2010 q-bio Summer School, Theme 2:

Stochastic Biochemistry

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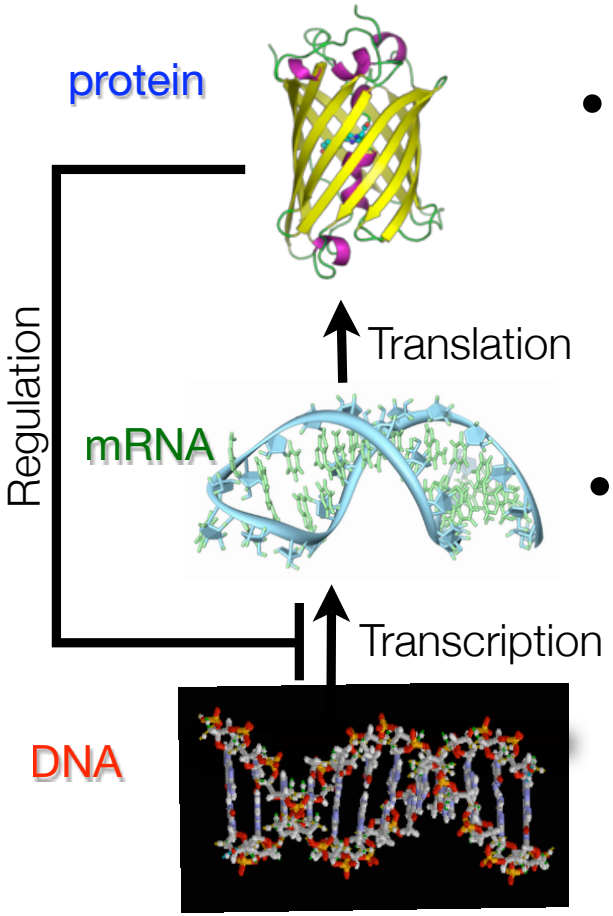
Stochastic Biochemistry: Theme Overview

1. Stochastic Phenomena: origins and consequences.

2. Single Cell Research.

Origins of Stochasticity:
1) Small molecular copy numbers



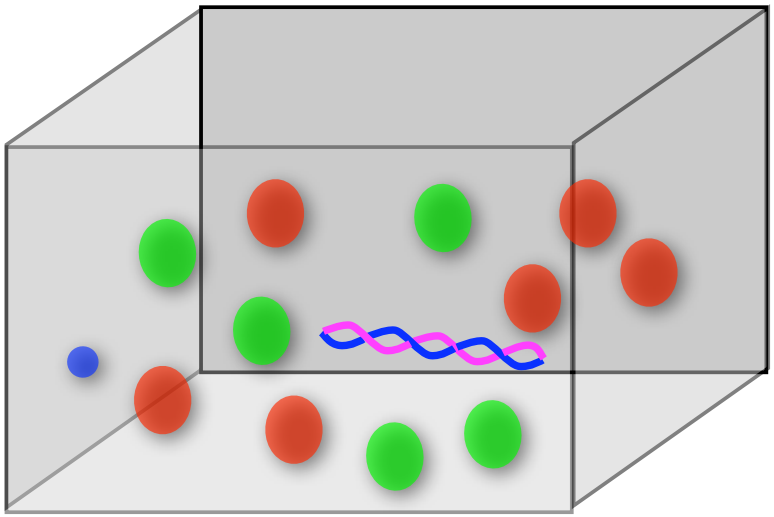
- Proteins build cellular structures, pass cellular information and regulate cellular activities. Variable copy numbers (~0-100,000/cell).

- mRNA transfer instructions for creating specific proteins. Low copy numbers (~0-100/cell).

- DNA contains all of the genetic instructions. Extremely low copy numbers (~0-5/cell).

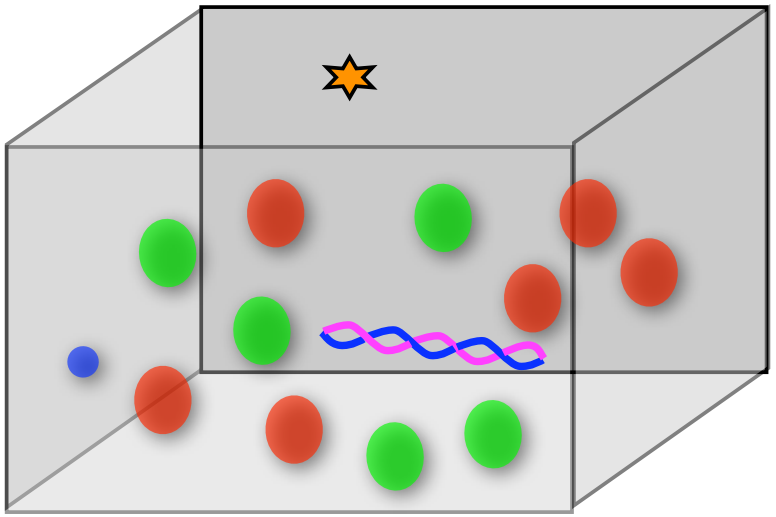
The Central Dogma of Molecular Biology

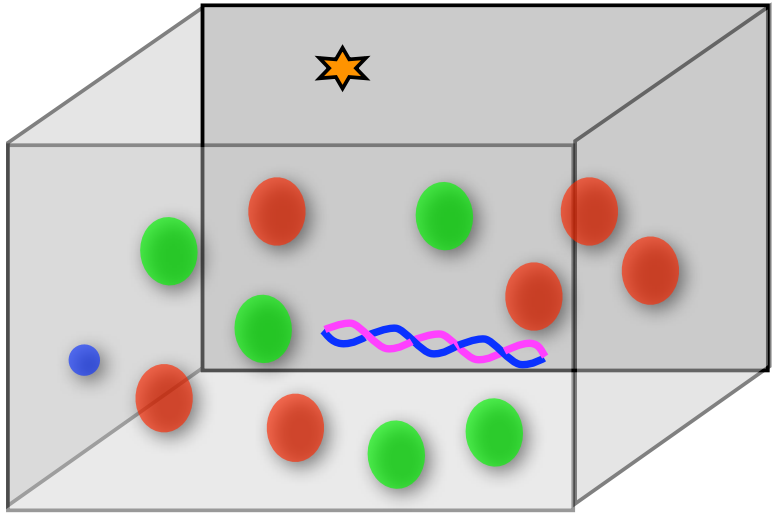
Origins of Stochasticity:
2) Spatial fluctuations of cellular constituents.



Thermal fluctuations will lead to randomness in times between reactions.

Origins of Stochasticity:
3) Competition of different events.





Different reactions will lead to different consequences.

Which ever molecule wins the race will define the reaction.

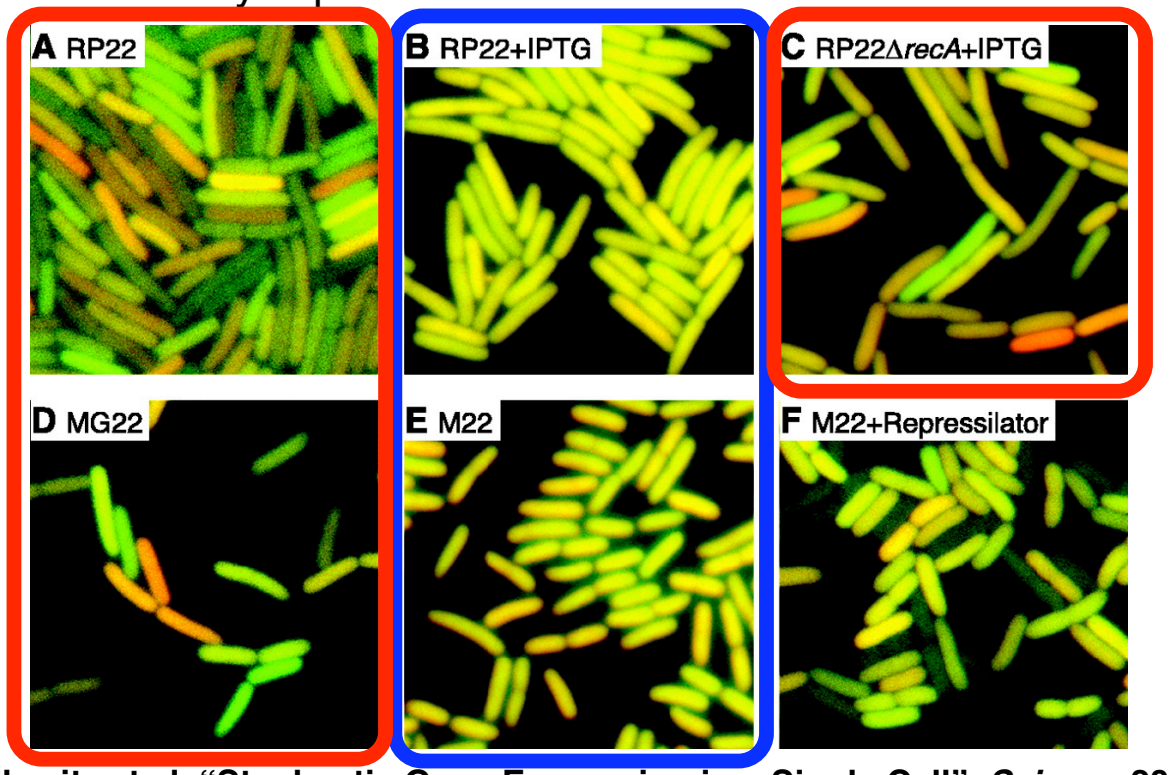
Origins of Stochasticity:
4) Extrinsic fluctuations.

Changes in temperature, nutrients, radiation, chemicals, pressure, etc...

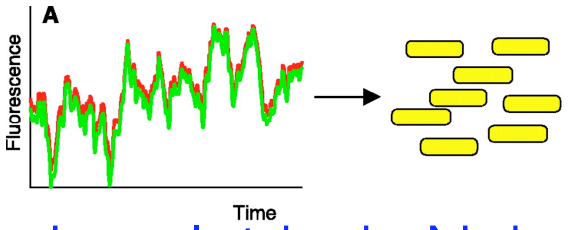
Fluctuations of upstream genes, intercellular signals.

Intrinsic versus Extrinsic Noise

- Variability is present and can be measured

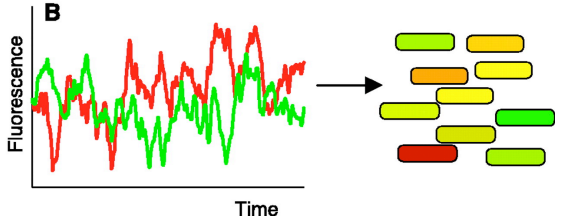


Elowitz et al, "Stochastic Gene Expression in a Single Cell", *Science* 2002



Low Intrinsic Noise

High Intrinsic Noise



- Inserted two reporter genes on the chromosome (cfp, yfp)
- Each was controlled by the same promoter
- Expression of cfp shown in green, yfp in red

Stochastic Effects Lead to Phenotypical Differences

Fingerprints of identical twins

Cc, the first cloned cat and her genetic mother, Rainbow

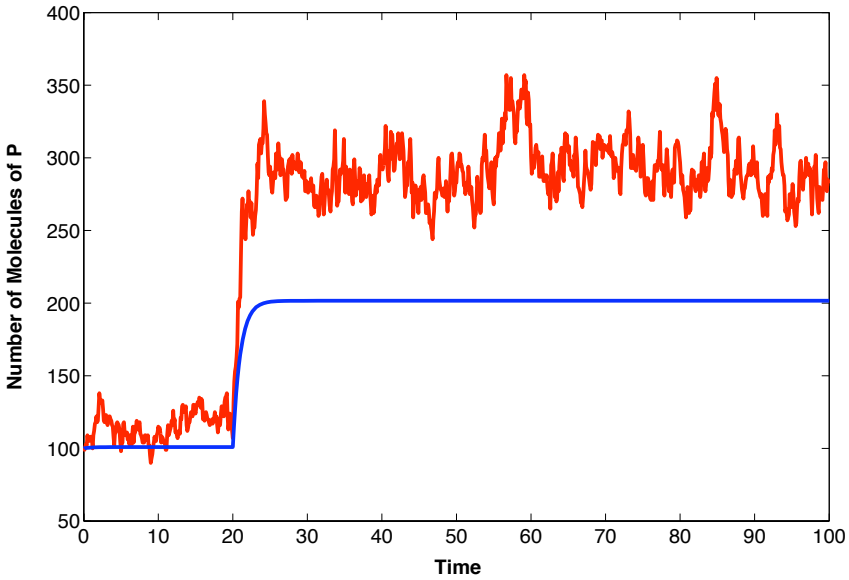
J. Raser and E. O'Shea, "Noise in Gene Expression: Origins, Consequences, and Control", *Science*, 2005

Slide Contributed by Mustafa Khammash

Stochastic Phenomena:
1) Signal Amplification (or damping).

$$\phi \underset{k_a S}{\overset{k}{\rightleftharpoons}} I \xrightarrow{k_p} P \xrightarrow{1} \phi$$

$$\phi \underset{k_d}{\overset{k_s}{\rightleftharpoons}} S$$

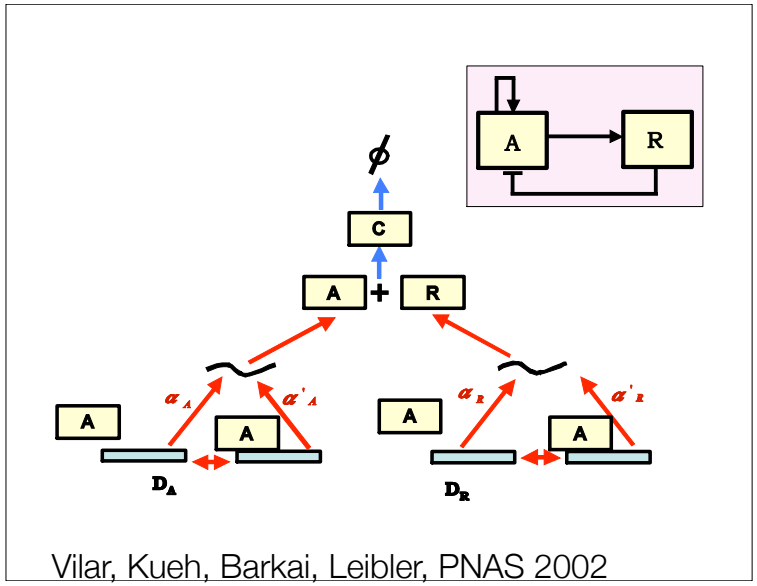


Johan Paulsson , Otto G. Berg , and Måns Ehrenberg, "Stochastic Focusing: Fluctuation-enhansed sensitivity of intracellular regulation" PNAS 2000

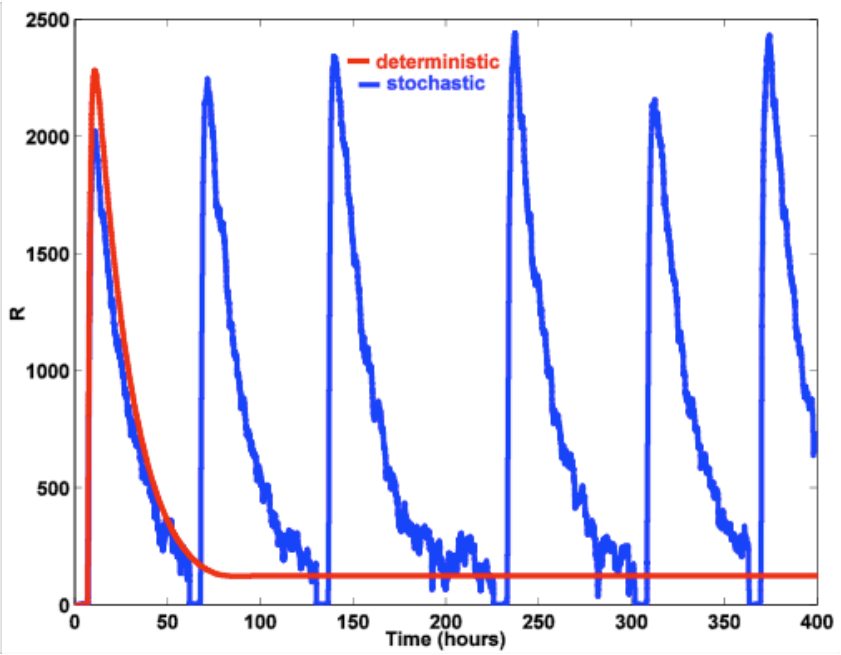
- Stochastic mean value different from deterministic steady state
- Noise *enhances* signal!

