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Module 4: Introduction to Master Equation Analyses of Single-Cell Gene Regulatory Processes

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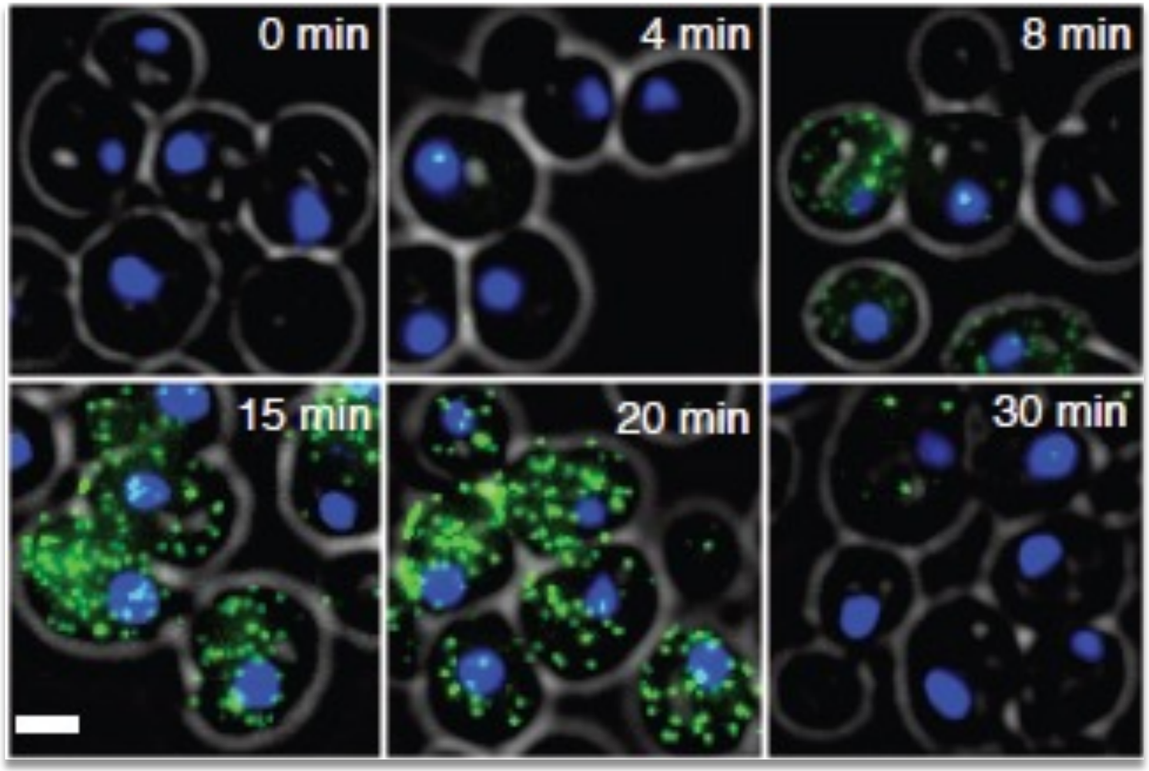
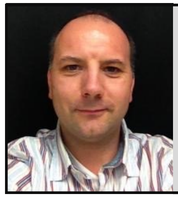
Motivation: How do we calculate time series distributions?

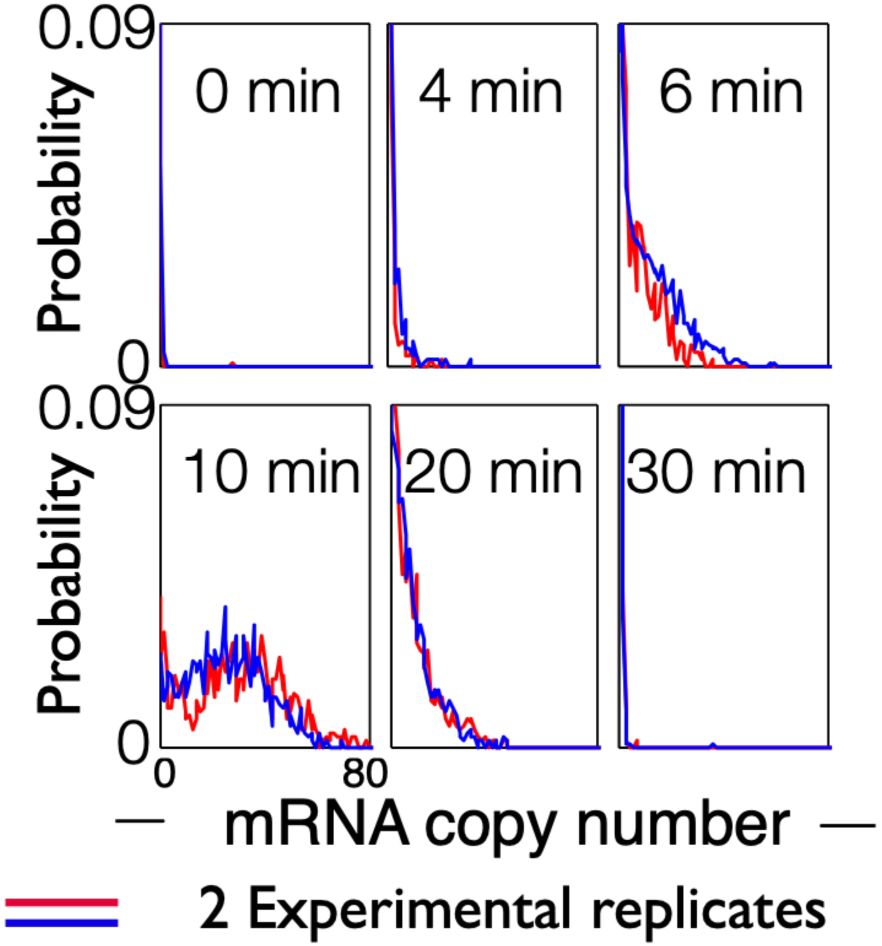
Outline
- State Space
- Markov Models
- Creating the Infinitesimal Generator
- Properties of the Inf. Generator
- Error
- Math Properties of the Matrix Exponential
- Tips
- Example

Osmotic stress response of many cells shows distribution P(x;t) which changes over time!




Gregor Neuert, *Vanderbilt*


Brian Munsky, *Colorado State Univ.*



Motivation: SSAs can only sample from a true distribution

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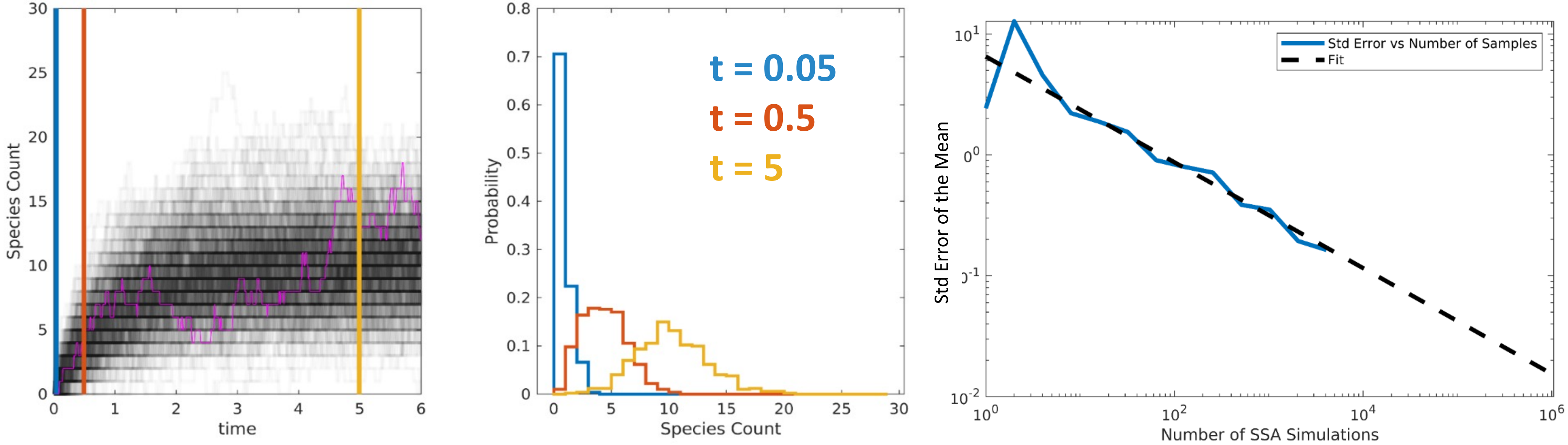
How do we get analytical solutions for P(x;t) for this birth decay process?

