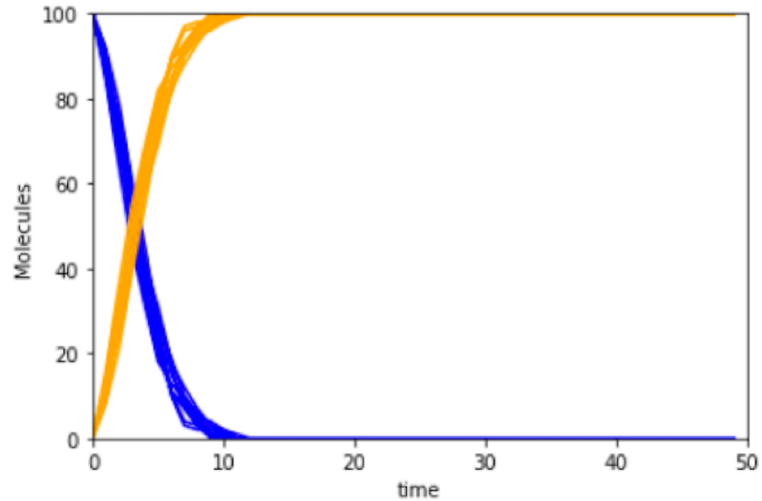


Stochastic



Effect of the Number of Molecules

100



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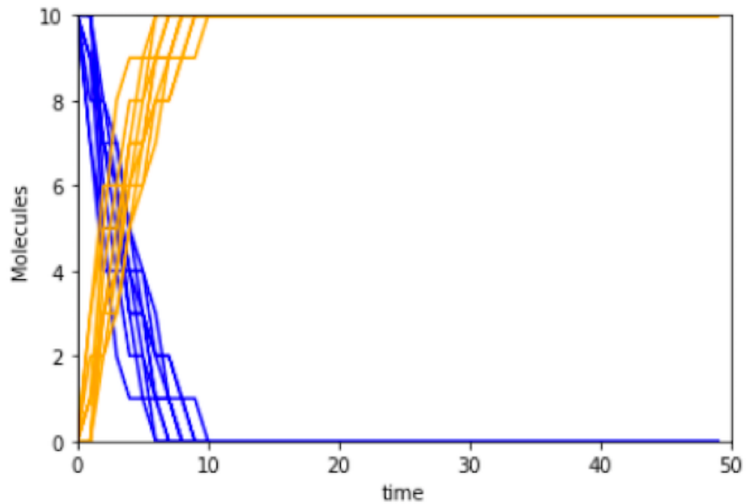

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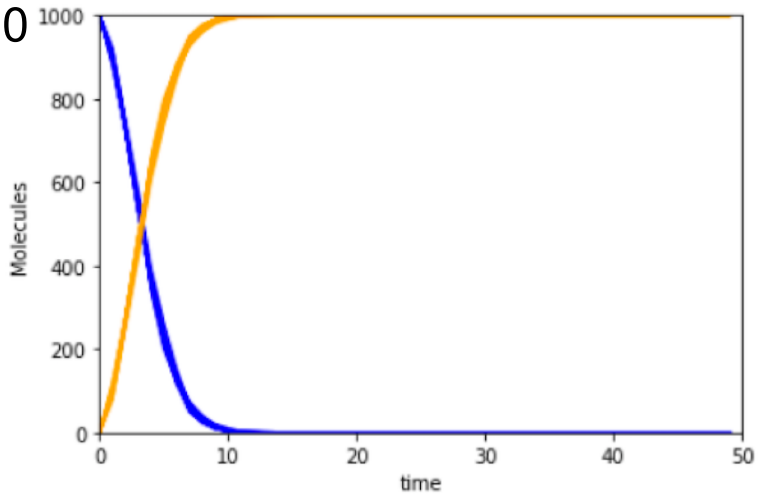
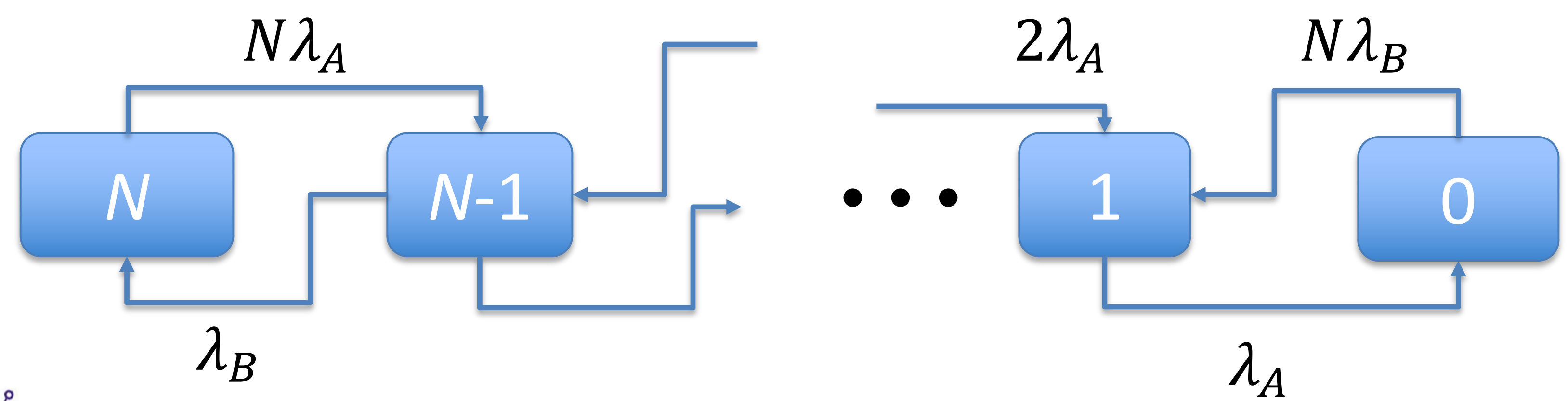


Markov Model Example: $A \leftrightarrow B$

- States?
  - Molecules of *A*
  - *N* is the sum of the molecules of *A, B*
- State Diagram?



Review

- Conceptual model and variable roles
  - Input, output, state
- Dimensional analysis
  - Rules
- Modeling workflow
  - System diagram, conceptual model, technical model
- Technical model: differential equations
  - Graphical solution
- Technical model: Markov Model
  - State, transition, transition rates