Stochastic Phenomena:
2) Noise Induced Oscillations

Circadian rhythm



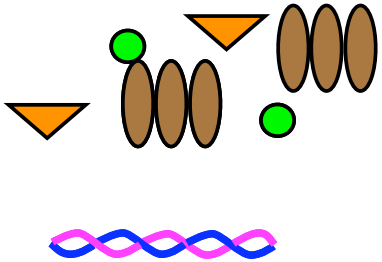
Vilar, Kueh, Barkai, Leibler, PNAS 2002



- Oscillations disappear from deterministic model after a small reduction in deg. of repressor
- (Coherence resonance) Regularity of noise induced oscillations can be manipulated by tuning the level of noise [*El-Samad, Khammash*]

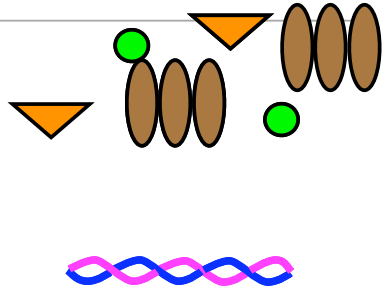
Slide Contributed by Mustafa Khammash

Stochastic Phenomena:
3) Stochastic Switching

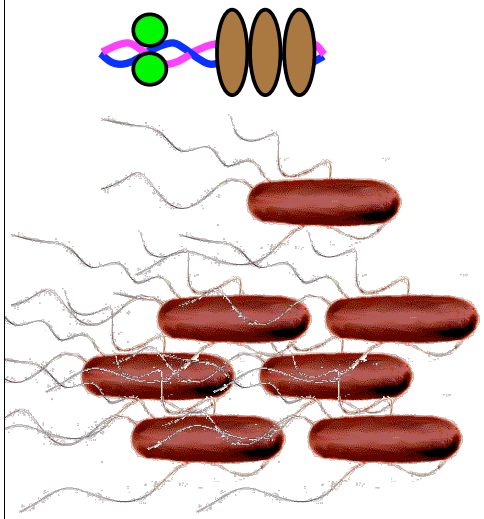


Same chemical environment.

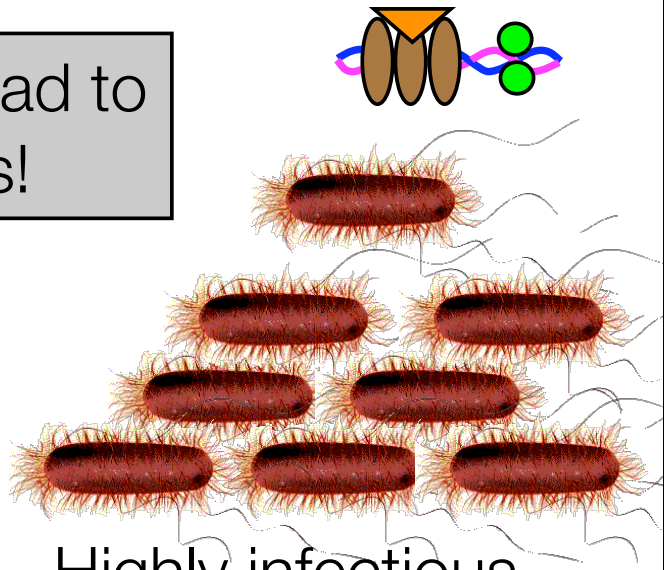
Same genetic code.



Random reactions can lead to vastly different results!



Harmless phenotype.



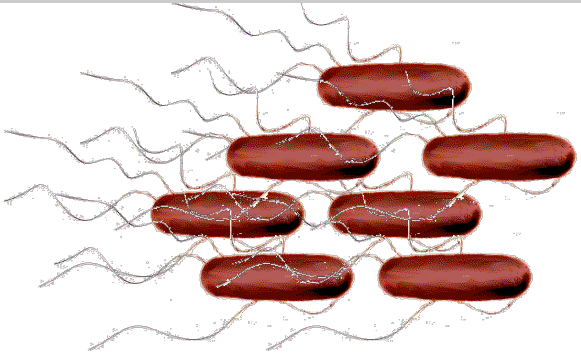
Highly infectious phenotype.

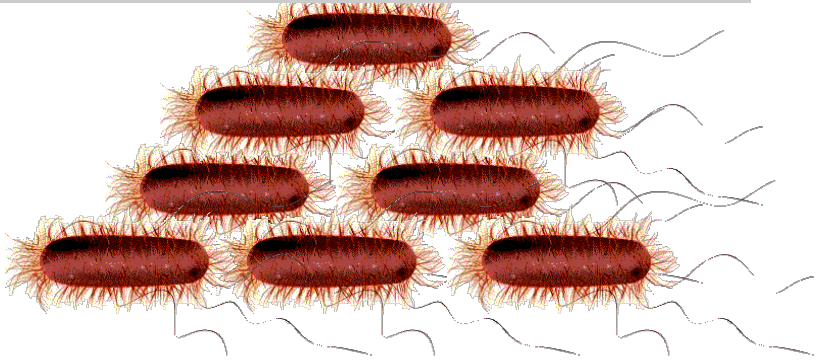
Munsky, Trinh, Hernday, Khammash, Low, *under preparation,* 2010

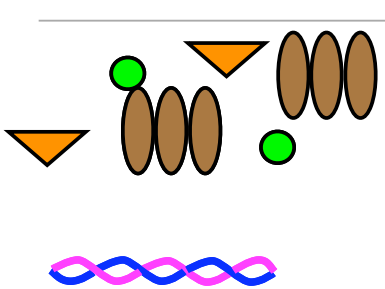
The Importance of Single Cell Analyses

For these systems, we need
single cell analyses to answer:

- ★ What will happen?
- ★ How frequently?
- ★ Why does it happen?
- ★ Under what conditions?
- ★ What advantages does it provide?
- ★ How can we prevent it?
- ★ How can we cause it?







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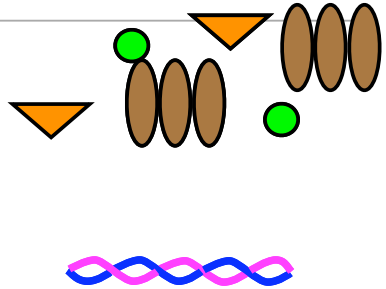

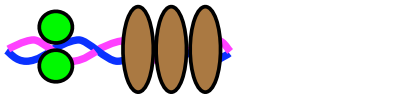

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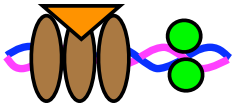
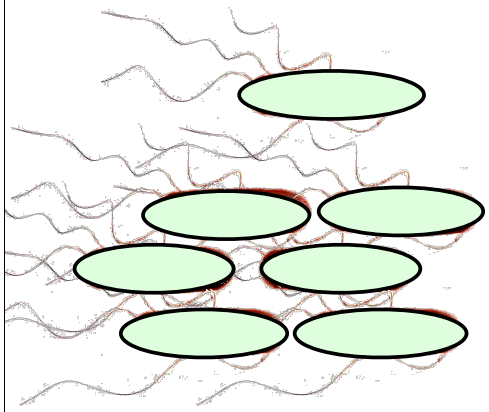
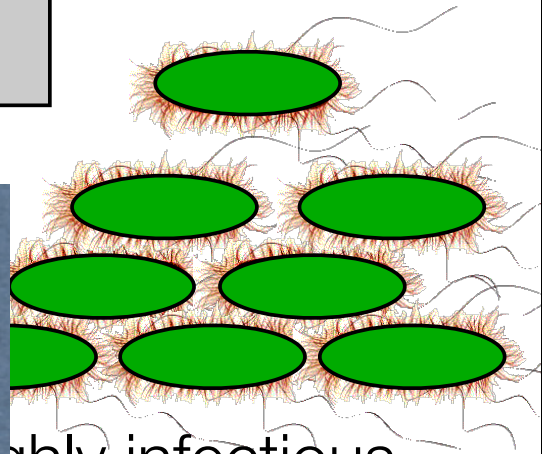




Harmless phenotype.

Genetic manipulations make it easy to see changes under the microscope.



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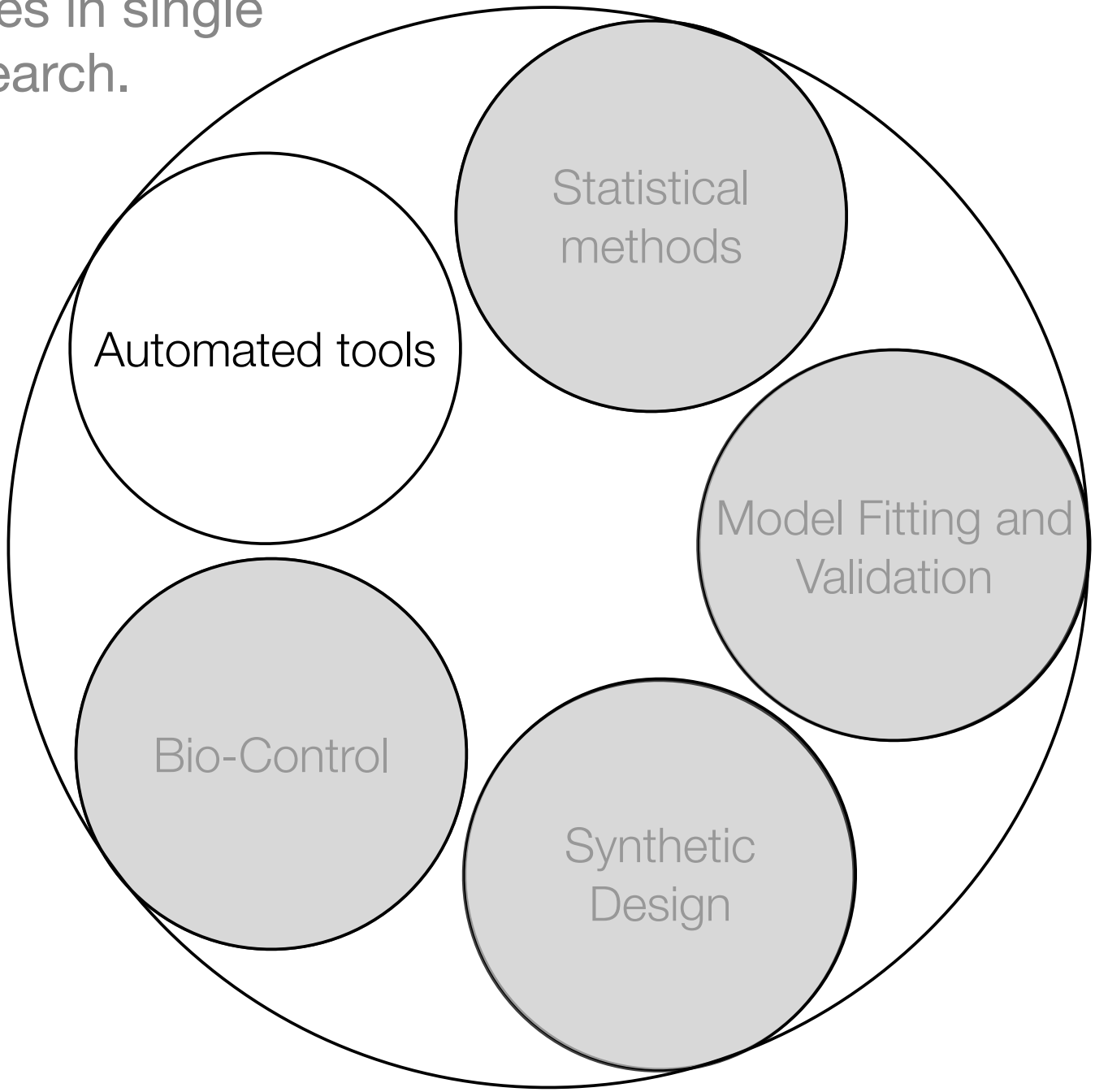
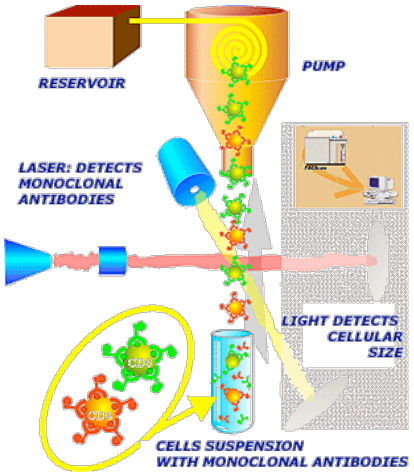
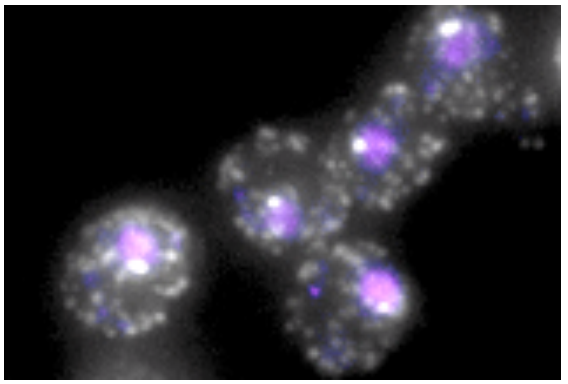