Plots of 500 SSAs trajectories show the formation of a distribution!



1. SSAs only sample the CME, they do not give its solution
2. SSA's only give one possibility out of many
3. $\frac{\sigma}{\mu}$ converges at rate $\frac{\alpha}{\sqrt{n}}$ (Standard Deviation of Mean = 10^{-4} $\rightarrow 314\ years$ assuming 1 second for each SSA)
4. No analytical solutions through SSA analysis

State Space

Outline

The state space of a set of chemical reactions describes each possible state that a chemical system can take on and can be used to model the stochasticity of a system

One Unique Species

State Space

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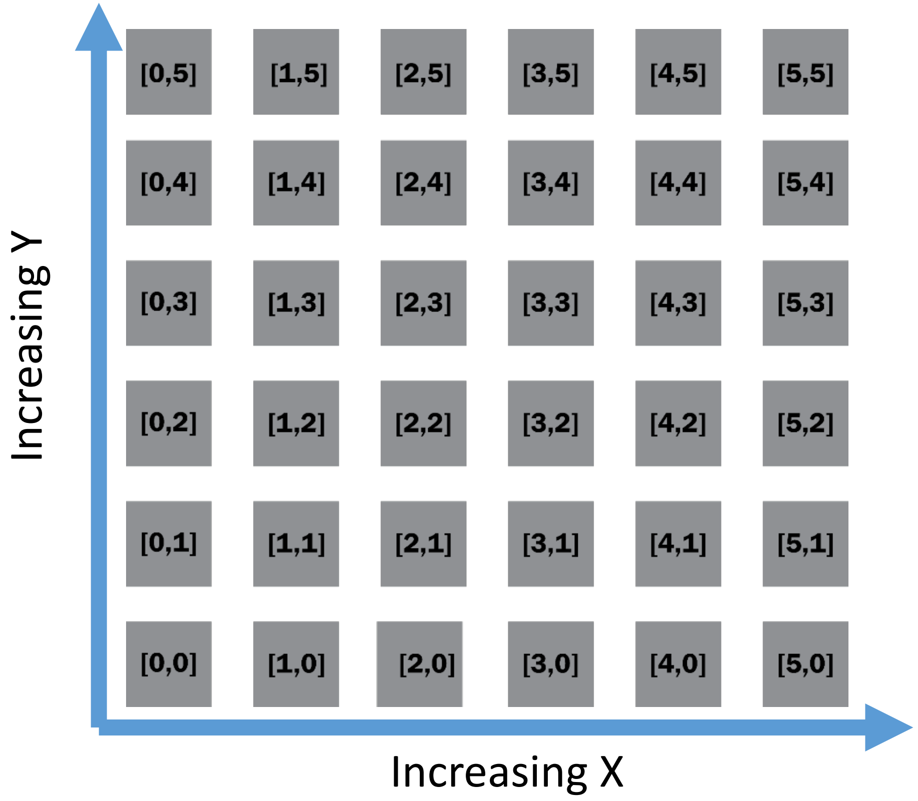
Two Unique Species



Markov Models

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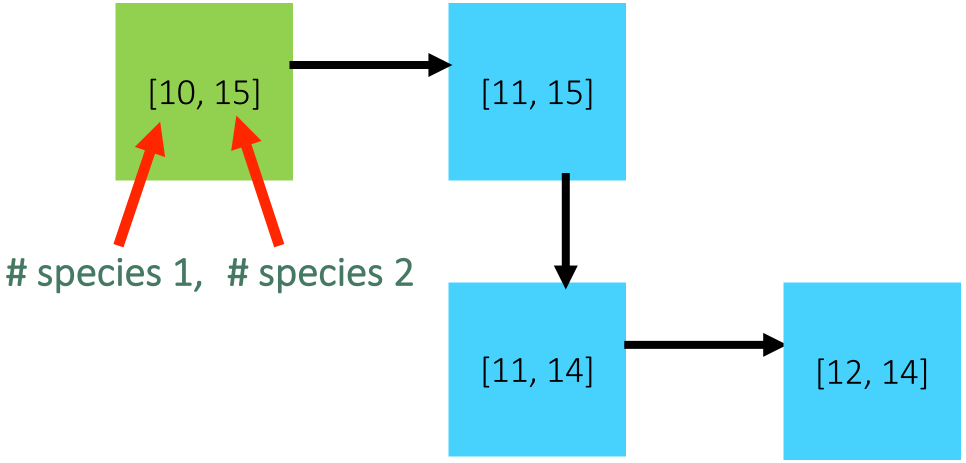
The state of the system is defined by its integer population vector

Reactions are transitions from one state to another:



Each block is a different state. [10,15] is one state and [11,15] is another state that is reached by a single reaction with stoichiometry [1,0].

Markov Models

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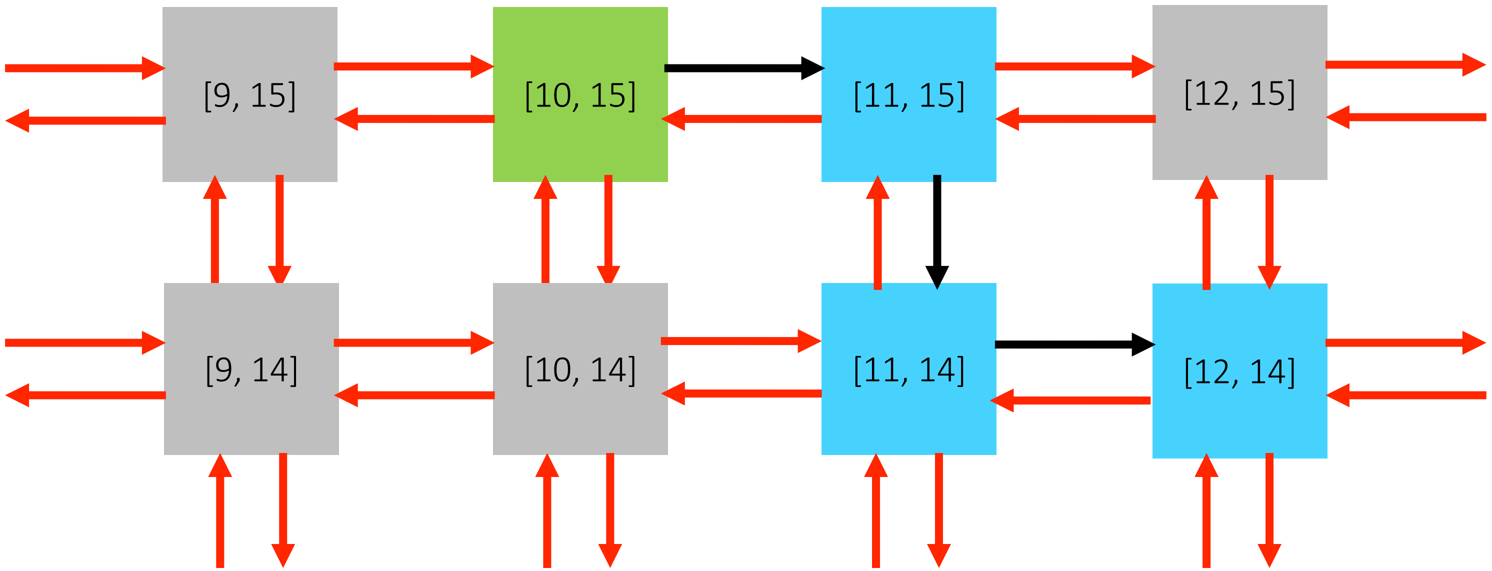

