**Module 3:** Introduction to Stoichiometry and Propensity Functions

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# Motivation

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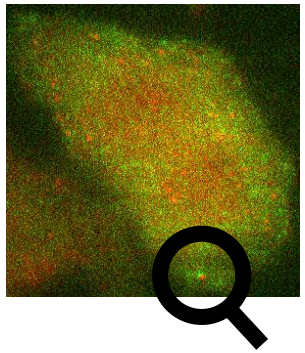
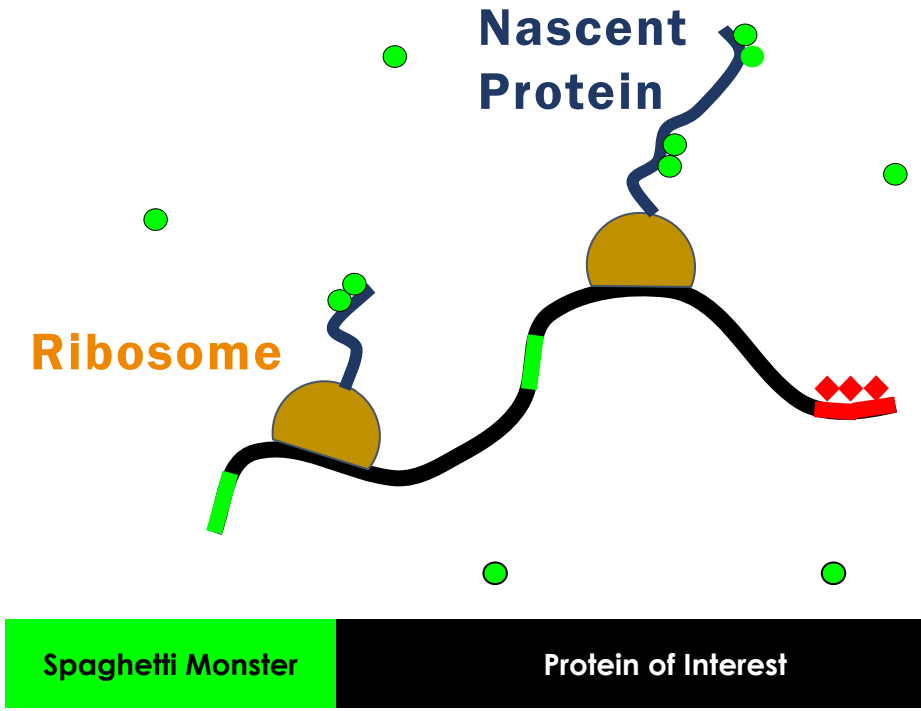
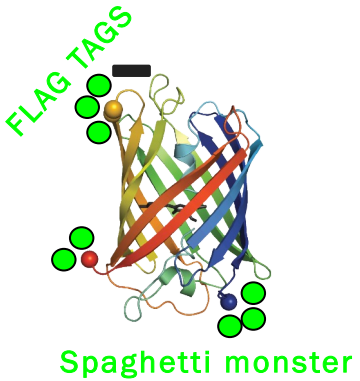
Outline
- Motivation & Intro
- Mechanistic Model
- Reaction Stoichiometry
- Reaction Propensity
- Law of Mass Action
- Putting it all Together
- Final Notes
- Example 1
- Example 2
- Example 3
- Example 4



What changes in a chemical reaction?
How quickly does it change?





**Intensity signals of nascent protein display fluctuations over time due to underlying transcription dynamics**

# Motivation: What are models good for?

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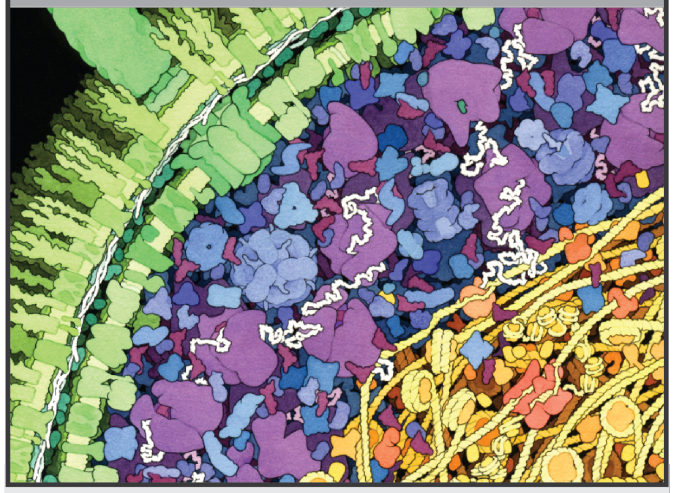
What are dynamic models useful for in biological processes?

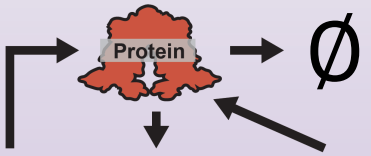
1. Mechanistic underpinning of real data
2. Predictive power in new circumstances
3. Biophysical based analysis

**Biophysical System**



Goodsell

**Mathematical Model of System**

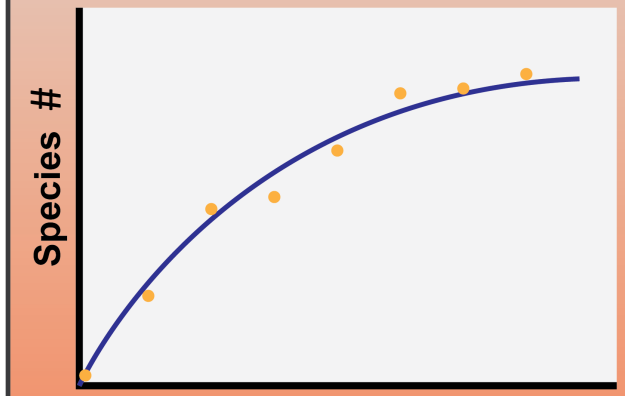




Stoichiometry=[ … ]
Propensity=[ … ]

$$\frac{dx}{dt} = S\,W(x,t) \qquad \frac{dP}{dt} = A\,P(x,t)$$

**Fitting to Real Data**




Many biological data can be explained by using deterministic or stochastic formulations of chemical reactions using the law of mass action!