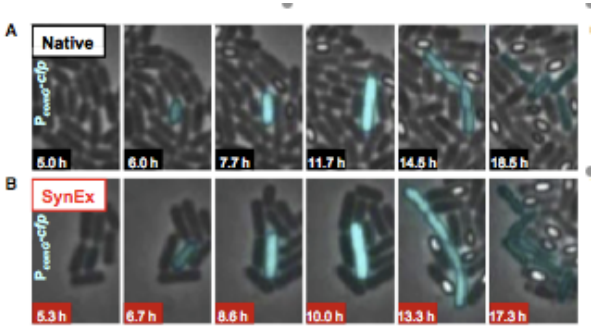
Automated tools



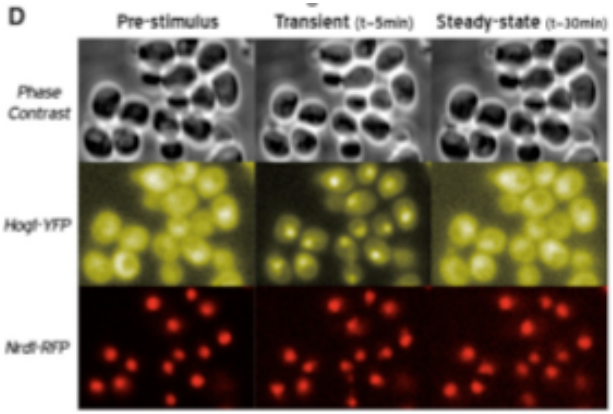
Flow Cytometry and fluorescence activated cell sorting



Single molecule Fluorescence *in situ* Hybridization (FISH)
Raj, Nature Methods 2007

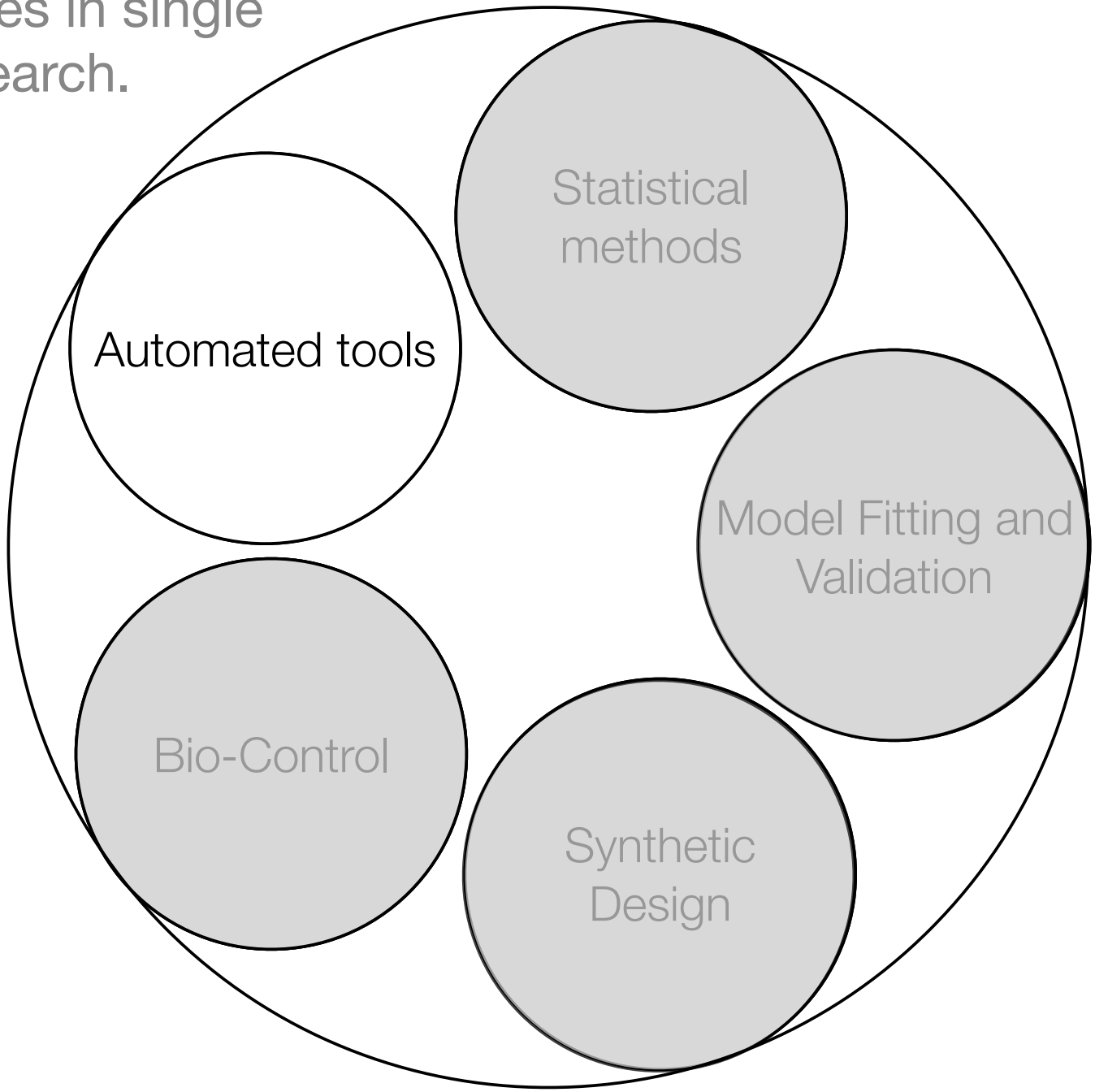


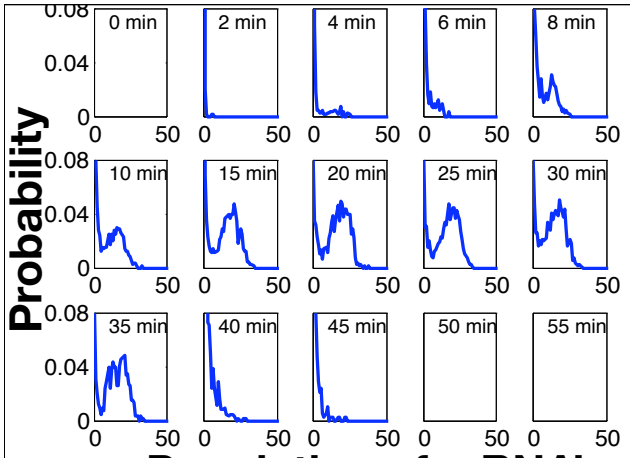
Time lapse fluorescence microscopy
Cagatay et al, Cell 2009



Fluorescence microscopy,
Muzzey et al, Cell 2009

Advances in single cell research.





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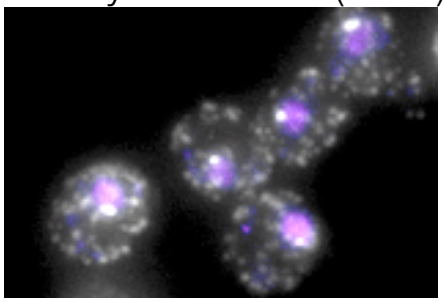
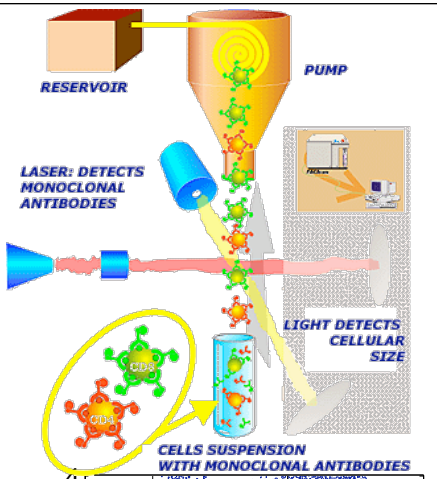
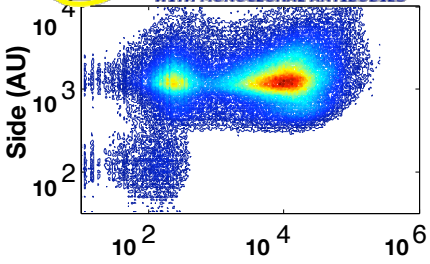
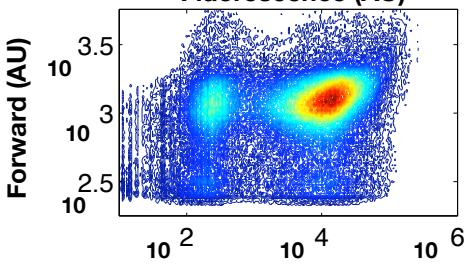
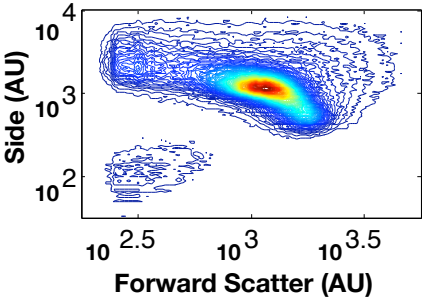


Statistical methods

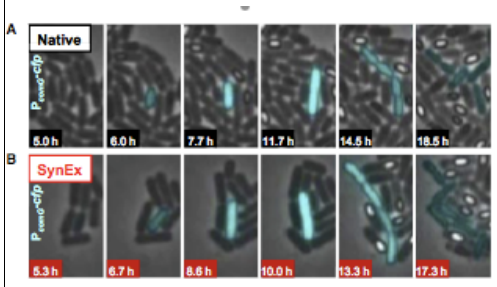


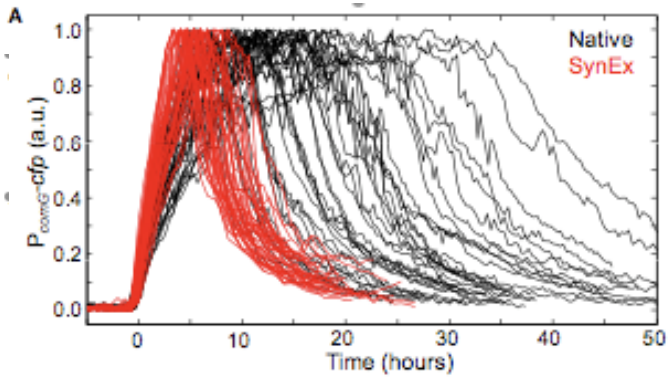






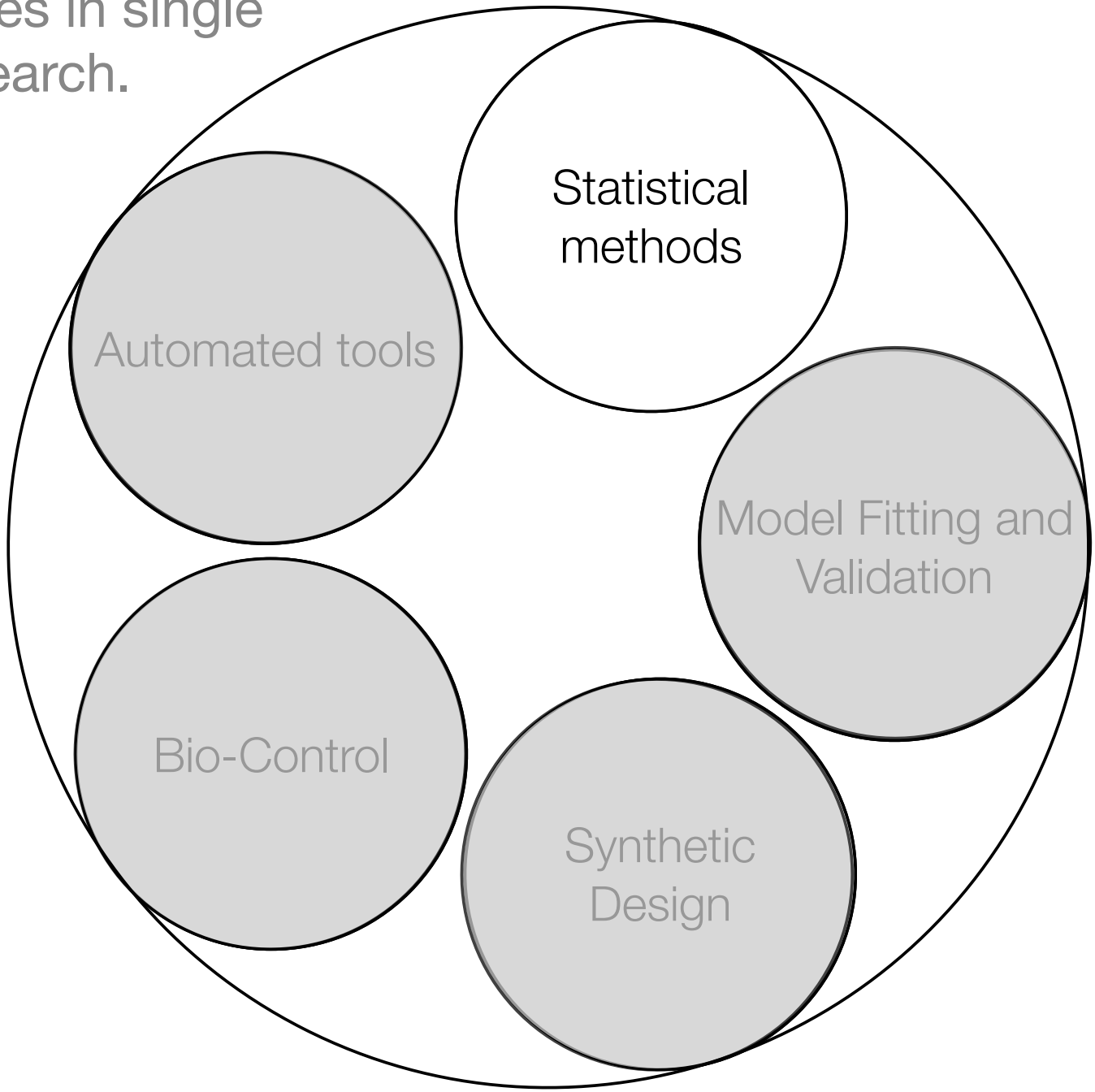
Flow Cytometry

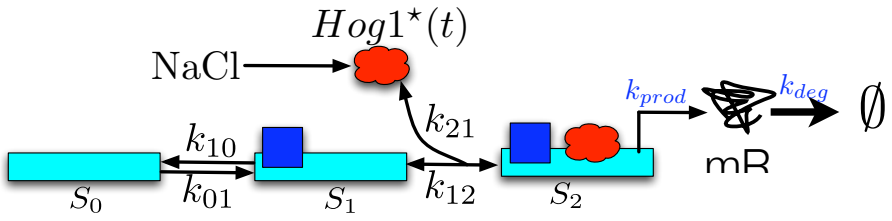


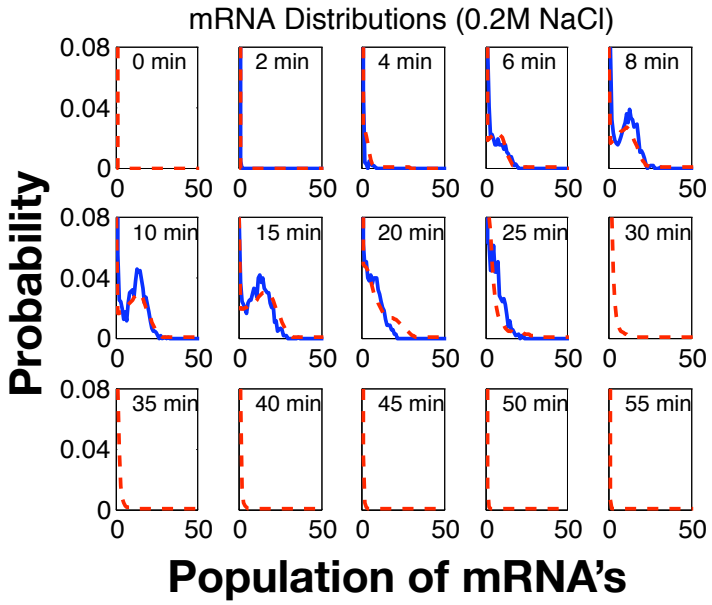


Time lapse fluorescence microscopy Cagatay et al, Cell 2009

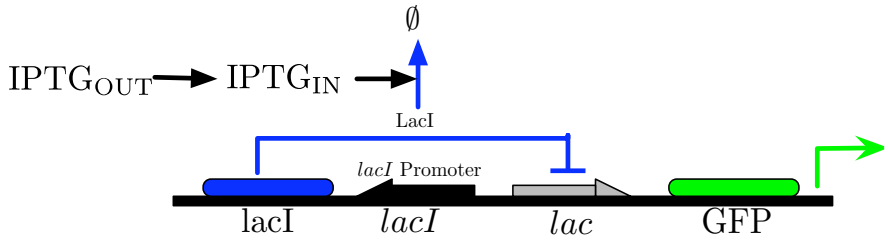
Advances in single cell research.