These reactions are random, and others could have occurred

Markov Models and Master Equation Models

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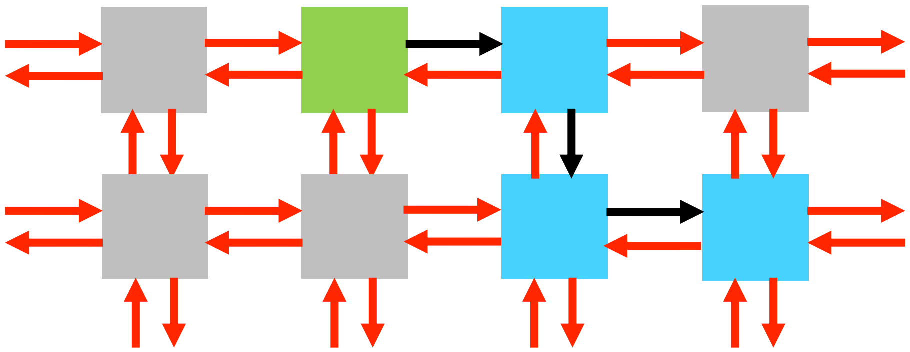
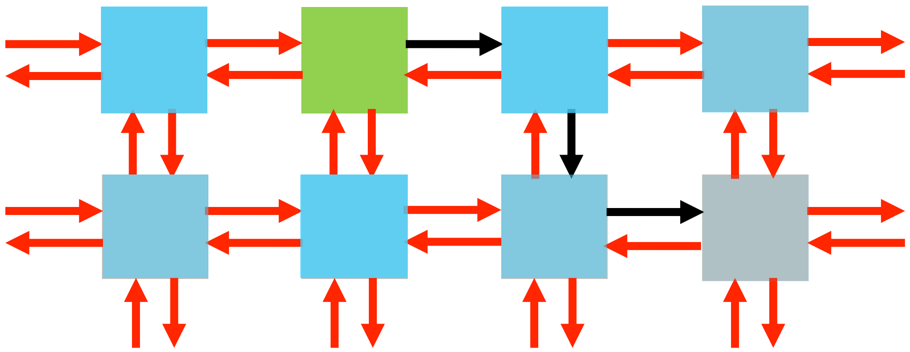
Frequentist Approach

Use many stochastic simulations and count the number of cells in each state



Master Equation Approach

Breakdown a system into all of its possible states and describe the flow of probability between them



Frequentist approach requires a large amount of SSA data

Reaction propensity tells us about how SSA's transition from one state to the next

Reaction propensity tells us about the rate that probability moves to other states

Reaction stoichiometry tells us how states connect

Creating the Master Equation

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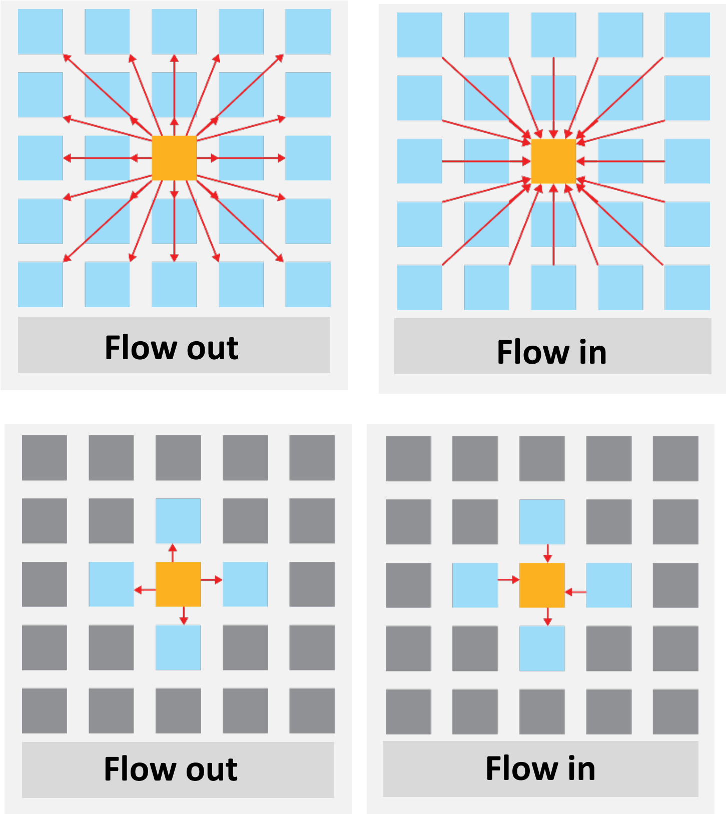

Examine the flow of probability in a small area apply to state space

Over large time steps:
Probability flows from **any state to any other state**
Over dt time steps:
Probability **only** flows to **nearby** states using **one** chemical rxn

Prob. that no reactions fire in $[t, t+dt] = 1 - \sum_k w_k(x)dt + \mathcal{O}(dt^2)$
Prob. that reaction R_k fires once in $[t, t+dt] = w_k(x)dt + \mathcal{O}(dt^2)$
Prob. that more than one reaction fires in $[t, t+dt] = \mathcal{O}(dt^2)$

$$p(x, t+dt) = \underbrace{p(x,t)}_{\text{at } x} \underbrace{\left(1 - \sum_k w_k(x)dt + \mathcal{O}(dt^2)\right)}_{\text{No reaction fires}} + \sum_k \underbrace{p(x - s_k, t)}_{R_k \text{ reaction away from } x} \underbrace{\left(\sum_k w_k(x)dt + \mathcal{O}(dt^2)\right)}_{R_k \text{ fires once}} + \underbrace{\mathcal{O}(dt^2)}_{\text{more than one reaction in } dt}$$

$$p(x, t+dt) - p(x,t) = -p(x,t)\sum_k w_k(x)dt + \sum_k p(x - s_k, t) w_k(x) dt + \mathcal{O}(dt^2)$$

The Chemical Master Equation : A *linear* ordinary differential equation

$$\frac{dp(x,t)}{dt} = -p(x,t)\sum_k w_k(x) + \sum_k p(x - s_k, t) w_k(x - s_k)$$

Creating the Master Equation

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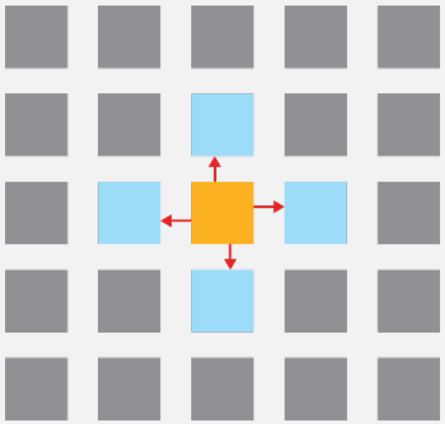
Outline