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## What changes in a dynamic chemical system?

1. Reactions have a ***propensity*** to cause a change in species count according to the ***stoichiometry*** of the system
2. The ***propensity*** to react changes depending on the instantaneous state of the system
3. The ***stoichiometry*** of a reaction tell us how each reaction changes on the number of species in the system

## What is a '***model***'?

A model is a combination of both ***stoichiometry, and propensity which can be used to capture the dynamics of a biological system***

Model time dynamics can be analyzed using differential equations, stochastic simulation algorithms and chemical master equations

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Different levels of model detail give arise to different levels of accuracy and complexity

| | **Deterministic Analysis** | **Stochastic Analysis** |
|---|---|---|
| Less Detail — Mixed Models | Ordinary Differential Equation | Chemical Master Equation Stochastic Simulation Alg. |
| Mid Detail — Compartmental Models | System of Ordinary Differential Equations | Chemical Master Equation Stochastic Simulation Alg. |
| More Detail — Spatial Models | Partial Differential Equations | Reaction-Diffusion Master Equation |

- Mixed models assume the the space where the chemical reactions occur are well mixed
- Compartmental models break down the space into a set of compartments
- Spatial models assume that each point in space has an associated local concentration

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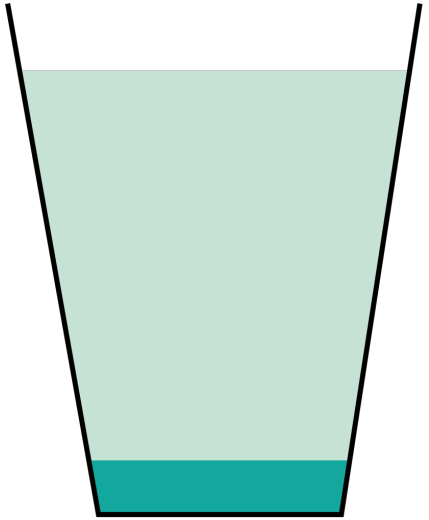
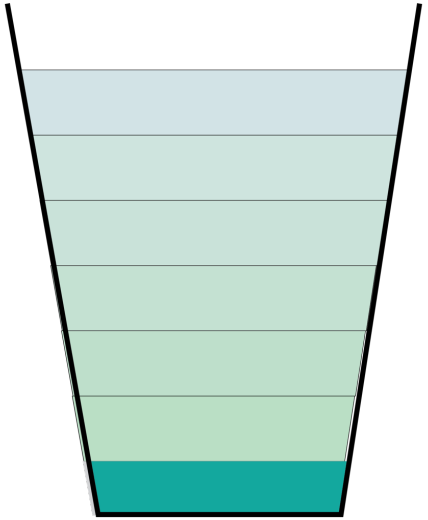
Example:
Modeling how sugar dissolves in a cup in 3 different ways

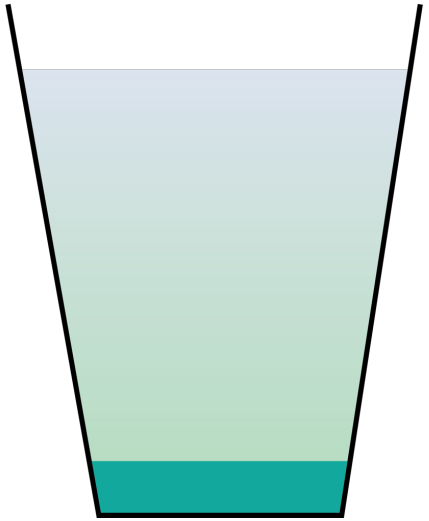
**Mixed Model**



**Compartmental Model**



**Spatial Model**



**Mixed Model:** One value for concentration everywhere
**Compartmental Model:** Different compartments share the same concentration
**Spatial Model:** Every point in space has its own concentration

# Intro- Deterministic vs Stochastic Models

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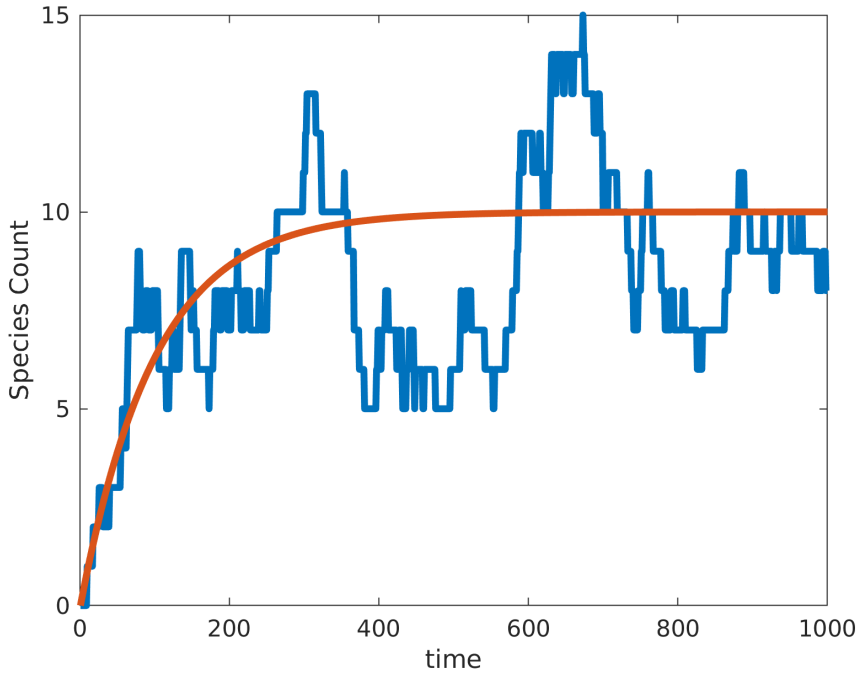
***Ordinary Differential Equations (ODE's)*** are used to solve a ***model***.