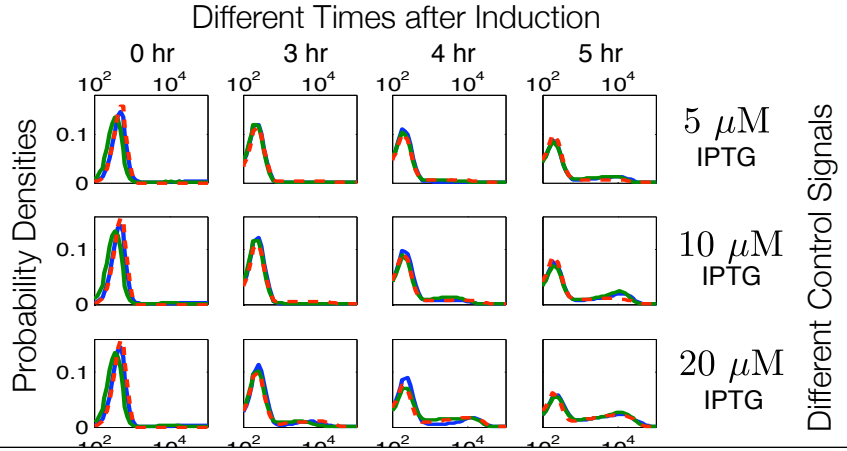






Model Fitting and Validation





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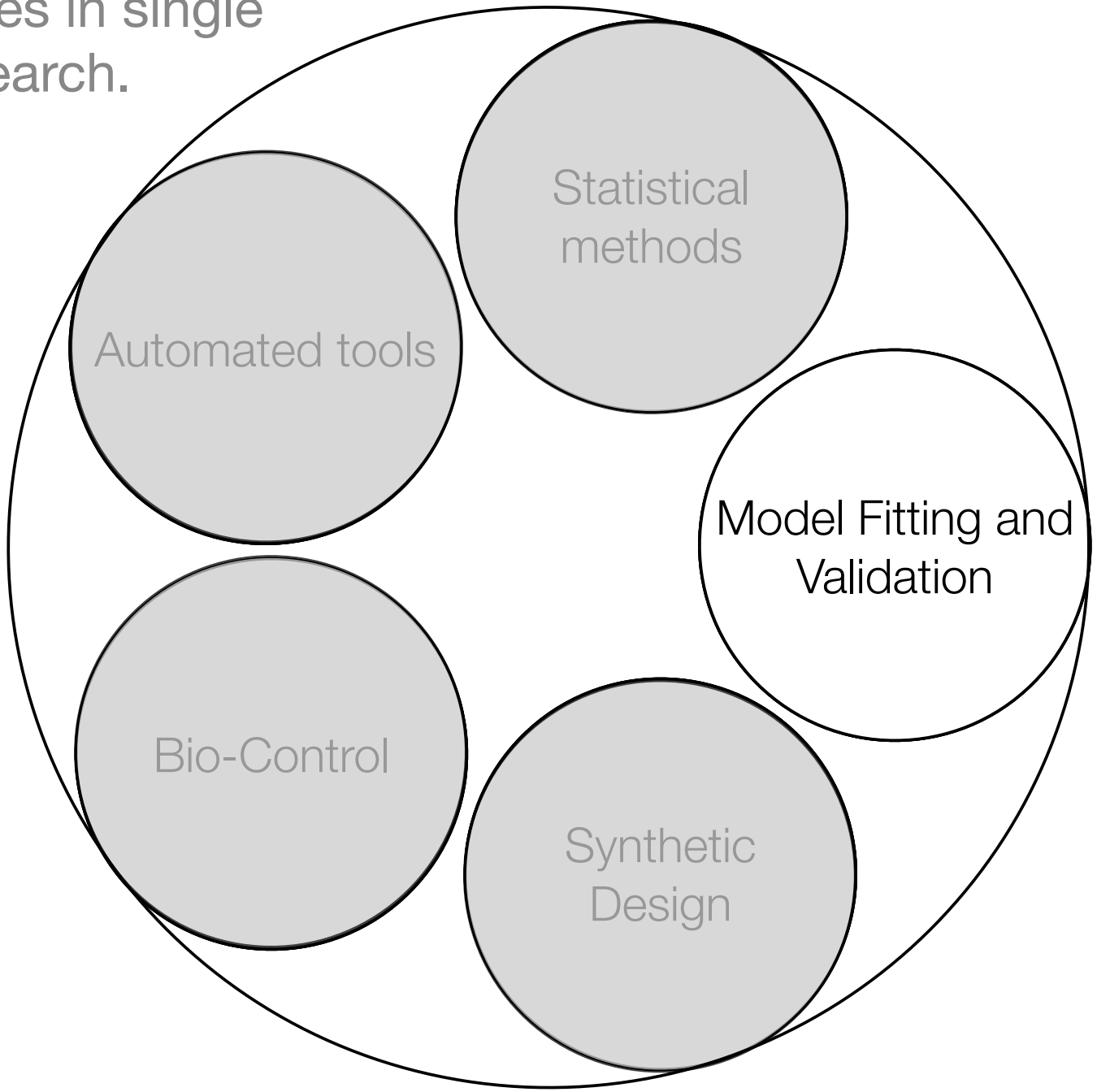
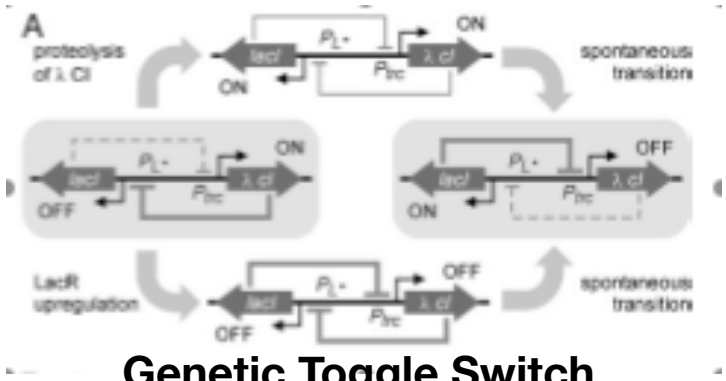
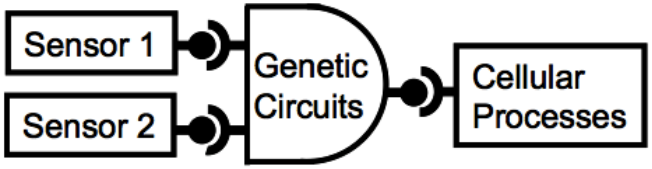
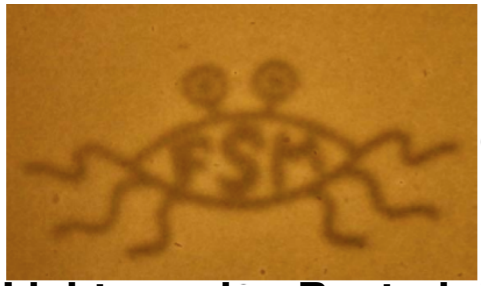