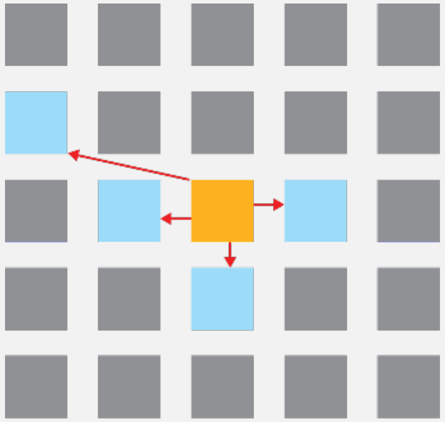
Stoichiometry defines how the FSP is connected

Stoichiometry



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

Stoichiometry



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Creating the Master Equation

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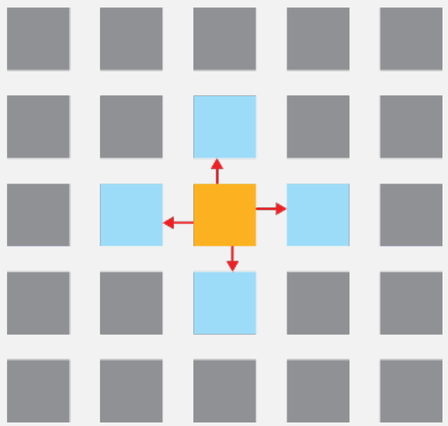
Stoichiometry defines how the FSP is connected

Stoichiometry



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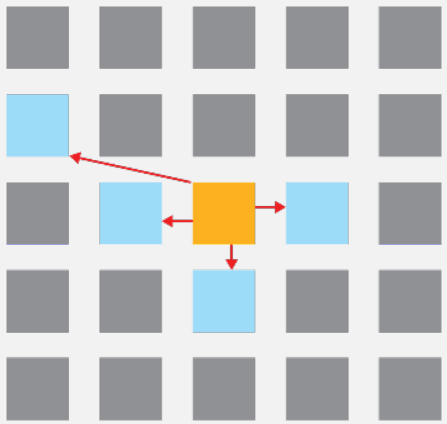
Stoichiometry



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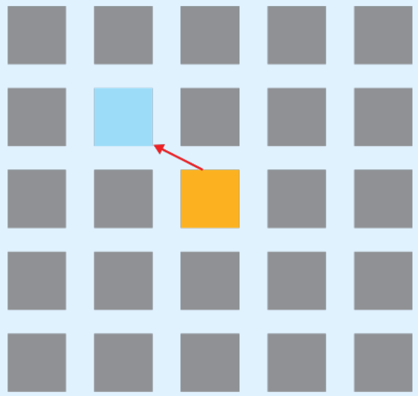
Write the stoichiometry vector for the reaction below.



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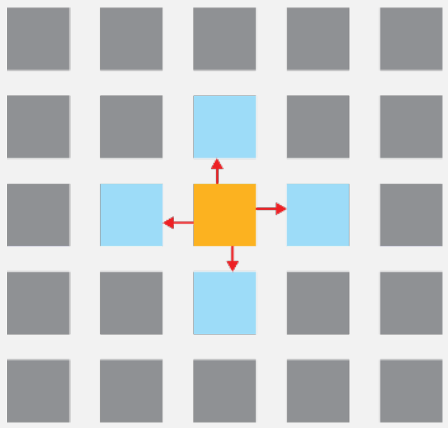
Stoichiometry defines how the FSP is connected

Stoichiometry



$s_1 = [\,1, 0\,]^T$
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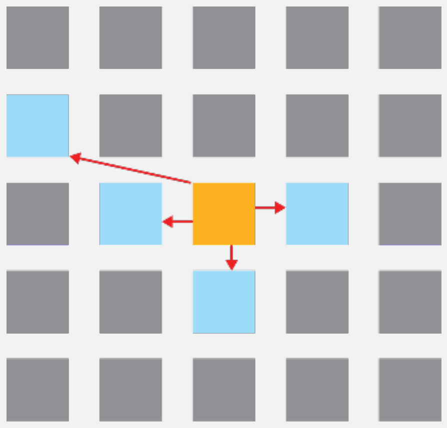
Stoichiometry



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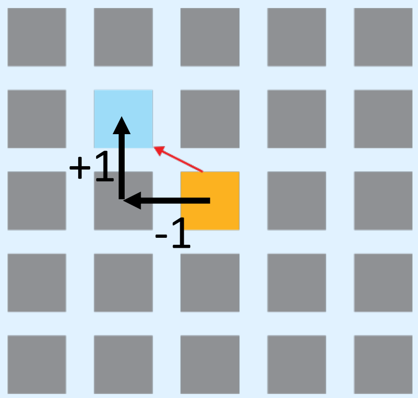

$s_1 = [-1,1]$

Creating the Infinitesimal Generator

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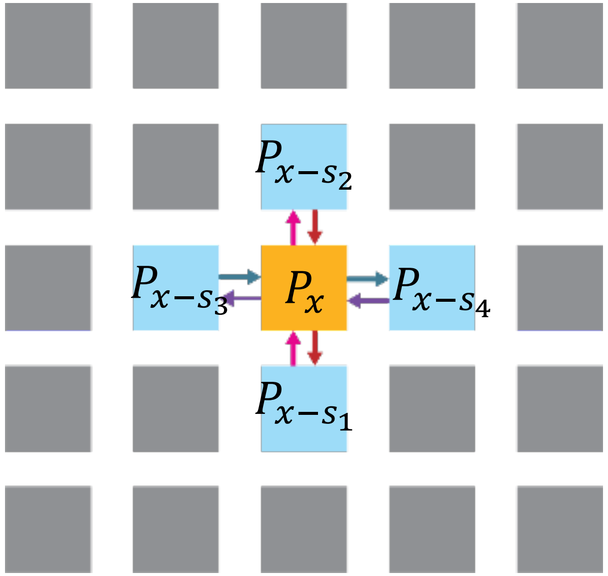
The rate of probability leaving due to reaction r_μ is equal to w_μ analyzed at that state
The rate of probability gained due to reaction r_μ is equal to w_μ analyzed at nearby connected states



Stoichiometry	Propensity
$s_1 = [\,1, 0\,]^T$	$w_1 = k_1$
$s_2 = [\,-1, 0\,]^T$	$w_2 = k_2 x_1$
$s_3 = [\,0, 1\,]^T$	$w_3 = k_3$
$s_4 = [\,0, -1\,]^T$	$w_4 = k_4 x_2$

Write the ODE that defines the flow of probability at $x = [5, 1]^T$.

$$\frac{dP_x}{dt} = (-w_1(x) - w_2(x) - w_3(x) - w_4(x))P_x + w_1(x - s_1)P_{x-s_1} + w_2(x - s_2)P_{x-s_2} + w_3(x - s_3)P_{x-s_3} + w_4(x - s_4)P_{x-s_4}$$

$$\frac{dP_{5,1}}{dt} = -(k_1 + 5k_2 + k_3 + 1k_4)P_{5,1} + k_1 P_{4,1} + 6k_2 P_{6,1} + k_3 P_{5,0} + 2k_4 P_{5,2}$$