ODE modeling methods for chemical reactions do not work well to model noise




$$\frac{dx}{dt} = k - \gamma x$$

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

**Where ODEs can be misleading:**
- Molecule counts aren't continuous, especially for small volumes like cells
- Real systems exhibit fluctuations

## Learning Objectives

**Learning objectives for this lecture:**
- Learn to define propensity functions and stoichiometry vectors for chemical reactions
- Learn how to use the law of mass action to estimate propensity functions

# Making chemical reaction sets out of mechanistic mo

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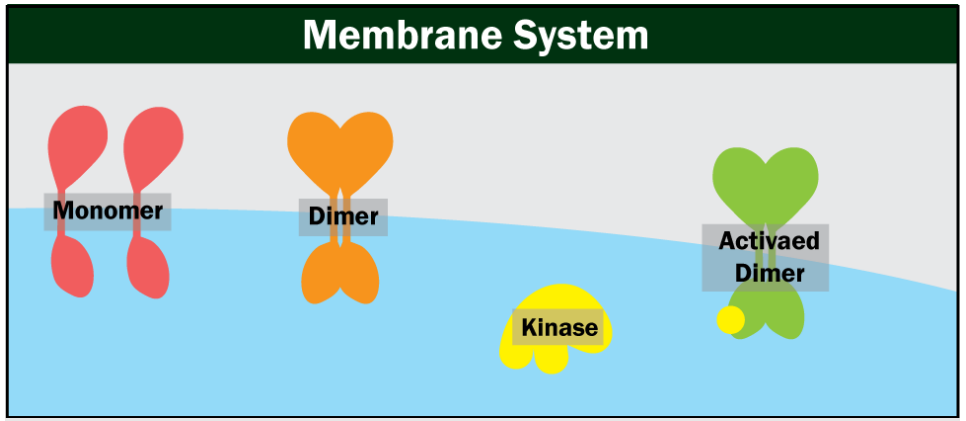
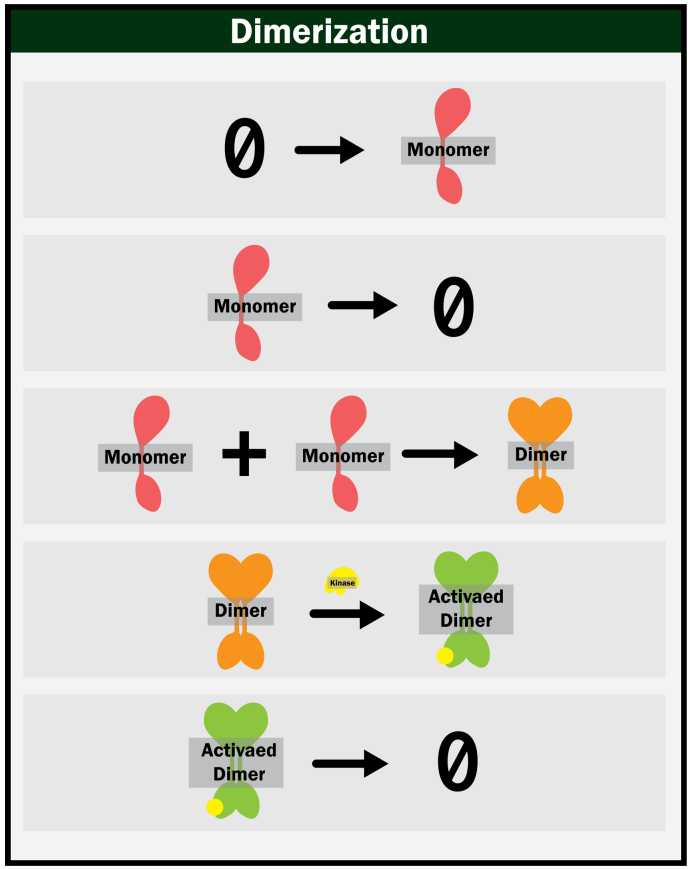
## Example: Model for membrane dimerization




**General Biological Process:**

1. **Monomers are brought to the cell membrane**
2. **Monomers can dimerize into dimers**
3. **Dimers become phosphorylated and become active dimers**




How would you model this using Spatial, Compartmental, or well-mixed?
How would you model this using deterministic vs stochastic assumptions?

# Making chemical reactions out of models

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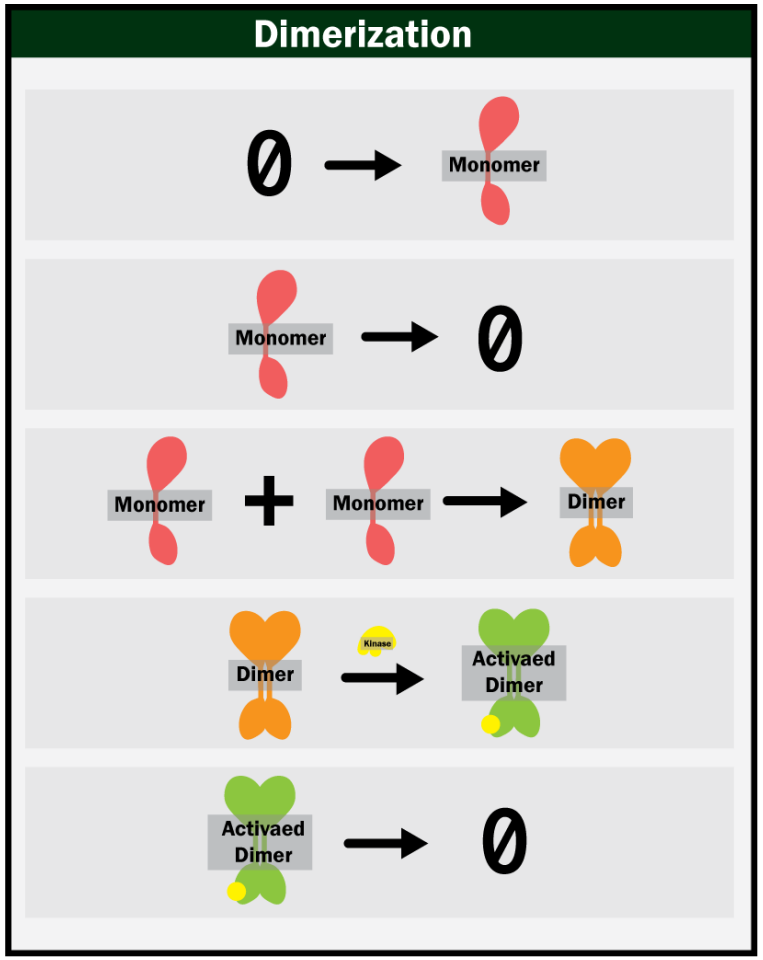
**Break down the system into five reactions**