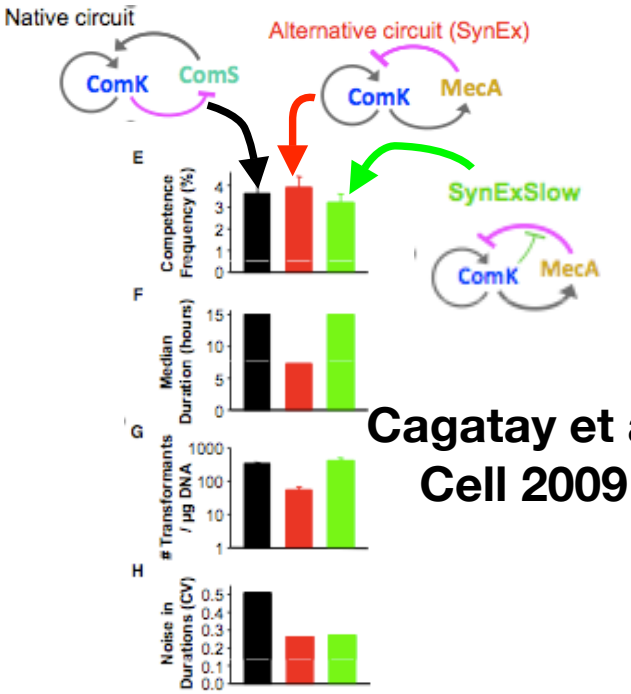


Genetic Toggle Switch, Kobayashi *et al,* 2004





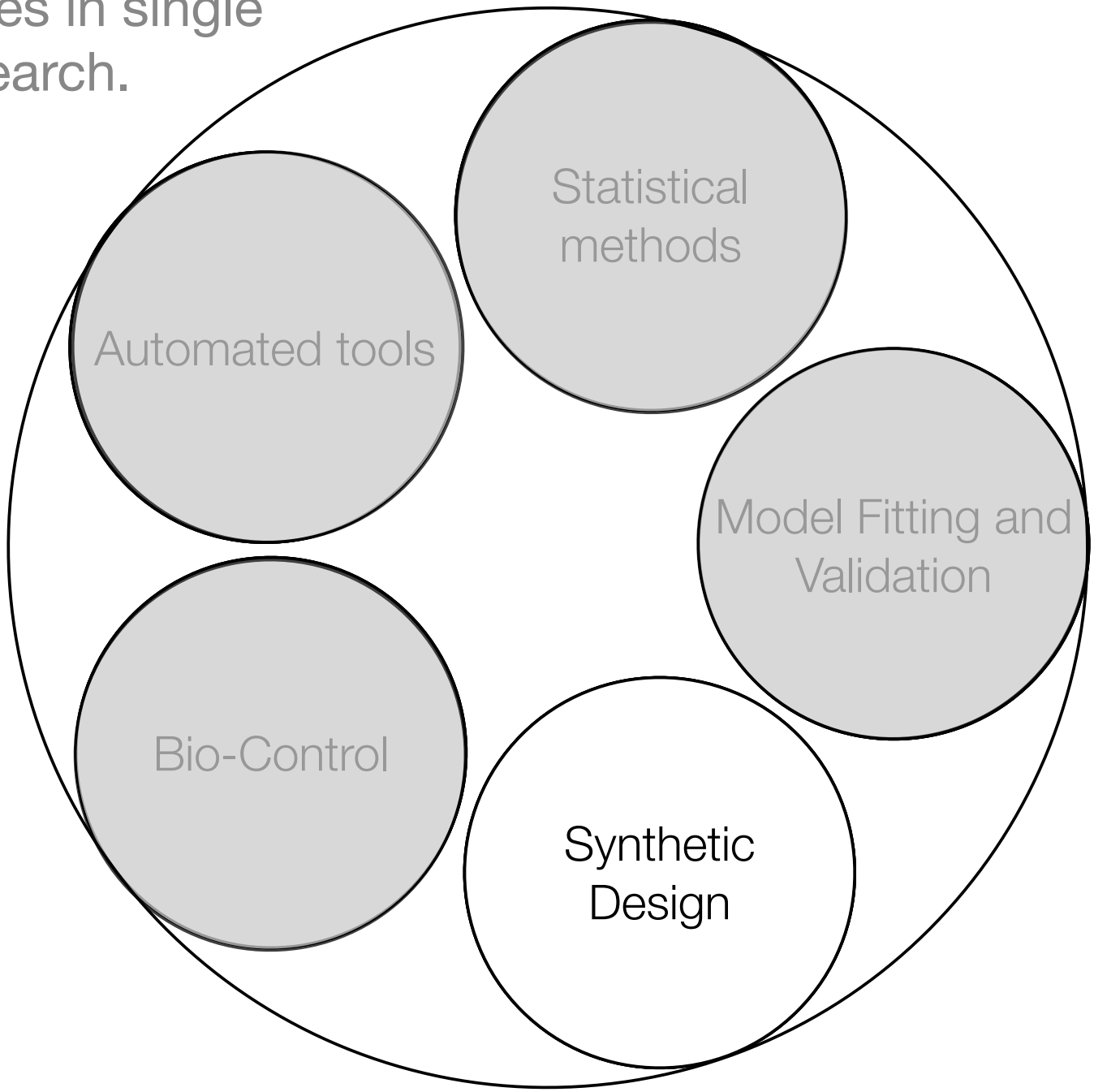
Light sensing Bacteria, Voigt Lab, 2005

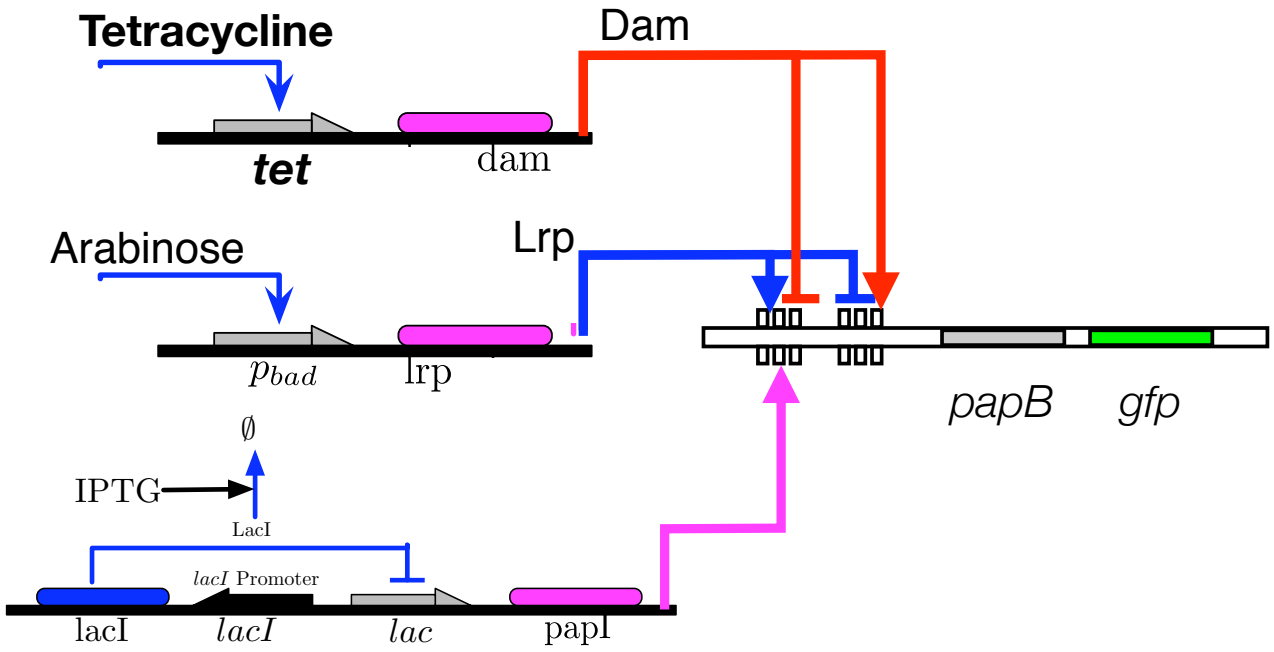


Cagatay et al, Cell 2009

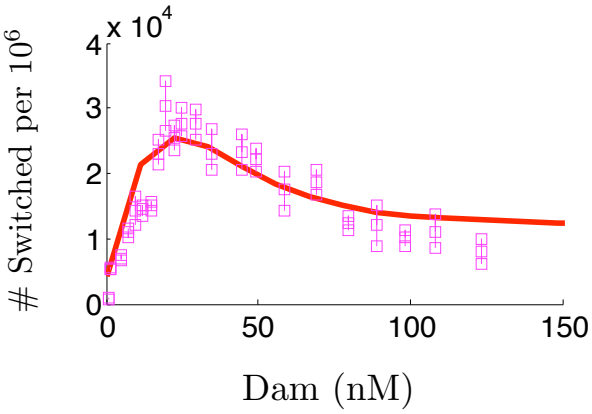
Synthetic Design

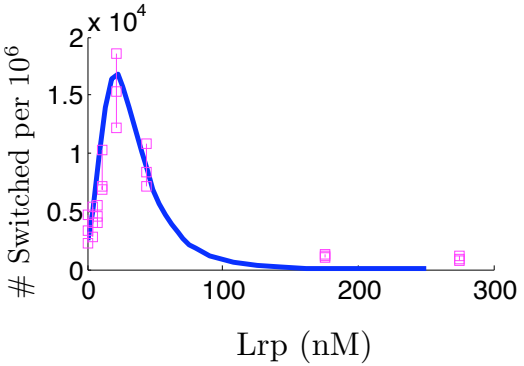
Advances in single cell research.

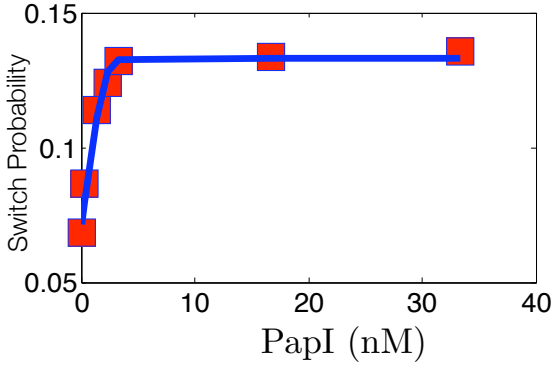



Tetracycline
Dam
tet
dam
Arabinose
Lrp
p_{bad}
lrp
papB
gfp
∅
IPTG
LacI
lacI Promoter
lacI
lacI
lac
papI

Bio-Control


Switched per 10^6
x 10^4
Dam (nM)


Switched per 10^6
x 10^4
Lrp (nM)


Switch Probability
PapI (nM)

Stochastic Biochemistry: Lecture Plan

1) Theoretical Techniques
(Munsky, Nemenman, Zilman)

2) Experimental Techniques
(Marrone, Raj, Werner, Voigt)

Lecture Plan:
1) Theoretical Techniques

- Today and Wednesday--Brian Munsky (LANL-CNLS)
  - Modeling of stochastic effects in systems biology.
- Friday, August 6--Ilya Nemenman (Emory)
  - Signal processing in biochemical networks: Fourier transforms, central limit theorem, linear feedback, and all that.
- Monday, August 9-- Anton Zilman (LANL-CNLS)
  - History of Stochastic Modeling in Physics.
  - Advanced stochastic analyses: Fokker Planck equation, Moment Generating Functions, etc...

Lecture Plan:
2) Experimental Techniques

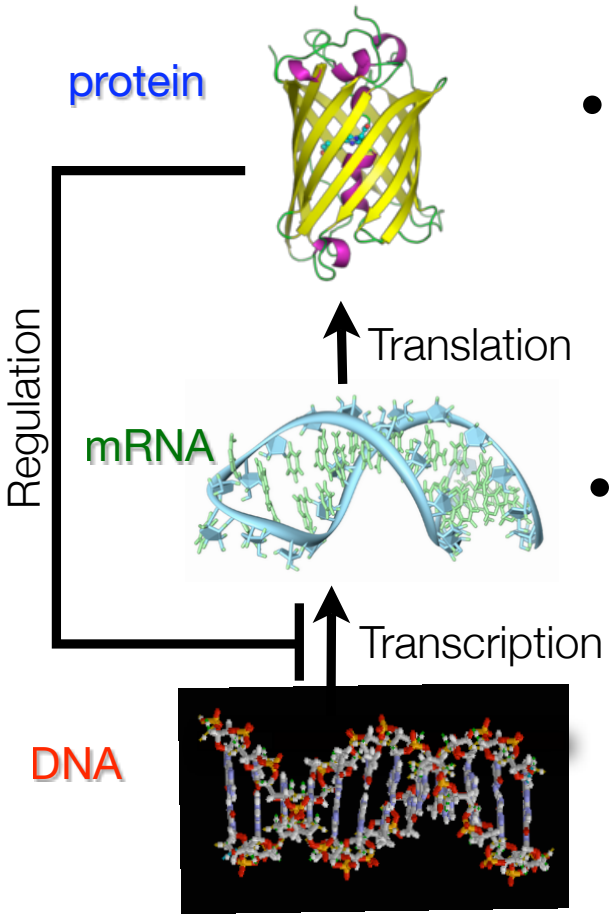
- Tuesday, August 3--Arjun Raj (U-Penn)
  - Measuring cell-to-cell variability with fluorescence microscopy and single molecule Fluorescence In Situ Hybridization (FISH) techniques.
- Tuesday, August 3--Babetta Marrone (LANL-B9)
  - Measuring cell-to-cell variability with flow cytometry and fluorescence activated cell sorting.
- Wednesday, August 4--Jim Werner (LANL-CINT)
  - Fluorescence Correlation Spectroscopy (FCS) and 3 Dimensional Single-Molecule Tracking
- Wednesday, August 4--Brian Munsky (LANL-CNLS)
  - Integrating single cell data and stochastic models.
- Tuesday, August 10--Christopher Voigt (UCSF)
  - Synthetic Biology

Lecture 1: Modeling of stochastic gene regulation (Part 1).

On the menu...

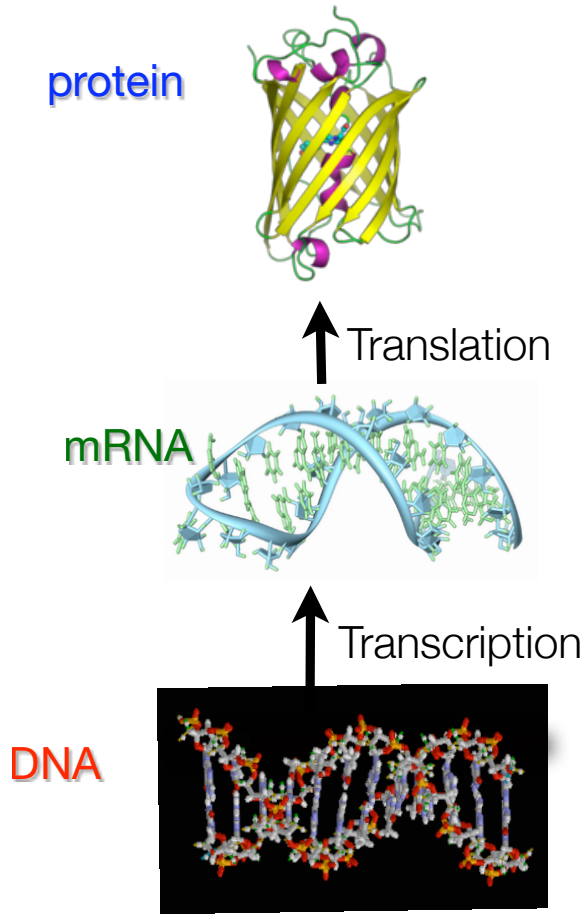
- Today (Part 1)
  - Solutions for Simple Stochastic Processes (Transcription)
  - Importance of Population Size
  - Stochastic Chemical Kinetics
  - Moment Computations for Linear Propensities
  - Moment Closures for Non-Linear Propensities
- Wednesday (8:40-10:25) (Part 2)
  - Monte Carlo Simulation Techniques
    - Gillespie (SSA), Tau leaping, Chemical Langevin (SDEs), Slow Scale SSA.
  - Density Computations with Finite State Projection Techniques
  - Switch and Trajectory Analyses
  - Examples and software

The Central Dogma of Molecular Biology



- Proteins assemble to build cellular structures, pass cellular information and regulate cellular activities.
- mRNA transfer instructions for the creation of specific proteins.
- DNA contains all of the genetic instructions.

The Central Dogma of Molecular Biology



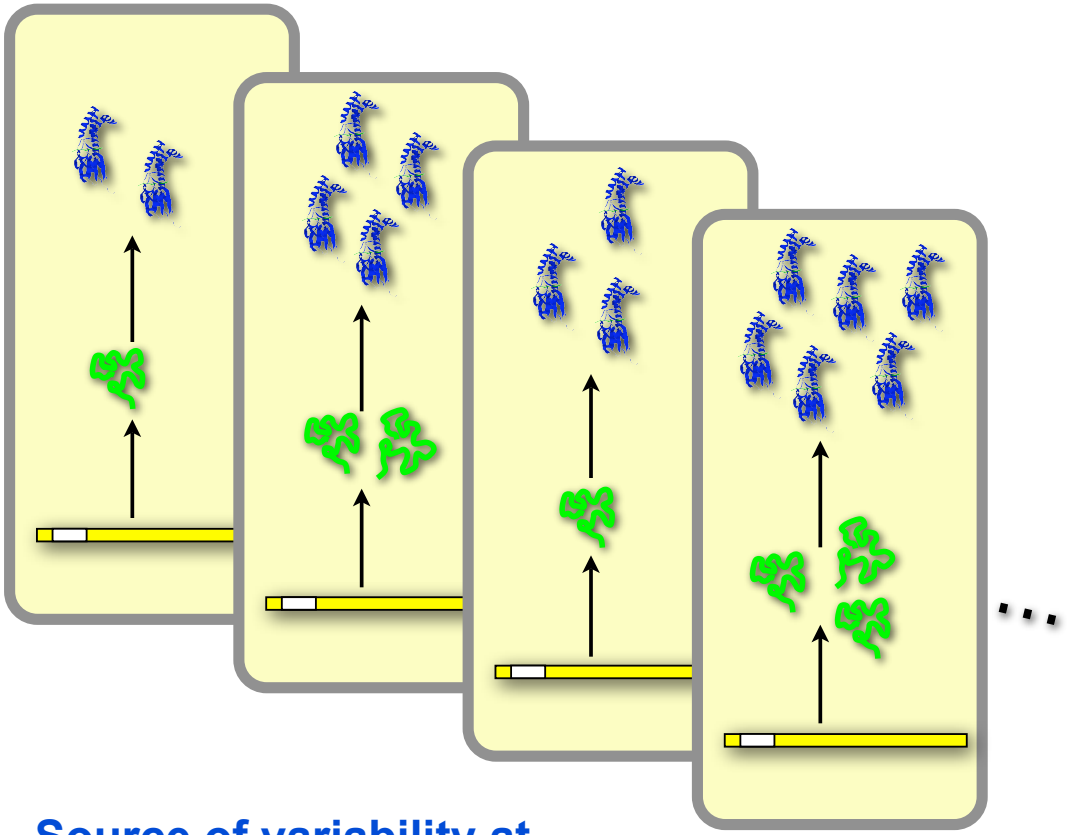
Deterministic model

$$\frac{d[mRNA]}{dt} = -\gamma_r[mRNA] + k_r$$
$$\frac{d[protein]}{dt} = -\gamma_p[protein] + k_p[mRNA]$$

Stochastic model

- Probability a single mRNA is transcribed in time dt is $k_r dt$.
- Probability a single mRNA is degraded in time dt is $(\#mRNA) \cdot \gamma_r dt$

Intrinsic Variability in Gene Expression



Source of variability at cellular level….