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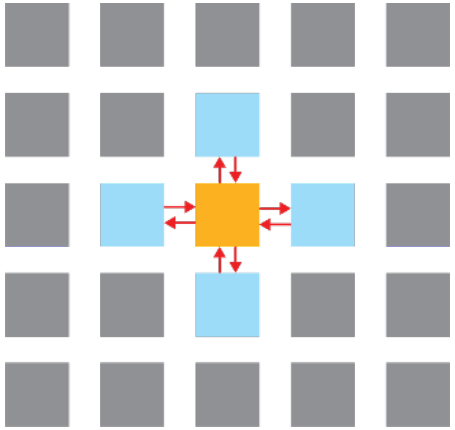
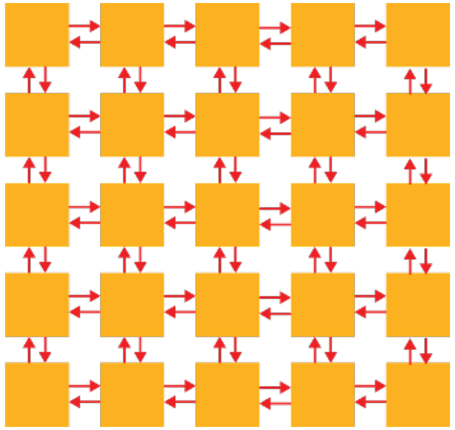


One State



All States

Each state in state space gets its own linear equation to describe the flow of probability to and from that state

From the Master Equation:

For X=[0,0]: $\frac{dP_{0,0}}{dt} = a_{0,0,0,0}P_{0,0} + \ \dots + a_{0,0,k,l}P_{k,l} + \dots$

For X=[i,j]: $\frac{dP_{i,j}}{dt} = a_{i,j,0,0}P_{0,0} + \ \dots + a_{i,j,k,l}P_{k,l} + \dots$

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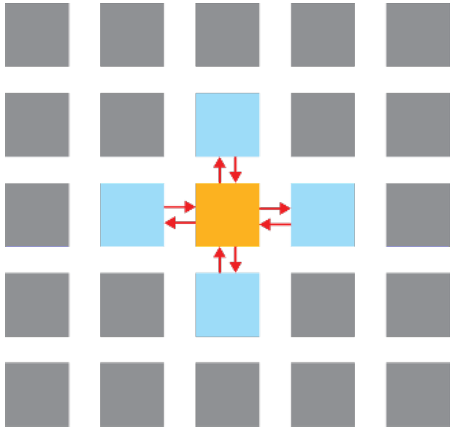

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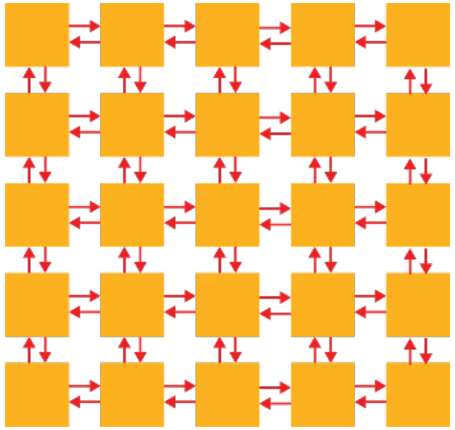

All States

Each state in state space gets its own linear equation to describe the flow of probability to and from that state

From the Master Equation:

For X=[0]: $\frac{dP_0}{dt} = a_{0,0}P_0 + \ \dots + a_{0,J}P_J + \dots$

For X=[I]: $\frac{dP_I}{dt} = a_{I,0}P_0 + \ \dots + a_{I,J}P_J + \dots$

$$\frac{d\boldsymbol{P}}{dt} = \boldsymbol{AP}$$

- The matrix A in the Linear ODE is known as the **Infinitesimal Generator.**
- This equation is the **Chemical Master Equation** in matrix form
- Changing Indexes from $(i, j) \rightarrow (I)$ is equivalent to vectorising the matrix

Properties of the Infinitesimal generator

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The CME conserves probability and its solution is non-negative

$$\frac{d\boldsymbol{P}_i}{dt} = \sum_j \boldsymbol{A}_{ij}\boldsymbol{P}_j$$

1. A_{ij} = rate of flow of probability **gained by state i from state j**
2. A_{jj} = total rate of probability **flowing out of state j**
3. $\sum_{i\neq j} A_{ij} = -A_{jj}$ and $\sum_i A_{ij}=0$
4. A is very sparse

The steady state solution is:

$$\frac{dP}{dt} = AP = 0 \qquad v = null(A)$$

$$\mathrm{P}_{ss} = \frac{v}{sum(v)}$$

Eigenvalue properties

$$[v_{ij}, \lambda_j] = eig(A) \qquad P_{ss} = \frac{v_{i0}}{\sum v_{i0}}$$

We know that 0 is an eigenvalue of A.
Its eigenvector is given by v_i0(this is a non-negative vector)
Normalization of the eigenvector gives the stationary distribution

All eigenvalues of A are zero or have negative real parts (i.e., they are stable)
Least negative $real(\lambda_j)$ determines timescale of the system relaxation to steady state

Approximating the Infinite State Space of the CME

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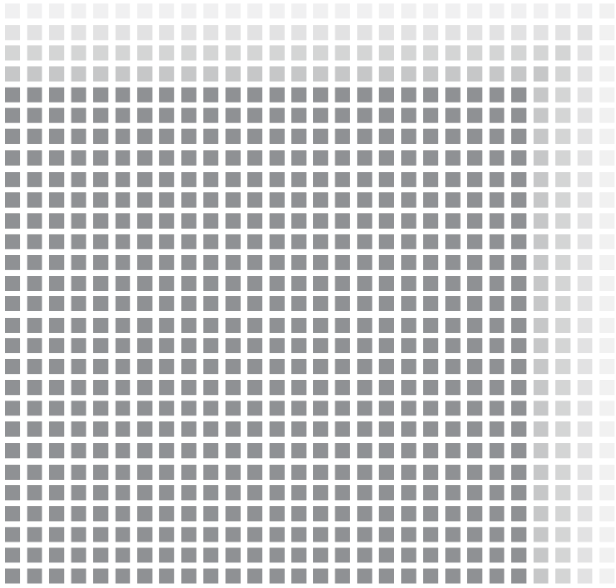
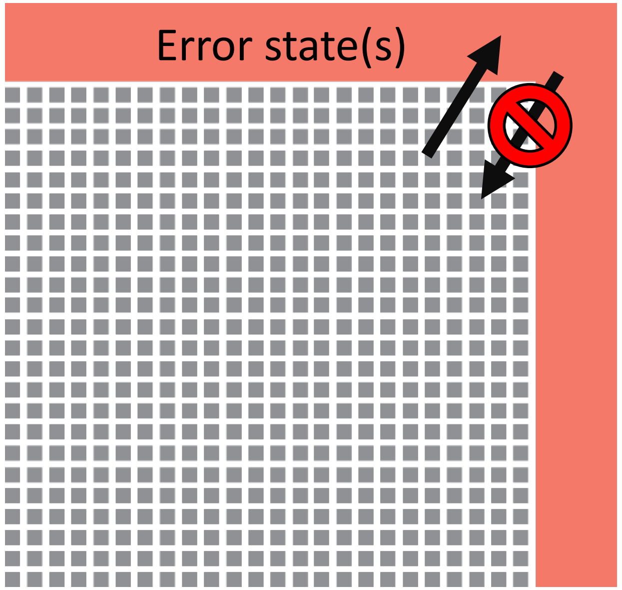
Error describes the flow leaving the state space due to truncation

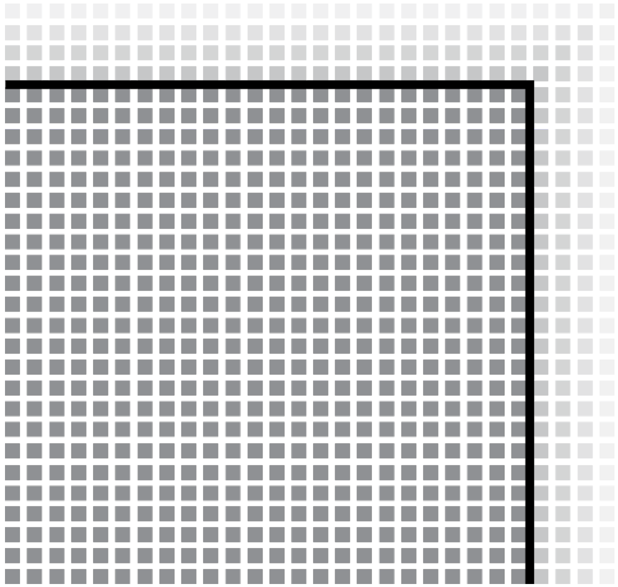
Can't solve (or even write) the infinite dimensional problem.