$$\emptyset \rightarrow x_1$$
$$x_1 \rightarrow \emptyset$$
$$x_1 + x_1 \rightarrow x_2$$
$$x_2 \rightarrow x_3$$
$$x_3 \rightarrow \emptyset$$

# Reaction Stoichiometry

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The stoichiometry matrix shows the net change in molecule count after each reaction

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$$x_2 \rightarrow x_3$$
$$x_3 \rightarrow \emptyset$$

**Steps to Defining Stoichiometry Vectors:**
- Identify the number of unique species (N=3)
- Identify the number of reactions (M=5)
- The stoichiometry vector of a reaction is the ***net change*** of each species
- Stoichiometry matrix is a bundle of all the vectors

**There are M stoichiometry vectors, and each is a Nx1 vector.**

**The stoichiometry of a reaction system can be represented as a NxM matrix:**

$$\boldsymbol{S} = [s_1, s_2, \ldots, s_M]$$

**Write the Stoichiometry matrix for the chemical reaction set above.**

# Reaction Stoichiometry

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$$\boldsymbol{S} = [s_1, s_2, \ldots, s_M]$$

**Write the Stoichiometry matrix for the chemical reaction set above.**

$$\boldsymbol{s_1} = [\ \mathbf{1}, \mathbf{0}, \mathbf{0}]^T$$
$$\boldsymbol{s_2} = [-\mathbf{1}, \mathbf{0}, \mathbf{0}]^T$$
$$\boldsymbol{s_3} = [-\mathbf{2}, \mathbf{1}, \mathbf{0}]^\intercal$$
$$\boldsymbol{s_4} = [\mathbf{0}, -\mathbf{1}, \mathbf{1}]^\intercal$$
$$\boldsymbol{s_5} = [\mathbf{0}, \mathbf{0}, -\mathbf{1}]^T$$

$$S = \begin{bmatrix} 1 & -1 & -2 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix}$$

# Reaction Rates and Propensity Functions

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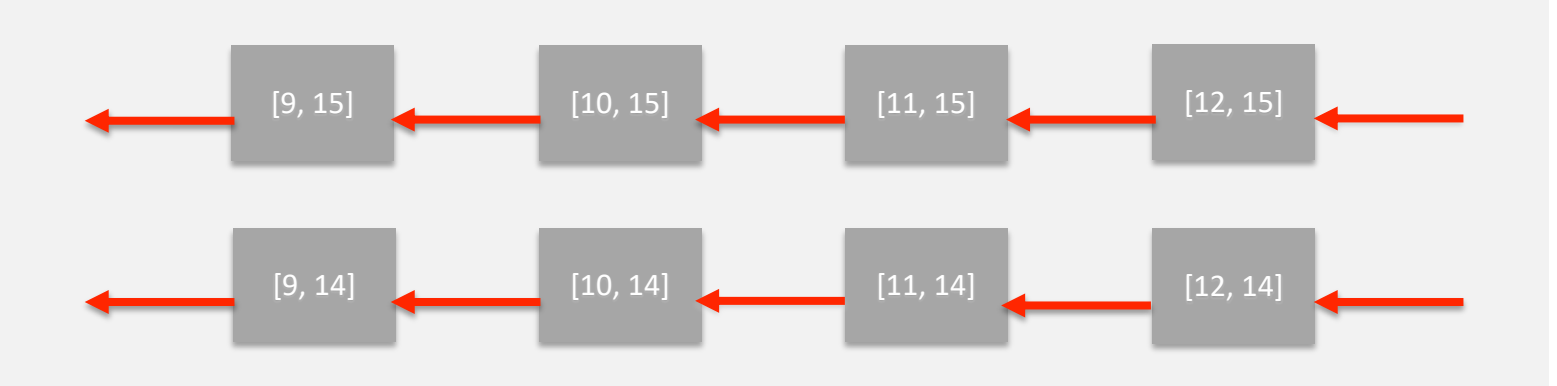
Reaction rates are functions of the state $\mathbf{w}_\mu$(x1,x2,...) that describes the instantaneous speed of chemical reaction.