- Small # of molecules
- Random events

"Intrinsic noise"

Impact of variability

- Noise propagates through the network
- Its amount depends on
  - # of molecules
  - stoichiometry
  - regulation
  - ...
- Sometimes it is suppressed; other times it is exploited
- Deterministic models are not adequate

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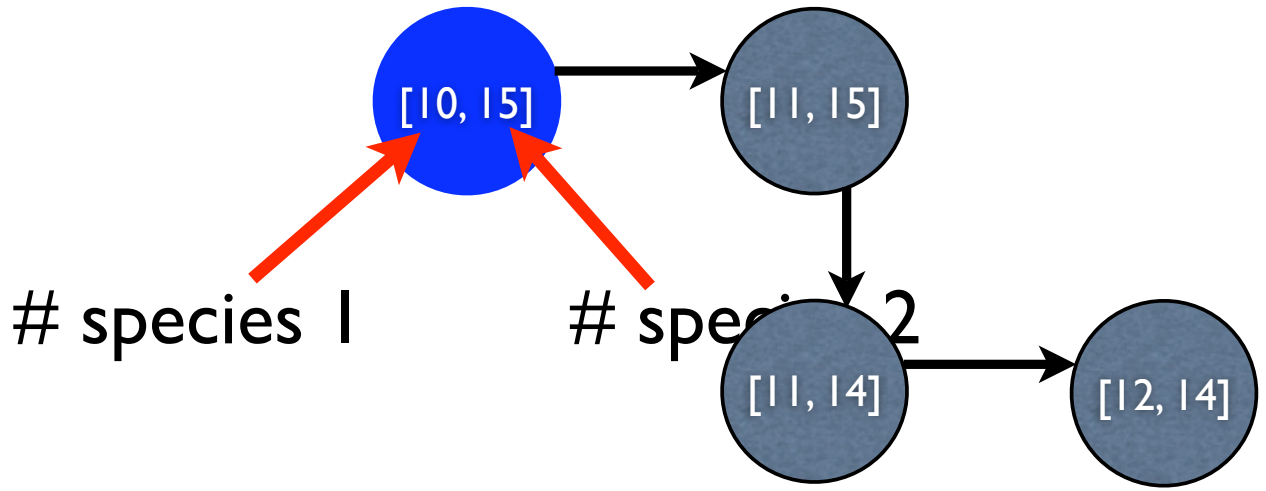
The Markov Description of Biochemical Processes

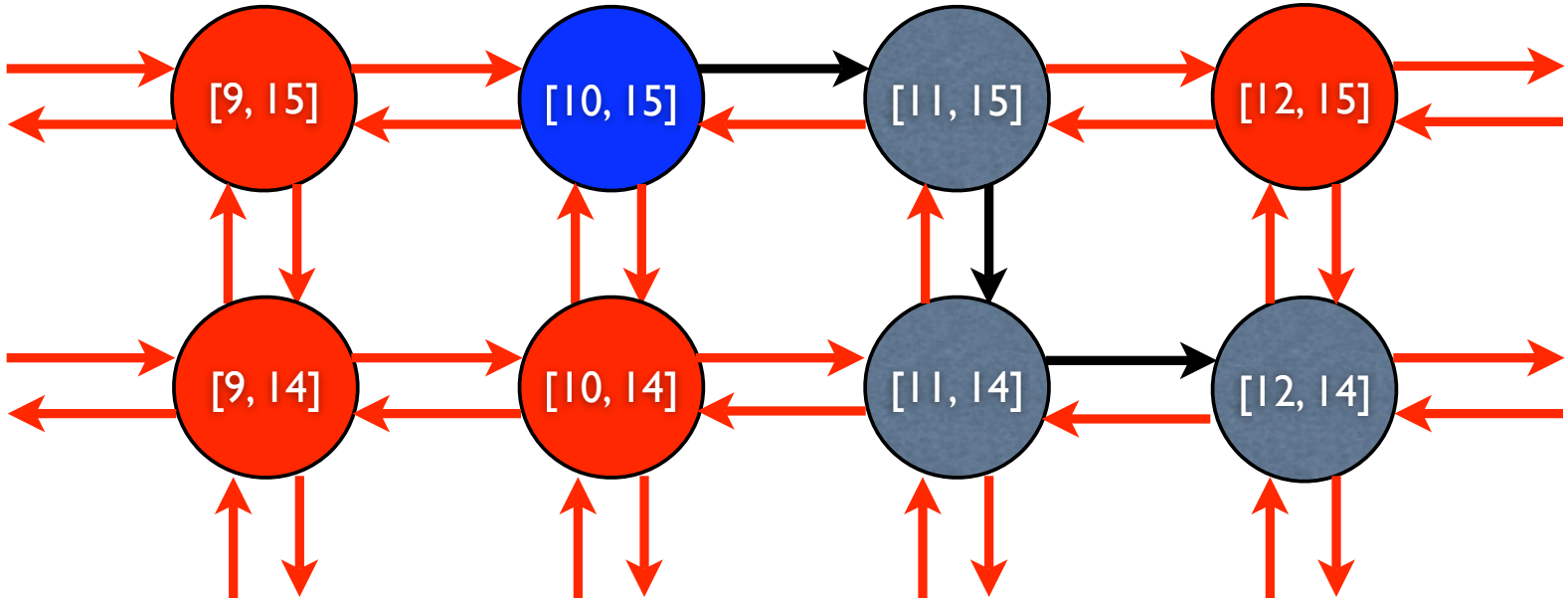
A Jump-Markov description of chemical kinetics

- At any time, the state of the system is *defined* by its integer population vector: $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another:

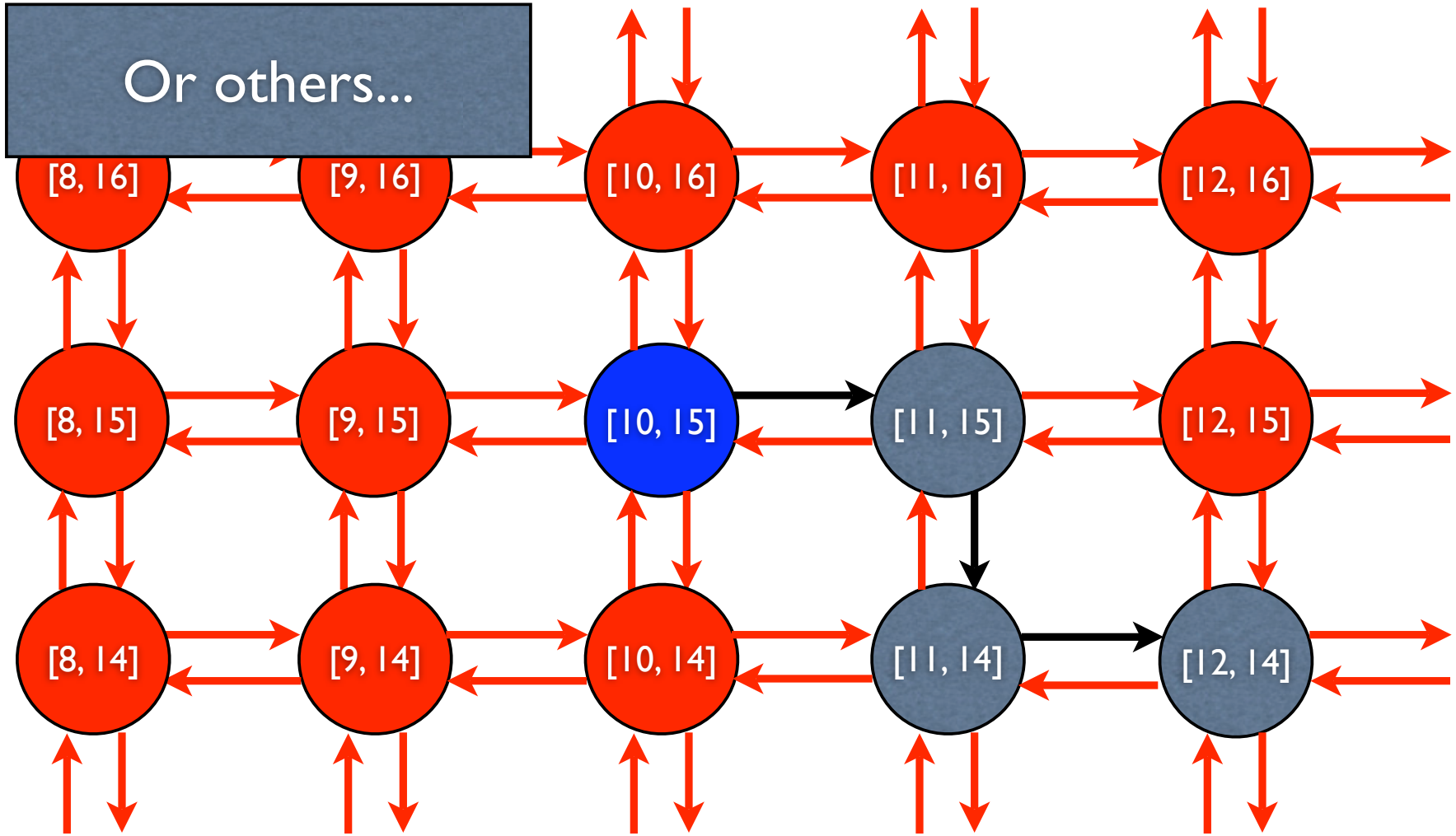


A Jump-Markov description of chemical kinetics

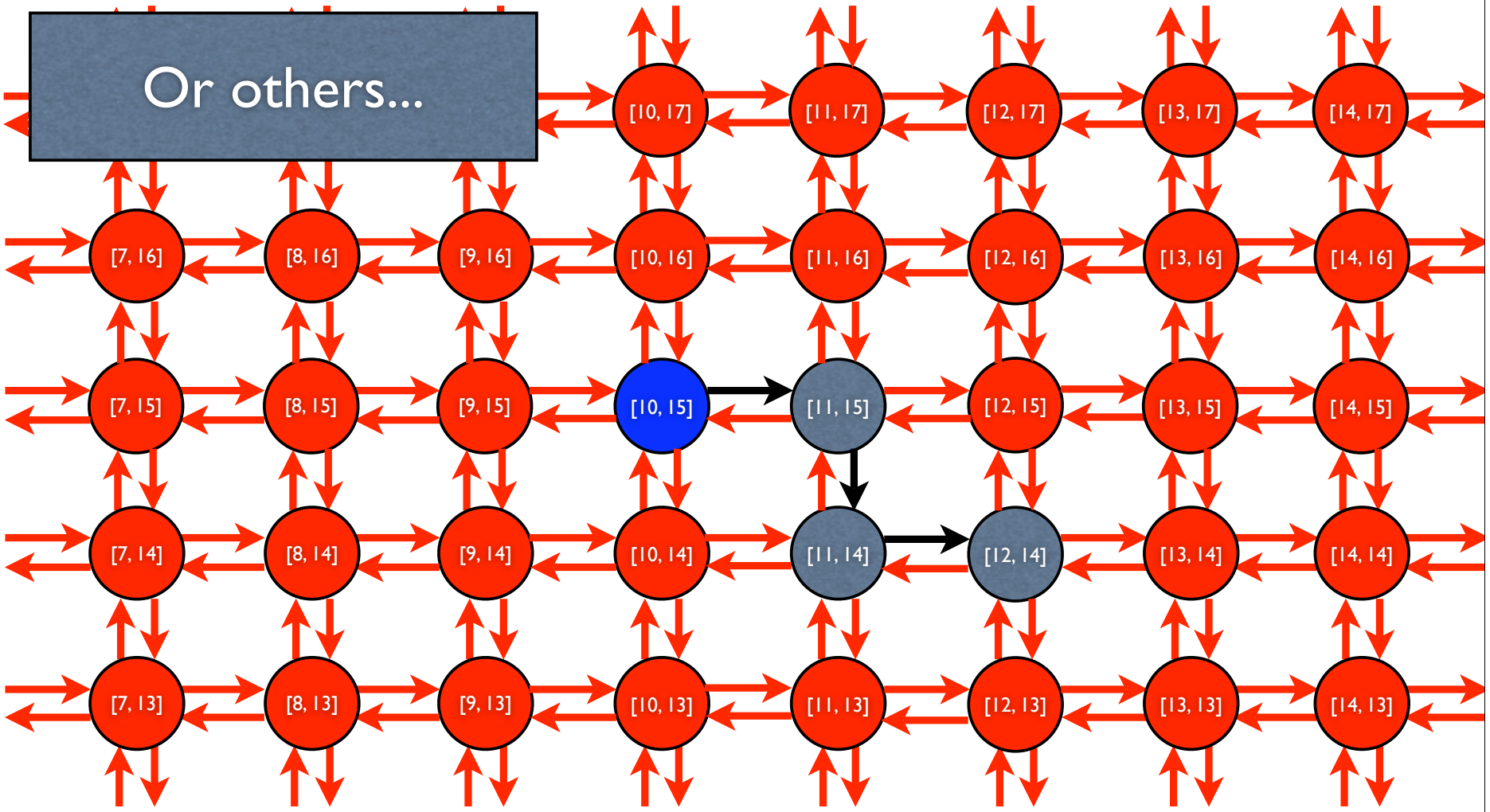
- At any time, the state of the system is *defined* by its integer population vector: $\mathbf{x} \in \mathbb{Z}^N$
- Reactions are transitions from one state to another:
- These reactions are random, others could have occurred:



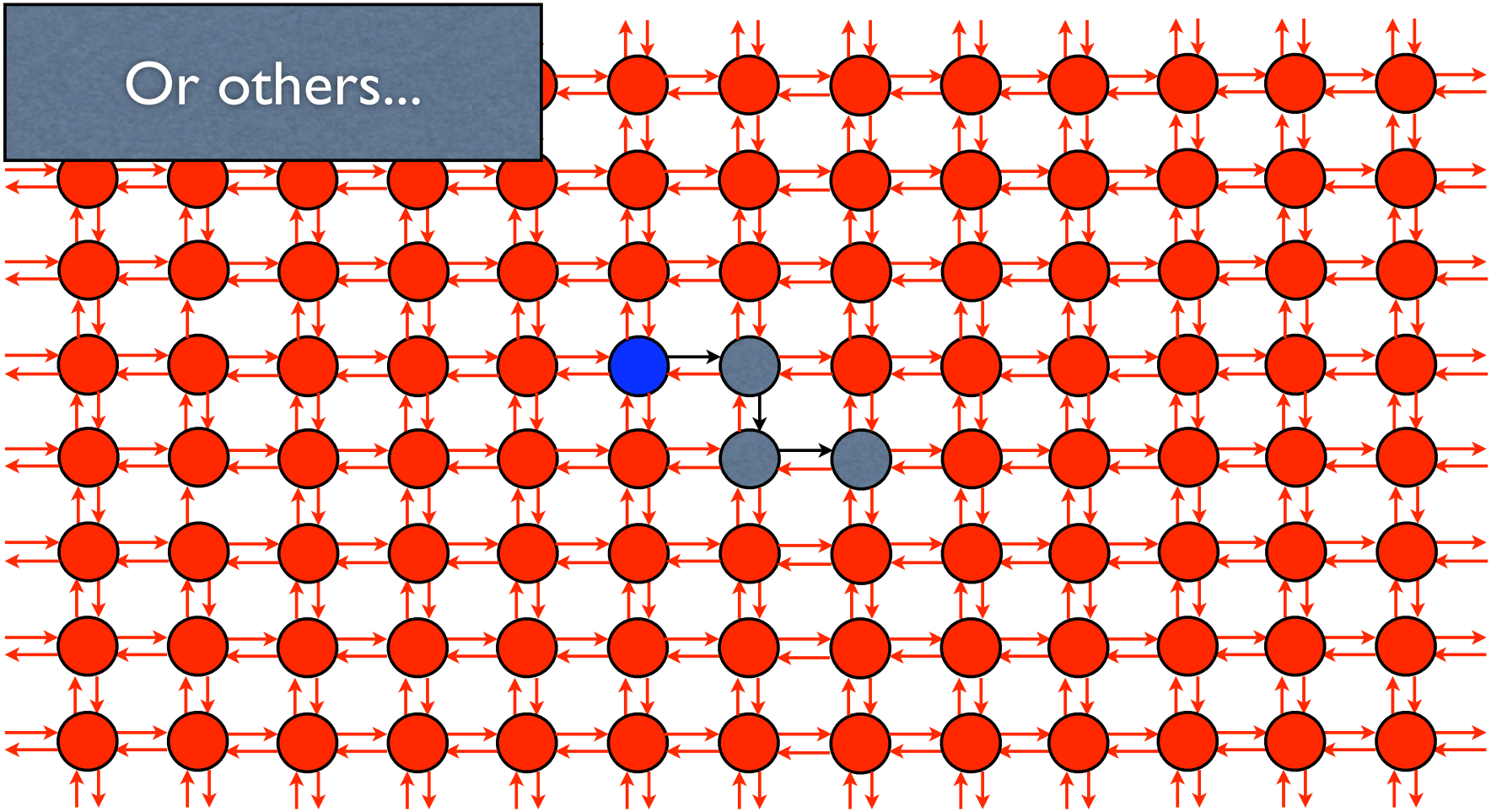
A Jump-Markov description of chemical kinetics