Infinite dimensional



Finite dimensional + error



Finite dimensional + Reflecting Boundary

Truncate the infinite system into a finite system + an error state or a finite system + reflecting boundary

The Finite State Projection

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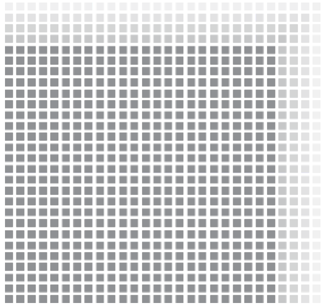
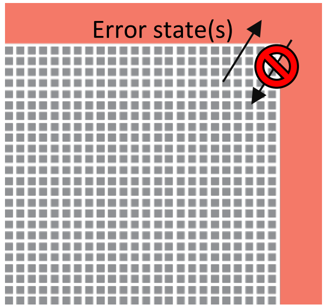


Infinite dimensional



Finite dimensional + error

$$\frac{d}{dt}\begin{bmatrix}\boldsymbol{P}\\ \boldsymbol{E}\end{bmatrix} = \begin{bmatrix}\boldsymbol{A} & B\\ \boldsymbol{C} & D\end{bmatrix}\begin{bmatrix}\boldsymbol{P}\\ \boldsymbol{E}\end{bmatrix} = \begin{bmatrix}\boldsymbol{A} & 0\\ \boldsymbol{C} & 0\end{bmatrix}\begin{bmatrix}\boldsymbol{P}\\ \boldsymbol{E}\end{bmatrix}$$

Munsky, Brian, and Mustafa Khammash. "The finite state projection algorithm for the solution of the chemical master equation." *The Journal of chemical physics* 124.4 (2006): 044104.

Solution: Truncate the infinite system into a finite system + an error state

Error - State Space

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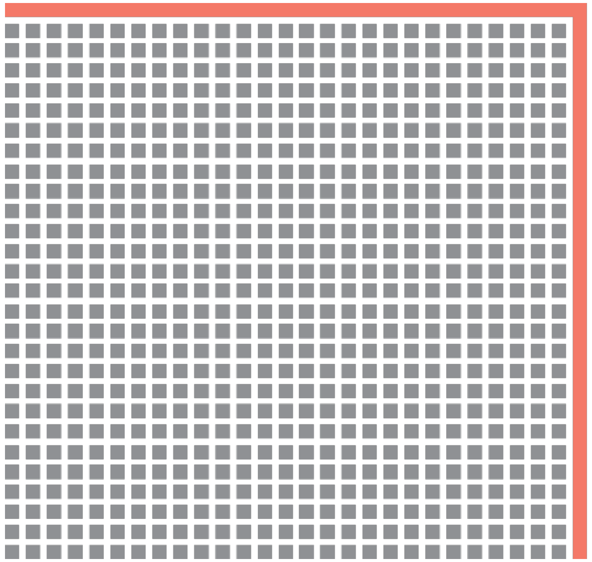
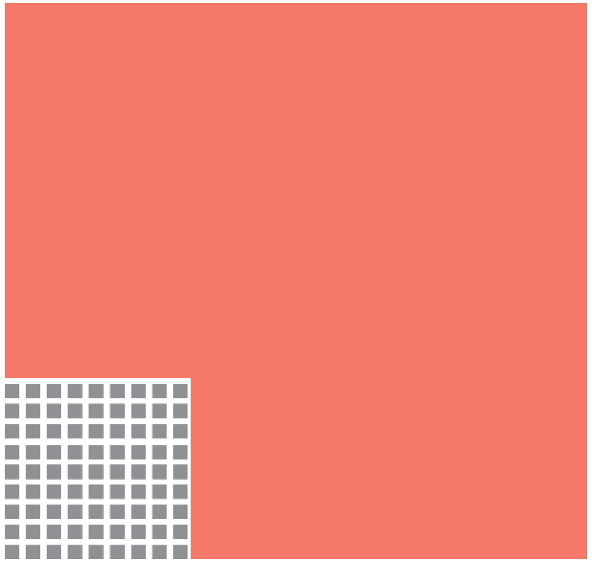
Outline

The amount of flow into the error states determines the magnitude of the error



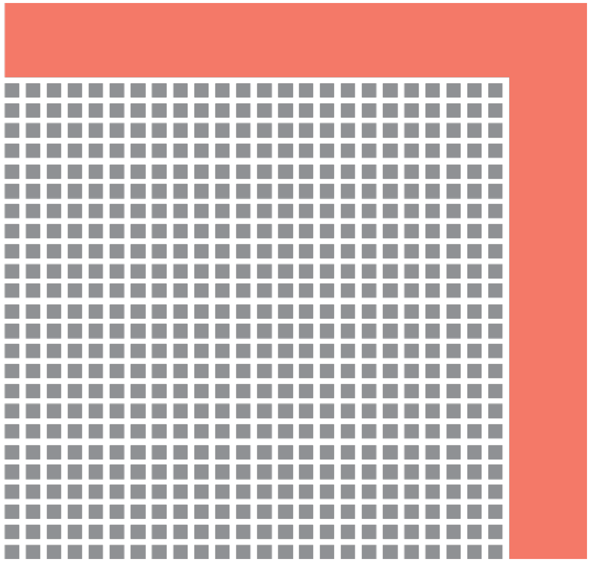
Too Big

System solves slowest
Smallest error



Too small

System solves quickest
Largest error



Just right

System solves modest
Modest error

Use the magnitude of the error to determine how big your states should be
Goldilocks zone for the size of states balances solving time and error

Math Properties – Matrix Exponential

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The Matrix Exponential is the matrix analog to the exponential function

System of Equations

$$\frac{dP}{dt} = AP$$

Solution to System of Equations

$$P(x,t) = EXPM(At)P_0$$

Definition of Exponential

$$exp(at) = 1 + \frac{at}{1!} + \frac{(at)^2}{2!} + \frac{(at)^3}{3!} + \cdots$$

Definition of Matrix Exponential

$$EXPM(At) = I + \frac{At}{1!} + \frac{(At)^2}{2!} + \frac{(At)^3}{3!} + \cdots$$