- For deterministic models $\mathbf{w}_\mu dt$ is the amount that the $\mu^{th}$ reaction occurs in a time step dt
- $\mathbf{w}_\mu dt$ is the probability that the $\mu^{th}$ reaction will occur in a time step of length $dt$.
- Reaction rate and propensities are usually dependent on the current state (x1,x2,...) of the system (e.g., law of mass action).
- Reaction rates and Propensities are always positive




**Reaction rates and propensities depend on the current state**

# Law of Mass Action

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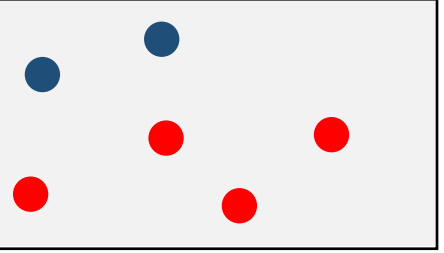
The law of mass action states that the rate of a chemical reaction is proportional to the number of unique combinations by which reactants can combine to form the products:

$$w_m \propto \prod_{n=1}^{N} (x_n \; choose \; R_{nm}) \qquad w_m = k \prod_{n=1}^{N} (x_n \; choose \; R_{nm})$$

where $R_{nm}$ is the number of *reactant* molecules of species *n* needed for the $m^{th}$ reaction and k arbitrary

$$n \; choose \; m = \frac{n!}{m!\,(n-m)!}$$



| Reaction | $x_n$ choose k | Propensity equation |
|---|---|---|
| $r_1: x_1 \rightarrow x_2$ | $x_1 \; choose \; 1 \; = \; x_1$ | $kx_1$ |
| $r_2: x_1 + x_1 \rightarrow x_2$ | $(x_1 \; choose \; 2) = \; x_1(x_1 - 1)/2$ | $kx_1(x_1 - 1)/2$ |
| $r_3: 2x_1 + x_2 \rightarrow x_3$ | $(x_1 \; choose \; 2)(x_2 \; choose \; 1)$ | $kx_1(x_1 - 1)(x_2)/2$ |
| $r_4: \emptyset \rightarrow x_1$ | $(x_1 \; choose \; 0) = 1$ | $k$ |

- When x is large, x(x-1) is approximately equal to $x^2$. This is the common form of mass action for ODE analyses.
- When x is small (integer copy numbers), the effect of finite molecule counts is far more important.
- k is an arbitrary proportionality coefficient – in many applications, the integer in the denominator of the combinatorial is lumped into this constant.
- Propensity functions depend only on the ***reactants*** – the products are irrelevant.

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**Propensity is a function of state and time which describes the instantaneous rate of reaction of chemical reactions**

$$\emptyset \rightarrow \boldsymbol{x_1}$$
$$\boldsymbol{x_1} \rightarrow \emptyset$$
$$\boldsymbol{x_1} + \boldsymbol{x_1} \rightarrow \boldsymbol{x_2}$$
$$\boldsymbol{x_2} \rightarrow \boldsymbol{x_3}$$
$$\boldsymbol{x_3} \rightarrow \emptyset$$

Each reaction has its own propensity to react.
The **propensity vector (W)** describes the propensity of each reaction in a vector:

$$w_1 = \ldots$$
$$w_2 = \ldots$$
$$w_{\ldots} = \ldots$$

**Use the Law of Mass action to write the propensity of the above reactions.**

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The **propensity vector (W)** describes the propensity of each reaction in a vector:

$$w_1 = \ldots$$
$$w_2 = \ldots$$
$$w_{\ldots} = \ldots$$

**Use the Law of Mass action to write the propensity of the above reactions.**

$$w_1(x,t) = k_1$$
$$w_2(x,t) = k_2 x_1$$
$$w_3(x,t) = k_3(x_1)(x_1 - 1)/2$$
$$w_4(x,t) = k_4 x_2$$
$$w_5(x,t) = k_5 x_3$$

$$W(x,t) = \begin{bmatrix} k_1 \\ k_2 x_1 \\ k_3(x_1)(x_1-1)/2 \\ k_4 x_2 \\ k_5 x_3 \end{bmatrix} \quad \text{or} \quad W'(x,t) = \begin{bmatrix} k_1 \\ k_2 x_1 \\ k'_3(x_1)(x_1-1) \\ k_4 x_2 \\ k_5 x_3 \end{bmatrix}$$

# Putting it all together

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The "mean field" ODE description for the instantaneous rate of change of the average system is given by:

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

$$S = \begin{bmatrix} 1 & -1 & -2 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix}$$

$$W(x,t) = \begin{bmatrix} k_1 \\ k_2 x_1 \\ k'_3(x_1)(x_1 - 1) \\ k_4 x_2 \\ k_5 x_3 \end{bmatrix}$$

**Write the equation for $\frac{dx}{dt}$ given the S and W defined above.**

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

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

$$\frac{dx_3}{dt} =$$

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The "mean field" ODE description for the instantaneous rate of change of the average system is given by:

$$\frac{\boldsymbol{dx}}{\boldsymbol{dt}} = \boldsymbol{S}\,\boldsymbol{W}(\boldsymbol{x}, \boldsymbol{t})$$

$$S = \begin{bmatrix} 1 & -1 & -2 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\boldsymbol{W}(\boldsymbol{x}, \boldsymbol{t}) = \begin{bmatrix} \boldsymbol{k_1} \\ \boldsymbol{k_2 x_1} \\ \boldsymbol{k'_3(x_1)(x_1 - 1)} \\ \boldsymbol{k_4 x_2} \\ \boldsymbol{k_5 x_3} \end{bmatrix}$$

**Write the equation for $\frac{dx}{dt}$ given the S and W defined above.**

$$\frac{dx_1}{dt} = k_1 - k_2 x_1 - 2k'_3 x_1(x_1 - 1)$$

$$\frac{dx_2}{dt} = k'_3 x_1(x_1 - 1) - k_4 x_2$$

$$\frac{dx_3}{dt} = k_4 x_2 - k_5 x_3$$

$$\frac{dx}{dt} = \begin{bmatrix} k_1 - k_2 x_1 - 2k'_3 x_1(x_1 - 1) \\ k'_3 x_1(x_1 - 1) - k_4 x_2 \\ k_4 x_2 - k_5 x_3 \end{bmatrix}$$