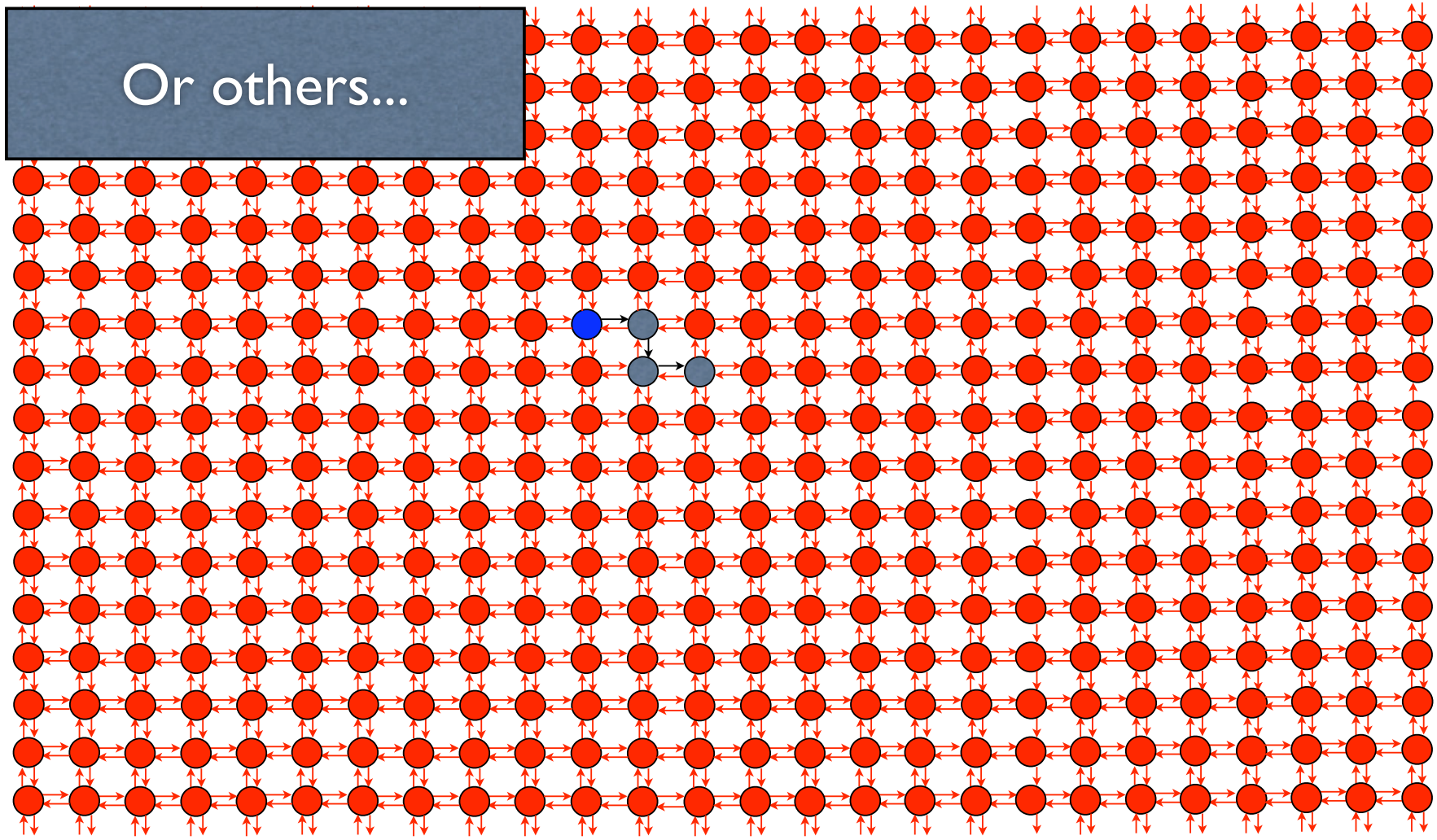
A Jump-Markov description of chemical kinetics



A Jump-Markov description of chemical kinetics



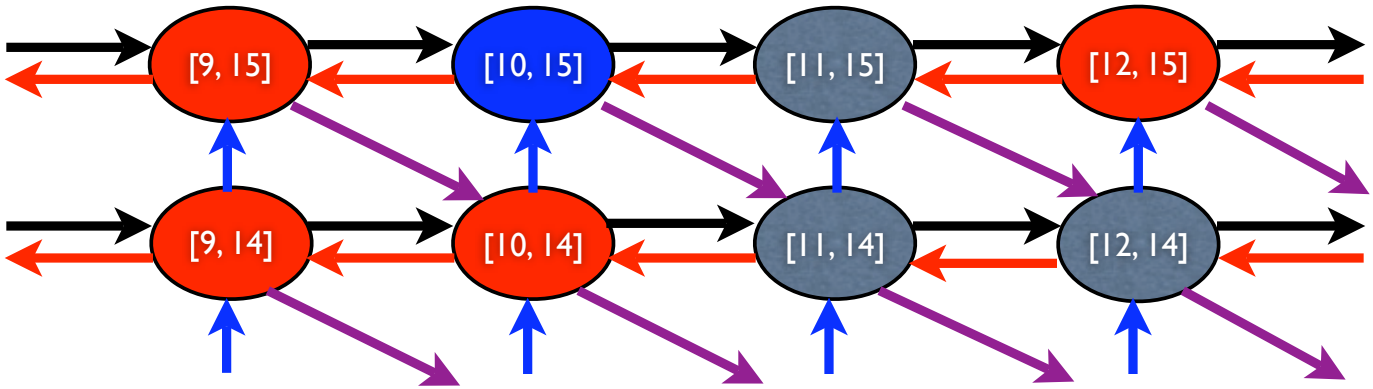
A Jump-Markov description of chemical kinetics



Reaction Stoichiometry

- The Stoichiometric vector, **s**, refers to the relative change in the population vector after a reaction.
- There may be many different reactions for a given stoichiometry.

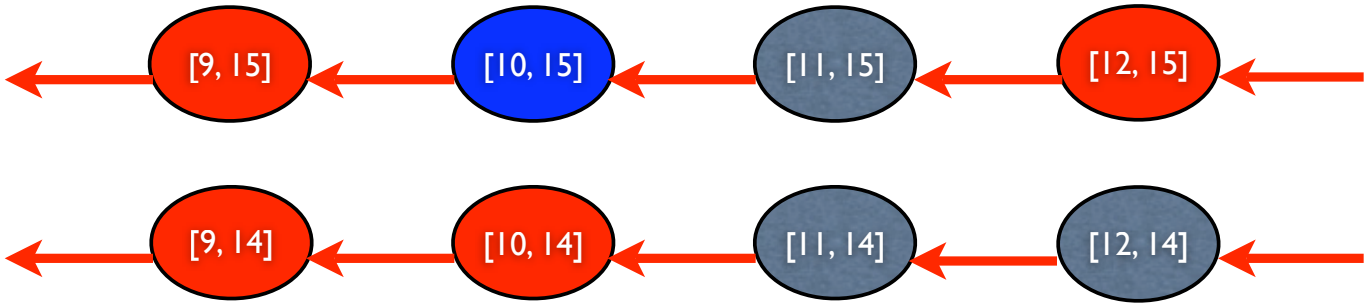
$\mathbf{s}_1 = [1, 0]^T$	$\mathbf{s}_2 = [-1, 0]^T$	$\mathbf{s}_3 = [0, 1]^T$	$\mathbf{s}_4 = [1, -1]^T$
$\mathcal{S}_1 \rightarrow \mathcal{S}_1 + \mathcal{S}_1$	$\mathcal{S}_1 + \mathcal{S}_1 \rightarrow \mathcal{S}_1$	$\mathcal{S}_2 \rightarrow \mathcal{S}_2 + \mathcal{S}_2$	$\mathcal{S}_2 \rightarrow \mathcal{S}_1$
$\mathcal{S}_2 \rightarrow \mathcal{S}_2 + \mathcal{S}_1$	$\mathcal{S}_1 + \mathcal{S}_2 \rightarrow \mathcal{S}_2$	$\mathcal{S}_1 \rightarrow \mathcal{S}_1 + \mathcal{S}_2$	$\mathcal{S}_1 + \mathcal{S}_2 \rightarrow \mathcal{S}_1 + \mathcal{S}_1$
$\emptyset \rightarrow \mathcal{S}_1$	$\mathcal{S}_1 \rightarrow \emptyset$	$\emptyset \rightarrow \mathcal{S}_2$	$\mathcal{S}_2 + \mathcal{S}_2 \rightarrow \mathcal{S}_1 + \mathcal{S}_2$



Reaction Propensities

- The propensity, $\mathbf{w}$, of a reaction is its rate.
- $\mathbf{w}_\mu dt$ is the probability that the μ^{th} reaction will occur in a time step of length dt.
- Typically, propensities depend only upon reactant populations.

$\mathbf{s}_2 = [-1, 0]^T$	$w_2(x_1, x_2)$
$\mathcal{S}_1 + \mathcal{S}_1 \rightarrow \mathcal{S}_1$	$k_1 x_2 (x_1 - 1)/2$
$\mathcal{S}_1 + \mathcal{S}_2 \rightarrow \mathcal{S}_2$	$k_2 x_1 x_2$
$\mathcal{S}_1 \rightarrow \emptyset$	$k_3 x_1$



Markov is a forgetful process

Markov Reaction Times

Probability reaction will occur in $[t, t+\Delta t)$: $w\Delta t + \mathcal{O}(\Delta t)^2$

Probability reaction *will not occur* in $[t, t+\Delta t)$ $1 - w\Delta t + \mathcal{O}(\Delta t)^2$

Probability a reaction *will not occur* in two such time intervals $[t, t+2\Delta t)$: $\left(1 - w\Delta t + \mathcal{O}(\Delta t)^2\right)^2 = 1 - 2w\Delta t + \mathcal{O}(\Delta t)^2$

Suppose that $\tau = K\Delta t$, then the probability that *no reaction will occur* in the interval $[t, t+\tau)$ is

$$\left(1 - w\frac{\tau}{K} + \mathcal{O}(K^{-2})\right)^K$$

Taking the limit as K goes to infinity yields that the probability that *no reaction will occur* in the interval $[t, t+\tau)$ is

$$\lim_{k\to\infty} \left(1 - w\frac{\tau}{K} + \mathcal{O}(K^{-2})\right)^K = \exp(-w\tau)$$

Markov Reaction Times

The probability that a reaction will occur in the interval $[t, t+\tau)$ is $F_T(\tau) = 1 - \exp(-w\tau)$. This is a cumulative distribution.

The density (derivative) of the random number, T, is:

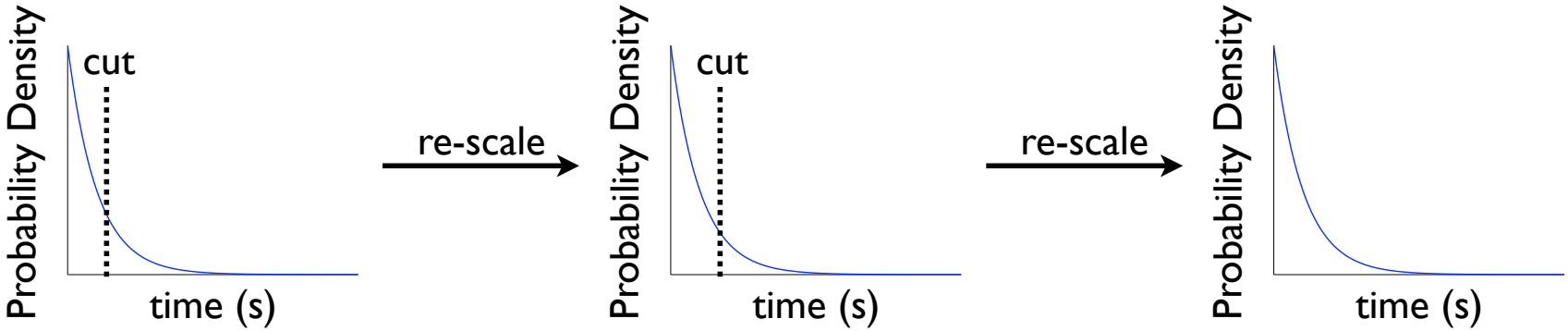
$$f_T(\tau) = \frac{1}{w} \exp(-w\tau)$$

Such a random number is known as an *exponentially* distributed random number.

Notation: $T \in \mathrm{EXP}(\lambda) \rightarrow$ T is an exponentially distributed r.v. with parameter: λ .

Markov Reaction Times

- We have assumed that the system is fully described by the population vectors.
- If no reaction occurs, then nothing will have changed.
- Waiting times must be *memoryless* random variables.



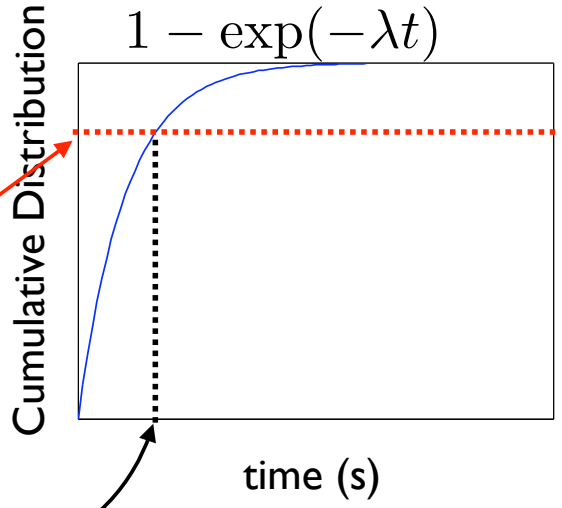
- No matter where we cut and scale the distribution, it must always looks the same.

The exponential is the *only* continuous r.v. with this property.