Tips: Creating the Infinitesimal Generator

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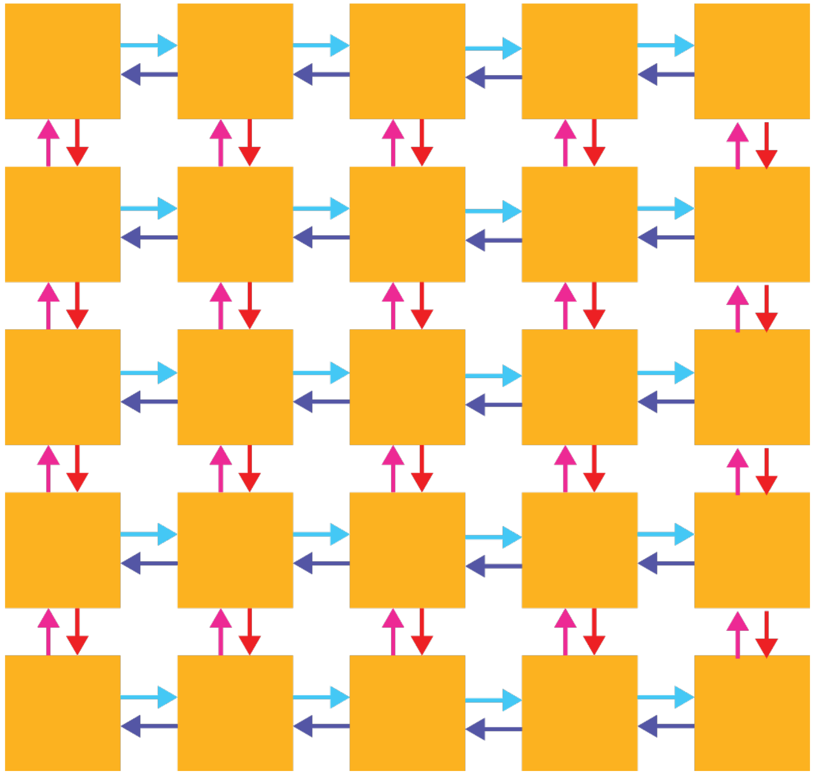
Group each reaction to make the creation easier



Stoichiometry	Propensity
$s_1 = [\,1, 0\,]^T$	$w_1 = k_1$
$s_2 = [\,-1, 0\,]^T$	$w_2 = k_2 x_1$
$s_3 = [\,0, 1\,]^T$	$w_3 = k_3$
$s_4 = [\,0, -1\,]^T$	$w_4 = k_4 x_2$

The infinitesimal generator is given by : $A = A_1 + A_2 + A_3 + A_4$

In this example it can be written by : $A = k_1 A'_1 + k_2 A'_2 + k_3 A'_3 + k_4 A'_4$

Example 1: Birth Decay Process

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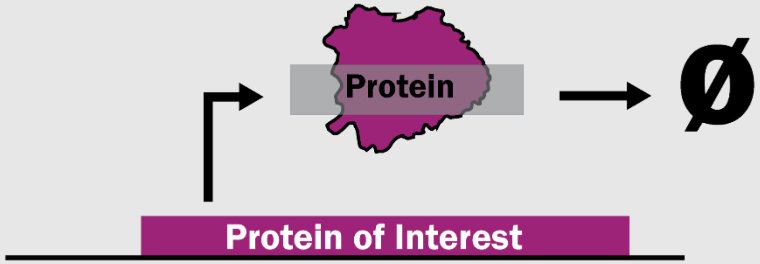
Birth-Decay Model



Birth Deacay Model Properties

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

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

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

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

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

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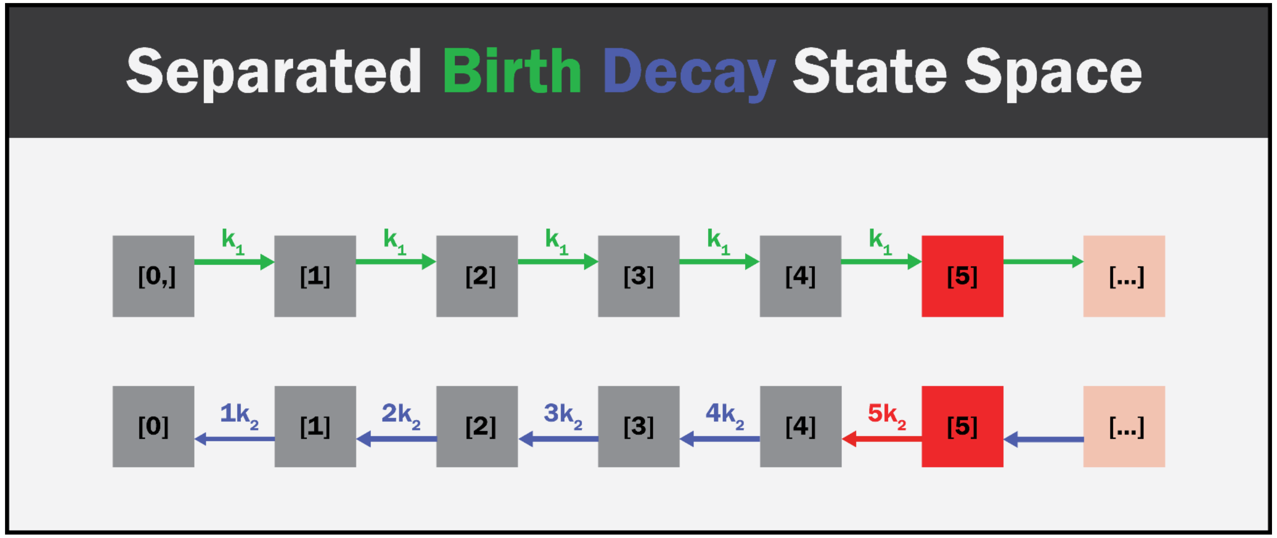
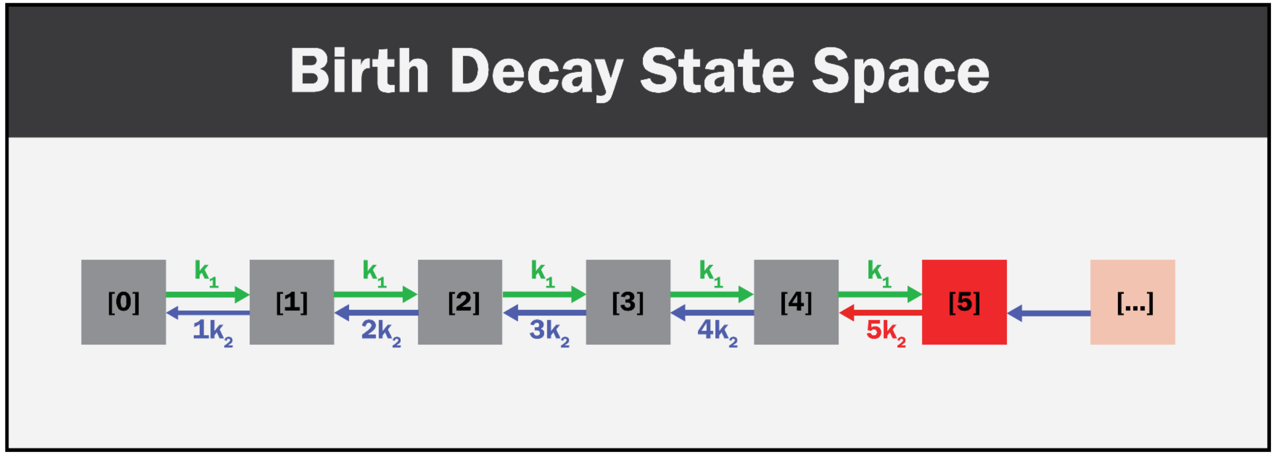
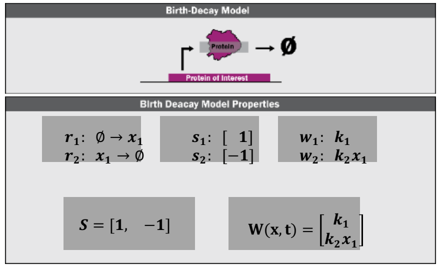
(optional) Break down the system into birth only, and decay only to make the creating of the A matrix easier







Example 1: Birth Decay Process

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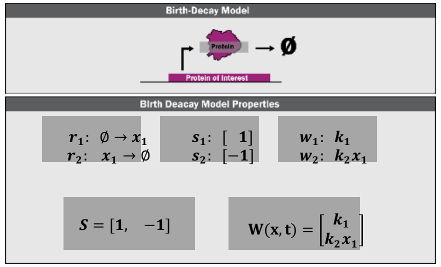
Birth Only