# Putting it all together

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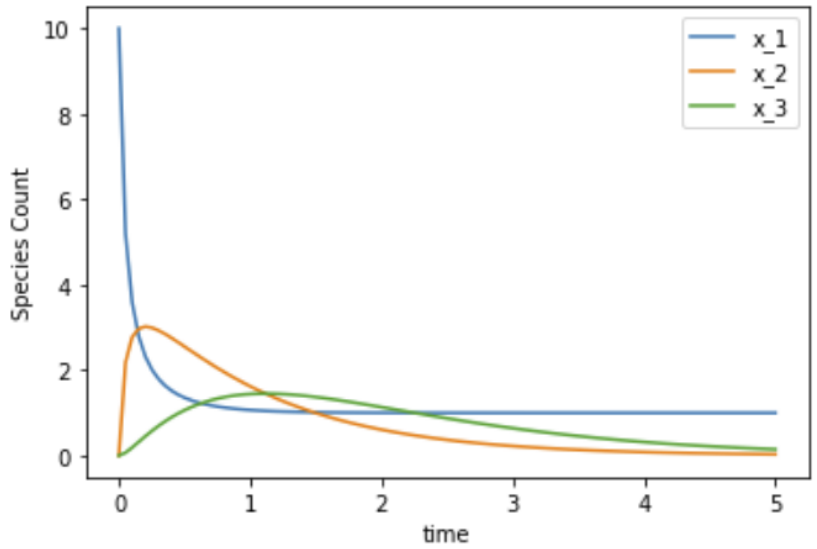
The ODE description for the instantaneous rate of change of the entire system is given by:

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

$$S = \begin{bmatrix} 1 & -1 & -2 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix}$$

$$W'(x,t) = \begin{bmatrix} k_1 \\ k_2 x_1 \\ k'_3(x_1)(x_1 - 1) \\ k_4 x_2 \\ k_5 x_3 \end{bmatrix}$$




$\frac{dx}{dt}$ can be integrated numerically to solve for the ODE solution of the model.

scipy.integrate.odeint

# Final Notes: Reaction Stoichiometry

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$$\mathbf{s}_1 = [1, 0]^T$$

$$\begin{aligned} \mathcal{S}_1 &\rightarrow \mathcal{S}_1 + \mathcal{S}_1 \\ \mathcal{S}_2 &\rightarrow \mathcal{S}_2 + \mathcal{S}_1 \\ \emptyset &\rightarrow \mathcal{S}_1 \end{aligned}$$

$$\mathbf{s}_2 = [-1, 0]^T$$

$$\begin{aligned} \mathcal{S}_1 + \mathcal{S}_1 &\rightarrow \mathcal{S}_1 \\ \mathcal{S}_1 + \mathcal{S}_2 &\rightarrow \mathcal{S}_2 \\ \mathcal{S}_1 &\rightarrow \emptyset \end{aligned}$$

$$\mathbf{s}_3 = [0, 1]^T$$

$$\begin{aligned} \mathcal{S}_2 &\rightarrow \mathcal{S}_2 + \mathcal{S}_2 \\ \mathcal{S}_1 &\rightarrow \mathcal{S}_1 + \mathcal{S}_2 \\ \emptyset &\rightarrow \mathcal{S}_2 \end{aligned}$$

$$\mathbf{s}_4 = [1, -1]^T$$

$$\begin{aligned} \mathcal{S}_2 &\rightarrow \mathcal{S}_1 \\ \mathcal{S}_1 + \mathcal{S}_2 &\rightarrow \mathcal{S}_1 + \mathcal{S}_1 \\ \mathcal{S}_2 + \mathcal{S}_2 &\rightarrow \mathcal{S}_1 + \mathcal{S}_2 \end{aligned}$$

The stoichiometry only measures the **net** change (increase in products – decrease in reactants), whereas propensities depend only on ***reactants***.

For this reason, the same stoichiometry can correspond to many different propensity functions.
Stoichiometry **should not** be used to guess the propensity – nor vice-versa!

# Final Notes: Reducing Model Size Using Separation of Timescales

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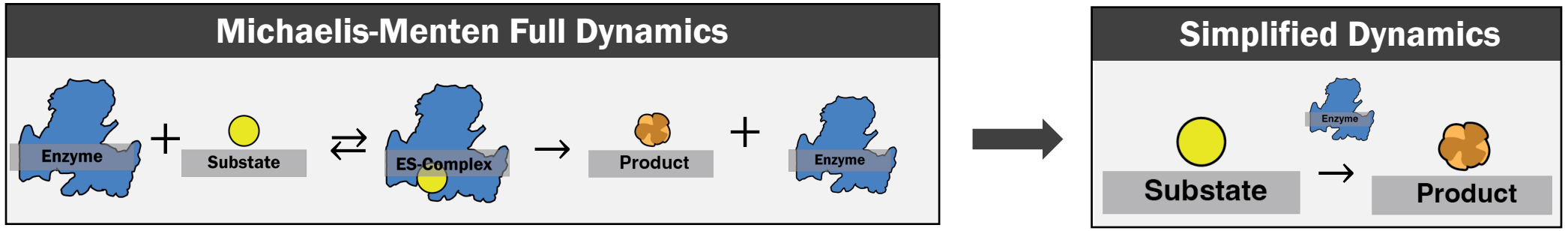
Is the law of mass action **required** for the definition of propensity functions?

## Michaelis-Menten Dynamics:




**Propensity is always given by Law of Mass Action**

$$r_1: \; x_1 + x_2 \rightarrow x_3 \qquad w_1 = k_1 x_1 x_2$$
$$r_2: \; x_3 \rightarrow x_1 + x_2 \qquad w_2 = k_2 x_3$$
$$r_3: \; x_3 \rightarrow x_1 + x_4 \qquad w_3 = k_3 x_3$$
$$r_3: \; x_4 \rightarrow \emptyset \qquad w_3 = k_3 x_3$$

**Quasi-steady equilibrium**:
$$k_1 x_1 x_2 = k_2 x_3$$

**Enzyme is Conserved**:
$$x_1 + x_3 = E_T$$

**Propensity appears to be complex**

$$r_1: \; x_1 \rightarrow x_2 \qquad w'_1 = \frac{k_3 k_1 E_T x_1}{k_1 x_1 + k_2}$$

$$r_2: \; x_2 \rightarrow \emptyset \qquad w_3 = k_3 x_3$$

Law of Mass action is always correct for a completely modeled system, but model simplifications can lead to different propensities not given by law of mass action

# Example 1: Birth Decay Process

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## Birth-Decay Model


$$r_1: \ \emptyset \rightarrow x_1$$
$$r_2: \ x_1 \rightarrow \emptyset$$

$$x_1: Protein$$

## Use the Law of Mass Action to find S, W(x,t) and the rate equation dx/dt

# Example 1: Birth Decay Process

uq-bio

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## Birth-Decay Model


$$r_1: \ \emptyset \rightarrow x_1$$
$$r_2: \ x_1 \rightarrow \emptyset$$

$$x_1: Protein$$

## Use the Law of Mass Action to find S, W(x,t) and the rate equation dx/dt

$$s_1: \ [\ 1]$$
$$s_2: \ [-1]$$

$$w_1: \ k_1$$
$$w_2: \ k_2 x_1$$

$$S = [1, \quad -1]$$

$$\mathbf{W}(\mathbf{x}, \mathbf{t}) = \begin{bmatrix} k_1 \\ k_2 x_1 \end{bmatrix}$$

$$\frac{dx}{dt} = k_1 - k_2 x_1$$

# Example 2: Bursting Gene Expression

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## Bursting Gene Model


$$r_1: \; x_1 \rightarrow x_2$$
$$r_2: \; x_2 \rightarrow x_1$$
$$r_3: \; x_2 \rightarrow x_2 + x_3$$
$$r_4: \; x_3 \rightarrow \emptyset$$

$$x_1: Gene\ OFF$$
$$x_2: Gene\ ON$$
$$x_3: Protein$$

**Use the Law of Mass Action to find S, W(x,t) and the rate equation dx/dt**

# Example 2: Bursting Gene Expression

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## Bursting Gene Model


$$r_1: \; x_1 \rightarrow x_2$$
$$r_2: \; x_2 \rightarrow x_1$$
$$r_3: \; x_2 \rightarrow x_2 + x_3$$
$$r_4: \; x_3 \rightarrow \emptyset$$

$$x_1: \textit{Gene OFF}$$
$$x_2: \textit{Gene ON}$$
$$x_3: \textit{Protein}$$

## Use the Law of Mass Action to find S, W(x,t) and the rate equation dx/dt

$$s_1: \; [-1, 1, 0\;]$$
$$s_2: \; [1, -1, 0]$$
$$s_3: \; [\;0, 0\;, 1]$$
$$s_4: \; [\,0, 0, -1]$$

$$w_1: \; k_1 x_1 = k_1(1 - x_2)$$
$$w_2: \; k_2 x_2$$
$$w_3: \; k_3 x_2$$
$$w_4: \; k_4 x_3$$

$$\boldsymbol{S} = \begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\mathbf{W}(\mathbf{x}, \mathbf{t}) = \begin{bmatrix} k_1 x_1 \\ k_2 x_2 \\ k_3 x_2 \\ k_4 x_3 \end{bmatrix}$$

$$\frac{\boldsymbol{dx}}{\boldsymbol{dt}} = \begin{bmatrix} -k_1 x_1 + k_2 x_2 \\ k_1 x_1 - k_2 x_2 \\ k_3 x_2 - k_4 x_3 \end{bmatrix}$$

# Example 4: Stochastic Oscillator

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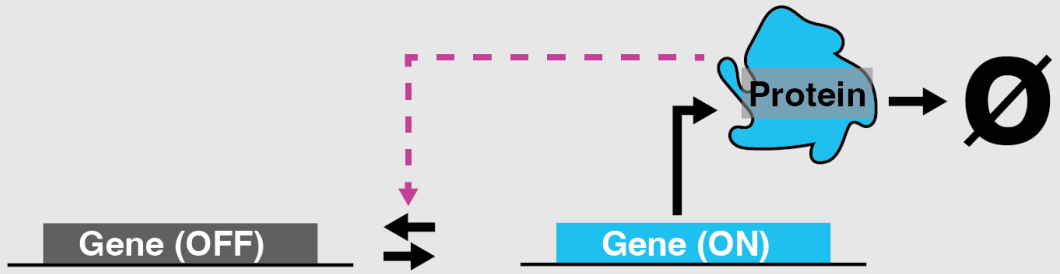
## Stochastic Oscillator Model




$$r_1: \; x_1 \rightarrow x_2$$
$$r_2: \; x_2 \rightarrow x_1$$
$$r_3: \; x_2 \rightarrow x_2 + x_3$$
$$r_4: \; x_3 \rightarrow \emptyset$$

$$w_1: x_1 x_3^{k_1} / (k_2^{k_1} + x_3^{k_1})$$
$$w_2: k_2 x_2 / (1 + x_3^{k_1})$$
$$w_3: \; k_3 x_2$$
$$w_4: \; k_5 x_3$$

## Use S, and W(x,t) to find the rate equation dx/dt

# Example 4: Stochastic Oscillator

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- Reaction Stoichiometry
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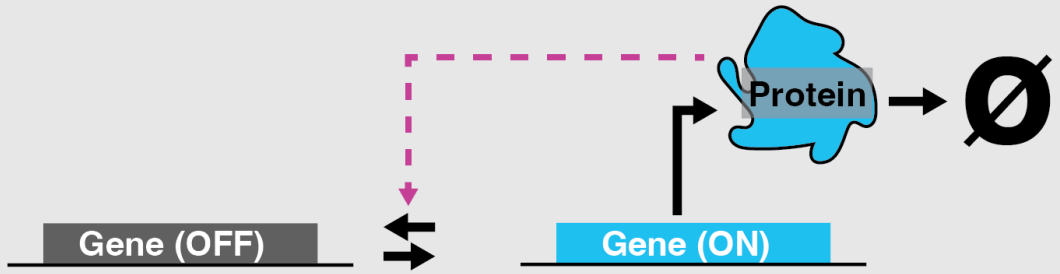
## Stochastic Oscillator Model




$$r_1: x_1 \rightarrow x_2 \qquad w_1: x_1 x_3^{k_1}/(k_2^{k_1}+x_3^{k_1})$$
$$r_2: x_2 \rightarrow x_1 \qquad w_2: k_2 x_2/(1+x_3^{k_1})$$
$$r_3: x_2 \rightarrow x_2 + x_3 \qquad w_3: k_3 x_2$$
$$r_4: x_3 \rightarrow \emptyset \qquad w_4: k_5 x_3$$