Write the Infinitesimal Generator for the Birth Only system above

$$r_1: \ \emptyset \to x_1$$
$$s_1: \ [1]$$
$$w_1: \ k_1$$

Example 1: Birth Decay Process

uq-bio

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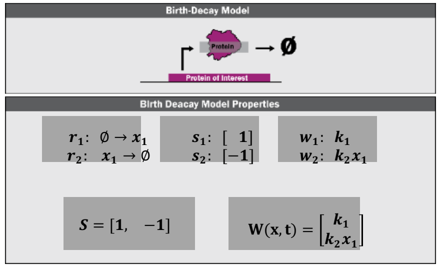
Birth Only



Write the Infinitesimal Generator for the Birth Only system above

$$\begin{bmatrix} A_1 \\ E_1 \end{bmatrix} = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 \\ k_1 & -k_1 & 0 & 0 & 0 & 0 \\ 0 & k_1 & -k_1 & 0 & 0 & 0 \\ 0 & 0 & k_1 & -k_1 & 0 & 0 \\ 0 & 0 & 0 & k_1 & -k_1 & 0 \\ 0 & 0 & 0 & 0 & k_1 & 0 \end{bmatrix}$$

$r_1: \; \emptyset \rightarrow x_1$

$s_1: \; [1]$

$w_1: \; k_1$

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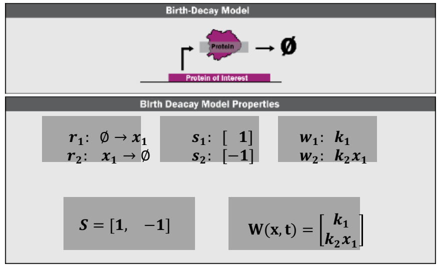
Decay Only



Write the Infinitesimal Generator for the Decay Only system above

$$r_2: \quad x_1 \rightarrow \emptyset$$

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

$$w_2: \quad k_2 x_1$$

Example 1: Birth Decay Process

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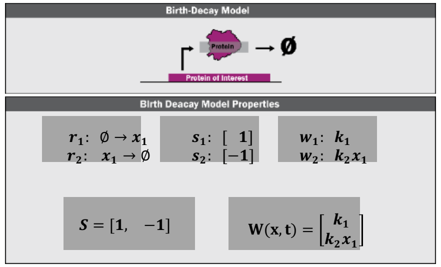
Decay Only



Write the Infinitesimal Generator for the Decay Only system above

$$\begin{bmatrix} A_1 \\ E_1 \end{bmatrix} = \begin{bmatrix} 0 & k_2(1) & 0 & 0 & 0 & 0 \\ 0 & -k_2(1) & k_2(2) & 0 & 0 & 0 \\ 0 & 0 & -k_2(2) & k_2(3) & 0 & 0 \\ 0 & 0 & 0 & -k_2(3) & k_2(4) & 0 \\ 0 & 0 & 0 & 0 & -k_2(4) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$r_2: \quad x_1 \to \emptyset$

$s_2: \quad [-1]$

$w_2: \quad k_2 x_1$

Example 1: Birth Decay Process

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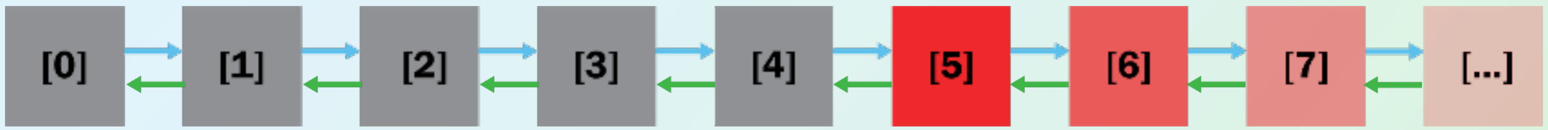
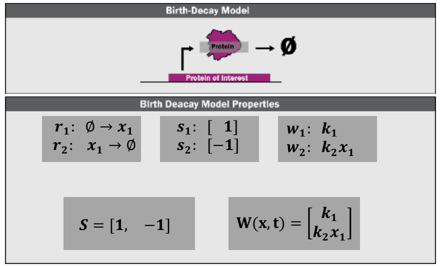
Birth and Decay





Write the Infinitesimal Generator for the Birth and Decay Only system above

$$\boldsymbol{A = A_1 + A_2}$$

$$\begin{bmatrix} A \\ E \end{bmatrix} = \begin{bmatrix} -k_1 & k_2(1) & 0 & 0 & 0 & 0 \\ k_1 & -k_2(1) - k_1 & k_2(2) & 0 & 0 & 0 \\ 0 & k_1 & -k_2(2) - k_1 & k_2(3) & 0 & 0 \\ 0 & 0 & k_1 & -k_2(3) - k_1 & k_2(4) & 0 \\ 0 & 0 & 0 & k_1 & -k_2(4) - k_1 & 0 \\ 0 & 0 & 0 & 0 & k_1 & 0 \end{bmatrix}$$

Example 1: Birth Decay Process

uq-bio

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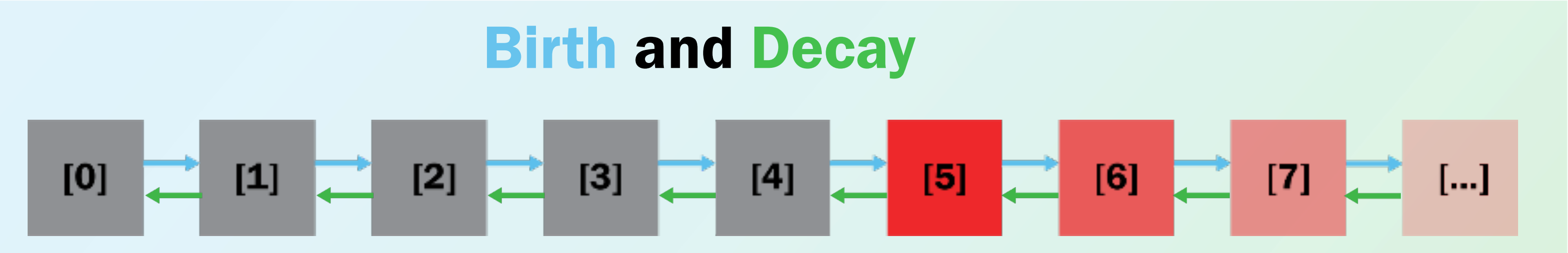

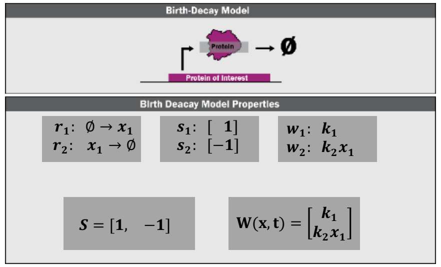

Write the Reflecting Boundary Condition for the Birth and Decay Only system above

$$\begin{bmatrix} A \\ {\color{red}0} \end{bmatrix} = \begin{bmatrix} -k_1 & k_2(1) & 0 & 0 & 0 & 0 \\ k_1 & -k_2(1)-k_1 & k_2(2) & 0 & 0 & 0 \\ 0 & k_1 & -k_2(2)-k_1 & k_2(3) & 0 & 0 \\ 0 & 0 & k_1 & -k_2(3)-k_1 & k_2(4) & 0 \\ 0 & 0 & 0 & k_1 & -k_2(4)-k_1+{\color{red}k_1} & 0 \\ {\color{red}0} & {\color{red}0} & {\color{red}0} & {\color{red}0} & {\color{red}0} & 0 \end{bmatrix}$$