## Use S, and W(x,t) to find the rate equation dx/dt

$$\boldsymbol{S} = \begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\mathbf{W}(\mathbf{x}, \mathbf{t}) = \begin{bmatrix} x_1 x_3^{k_1}/(k_2^{k_1}+x_3^{k_1}) \\ k_2 x_2/(1+x_3^{k_1}) \\ k_3 x_2 \\ k_5 x_3 \end{bmatrix}$$

$$\frac{\boldsymbol{dx}}{\boldsymbol{dt}} = \begin{bmatrix} \frac{k_2 x_2}{1+x_3^{k_1}} - x_1 x_3^{k_1}/(k_2^{k_1}+x_3^{k_1}) \\ x_1 x_3^{k_1}/(k_2^{k_1}+x_3^{k_1}) - k_2 x_2/(1+x_3^{k_1}) \\ k_3 x_2 - k_5 x_3 \end{bmatrix}$$

# Example 3: Genetic Toggle

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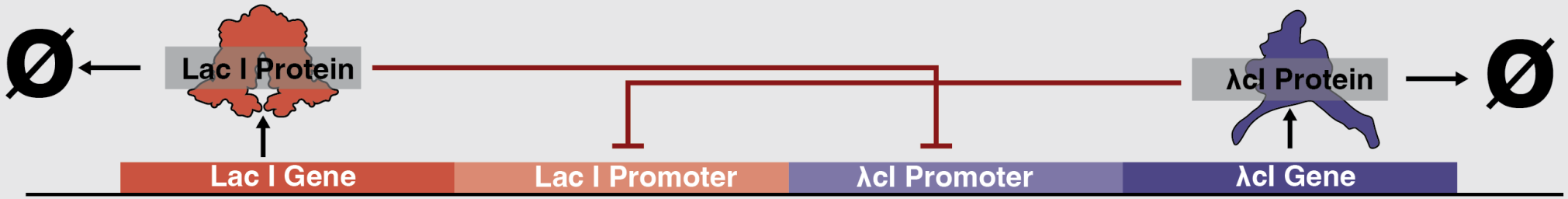
## Genetic Toggle Model




## Use S and W(x,t) to find the rate equation dx/dt

$$r_1: \ \emptyset \rightarrow x_1$$
$$r_2: \ x_1 \rightarrow \emptyset$$
$$r_3: \ \emptyset \rightarrow x_2$$
$$r_4: \ x_2 \rightarrow \emptyset$$

$$w_1: k_1 + k_2/(1 + k_3 x_2^{k_4})$$
$$w_2: k_5 x_1$$
$$w_3: k_6 + k_7/(1 + k_8 x_1^{k_9})$$
$$w_4: k_{10} x_2$$

# Example 3: Genetic Toggle

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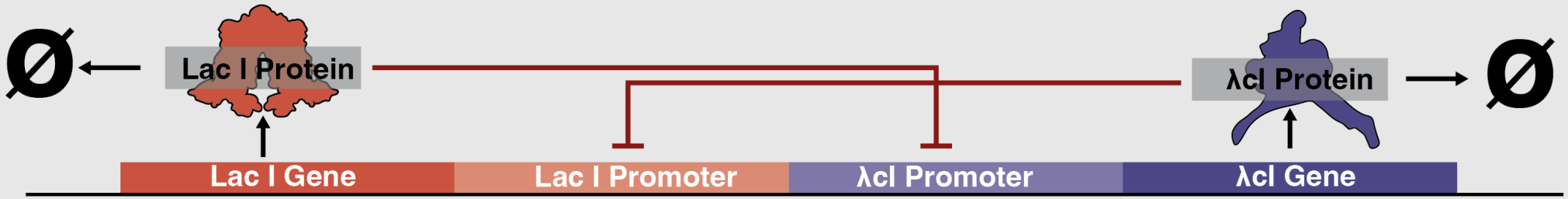
## Genetic Toggle Model




## Use S and W(x,t) to find the rate equation dx/dt

$$r_1: \emptyset \rightarrow x_1$$
$$r_2: x_1 \rightarrow \emptyset$$
$$r_3: \emptyset \rightarrow x_2$$
$$r_4: x_2 \rightarrow \emptyset$$

$$s_1: [1, 0]^T$$
$$s_2: [-1, 0]^T$$
$$s_3: [0, 1]^T$$
$$s_4: [0, -1]^T$$

$$w_1: k_1 + k_2/(1 + k_3 x_2^{k_4})$$
$$w_2: k_5 x_1$$
$$w_3: k_6 + k_7/(1 + k_8 x_1^{k_9})$$
$$w_4: k_{10} x_2$$

$$\boldsymbol{S} = \begin{bmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\mathbf{W}(\mathbf{x}, \mathbf{t}) = \begin{bmatrix} k_1 + k_2/(1 + k_3 x_2^{k_4}) \\ k_5 x_1 \\ k_6 + k_7/(1 + k_8 x_1^{k_9}) \\ k_{10} x_2 \end{bmatrix}$$

$$\frac{\boldsymbol{dx}}{\boldsymbol{dt}} = \begin{bmatrix} k_1 + \dfrac{k_2}{1 + k_3 x_2^{k_4}} - k_5 x_1 \\ k_6 + \dfrac{k_7}{1 + k_8 x_1^{k_9}} - k_{10} x_2 \end{bmatrix}$$