Generating Reaction Times

- To generate an exponentially distributed random number, all we need is a uniform random number generator.

- Find the cumulative distribution,
$$F(t) = 1 - \exp(-\lambda t)$$
- Generate uniform random number,
$$r \in \mathrm{U}[0, 1]$$
- Find intersection where $F(t) = r$:
$$\tau = \frac{1}{\lambda} \log \frac{1}{1 - r}$$
- This is the time of the next reaction.



The (Chemical) Master Equation

(Forward Kolmorogrov Equation)

The Chemical Master Equation

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 $[t, t+dt] = \mathcal{O}(dt^2)$

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

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

The Chemical Master Equation

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

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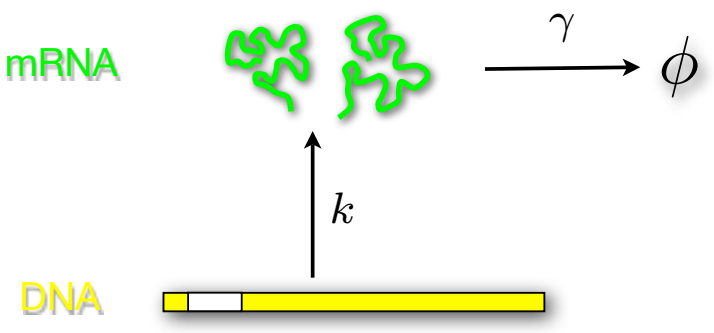
Example: Transcription and degradation of mRNA

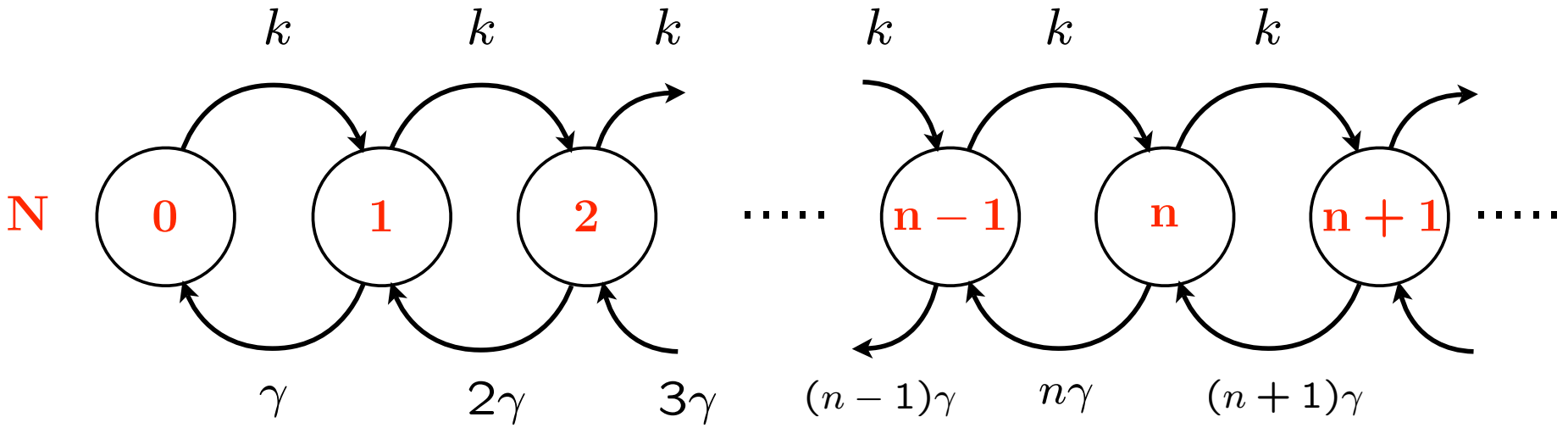
RNA Copy Number as a Random Variable



mRNA copy number $N(t)$ is a random variable

Transcription: Probability a single mRNA is transcribed in time dt is $k\ dt$

Degradation: Probability a single mRNA is degraded in time dt is $n\gamma dt$



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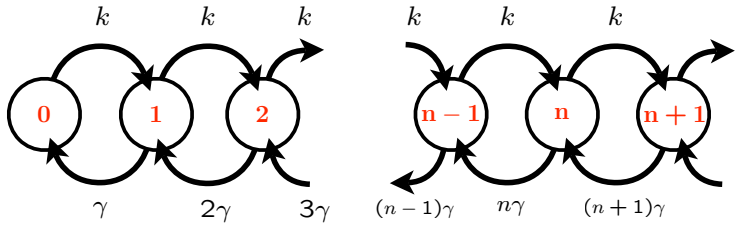
Key Question:



Find $p(n,t)$, the probability that $N(t) = n$.

$$P(n, t+dt) = P(n-1, t) \cdot k dt$$ Prob.$\{N(t) = n-1$ and mRNA created in [t,t+dt)$\}$

$$+ \; P(n+1, t) \cdot (n+1)\gamma dt$$ Prob.$\{N(t) = n+1$ and mRNA degraded in [t,t+dt)$\}$

$$+ \; P(n, t) \cdot (1 - kdt)(1 - n\gamma dt)$$ Prob.$\{N(t) = n$ and mRNA not created nor degraded in [t,t+dt)$\}$

$$P(n, t+dt) - P(n,t) = P(n-1,t)kdt + P(n+1,t)(n+1)\gamma dt - P(n,t)(k + n\gamma)dt + O(dt^2)$$

Dividing by dt and taking the limit as $dt \to 0$

The Chemical Master Equation

$$\frac{d}{dt}P(n,t) = kP(n-1,t) + (n+1)\gamma P(n+1,t) - (k + n\gamma)P(n,t)$$

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mRNA Stationary Distribution

We look for the stationary distribution $P(n,t) = p(n)\ \forall t$

The stationary solution satisfies: $\frac{d}{dt}P(n,t) = 0$

From the Master Equation ...

$$(k + n\gamma)p(n) = kp(n-1) + (n+1)\gamma p(n+1)$$

$n = 0$ $\quad kp(0) = \gamma p(1)$

$n = 1$ $\quad kp(1) = 2\gamma p(2)$

$n = 2$ $\quad kp(2) = 3\gamma p(3)$

$\vdots$

$$kp(n-1) = n\gamma\ p(n)$$

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$kp(n-1) = n\gamma\ p(n)$ We can express $p(n)$ as a function of $p(0)$:

$$\begin{aligned} p(n) &= \frac{k}{\gamma}\frac{1}{n}\,p(n-1) \\ &= \left(\frac{k}{\gamma}\right)^2 \frac{1}{n}\,\frac{1}{n-1}\,p(n-2) \\ &\vdots \\ &= \left(\frac{k}{\gamma}\right)^n \frac{1}{n!}\,p(0) \end{aligned}$$

We can solve for $p(0)$ using the fact $\sum_{n=0}^{\infty} p(n) = 1$

$$\begin{aligned} 1 &= \sum_{n=0}^{\infty}\left(\frac{k}{\gamma}\right)^n \frac{1}{n!}\,p(0) \\ &= e^{k/\gamma}\,p(0) \quad \Longrightarrow \quad p(0) = e^{-k/\gamma} \end{aligned}$$

$$p(n) = e^{-a}\frac{a^n}{n!} \qquad a = \frac{k}{\gamma}$$ **Poisson Distribution**

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We can compute the mean and variance of the Poisson RV $\bar{N}$ with density $p(n) = e^{-a}\frac{a^n}{n!}$:

$$\mu = E[\bar{N}] = \sum_{n=0}^{\infty} np(n) = e^{-a} \sum_{n=0}^{\infty} n\frac{a^n}{n!} = a$$

The second moment

$$E[\bar{N}^2] = \sum_{n=0}^{\infty} n^2 p(n) = a^2 + a$$

Therefore,

$$\sigma^2 = E[\bar{N}^2] - E[\bar{N}]^2 = a$$

mean = variance = a

The coefficient of variation $C_v = \sigma/\mu$ is

$$C_v = \frac{1}{\sqrt{a}} = \frac{1}{\sqrt{\mu}}$$

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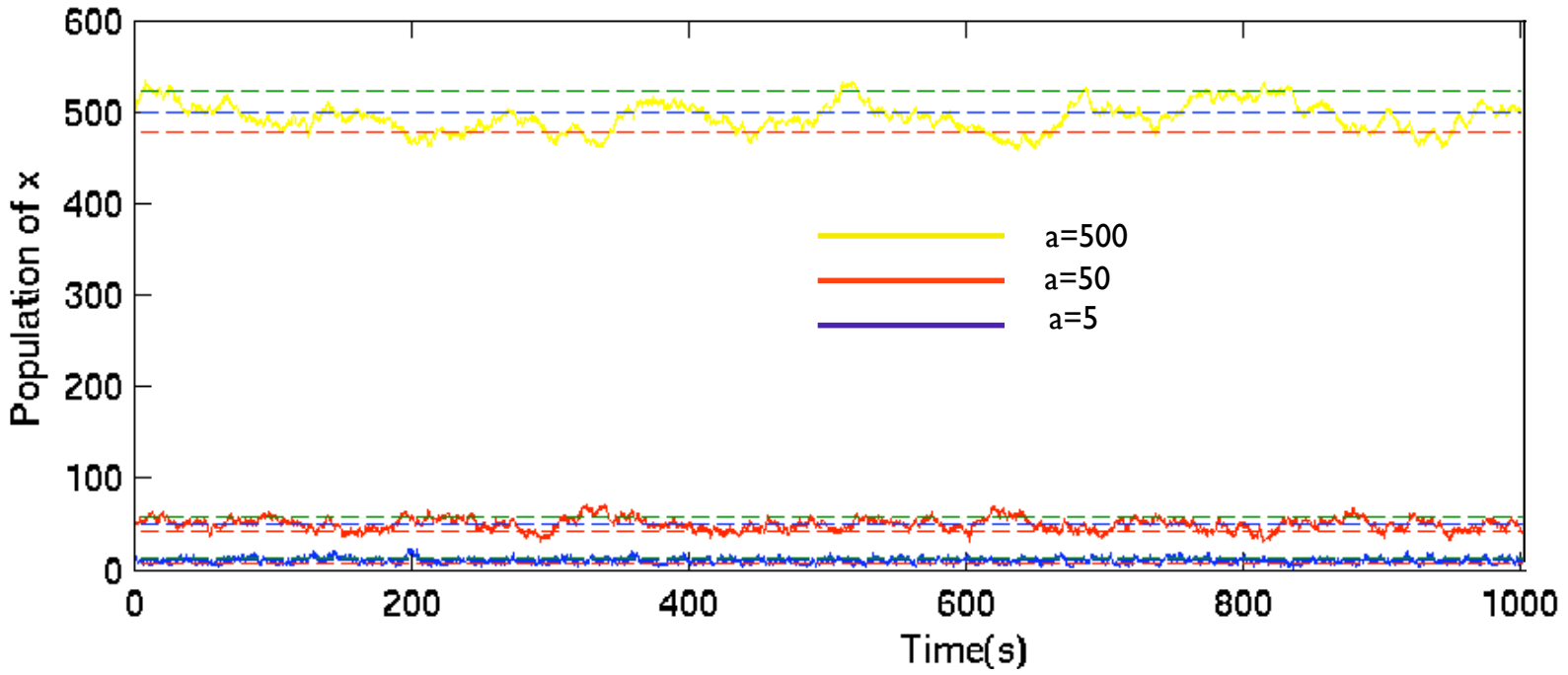
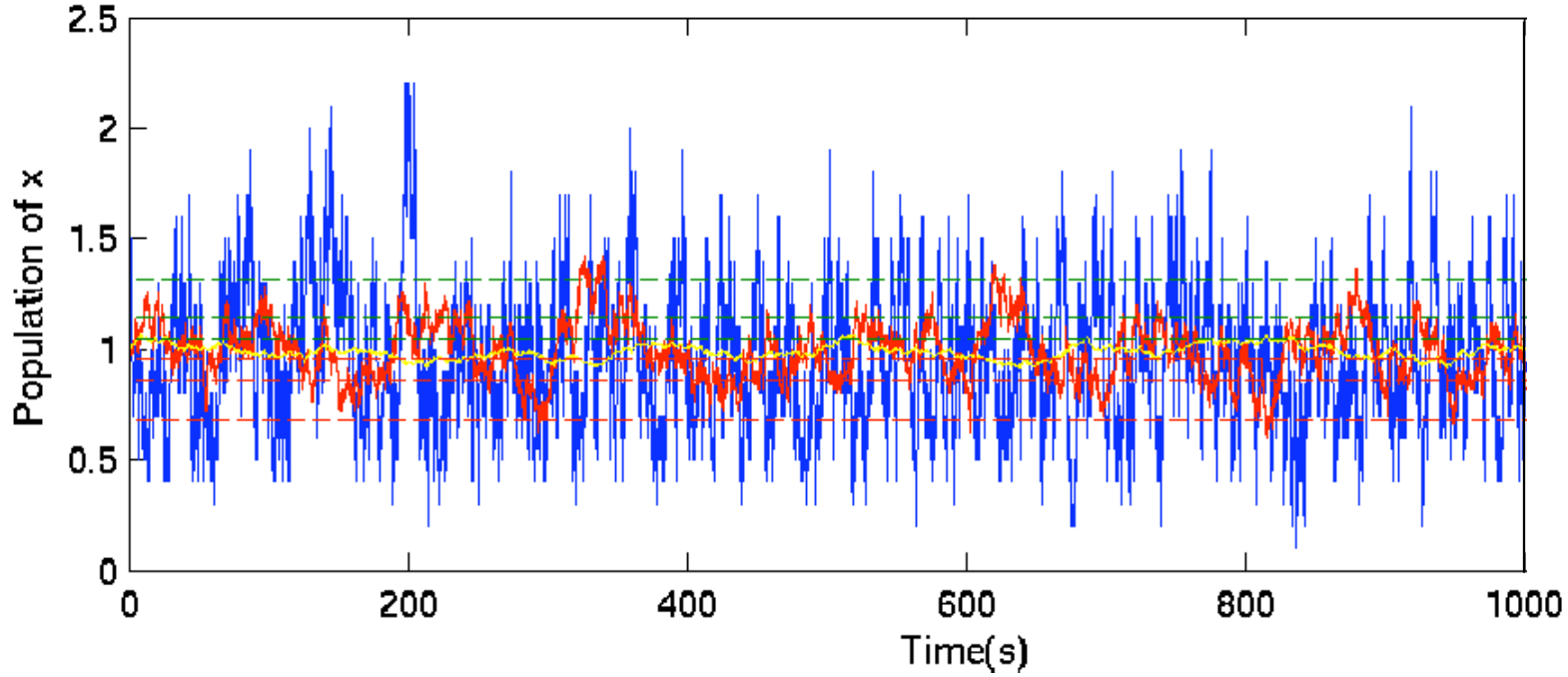

600
500
400
300
200
100
0
Population of x
a=500
a=50
a=5
0
200
400
600
800
1000
Time(s)


2.5
2
1.5
1
0.5
0
Population of x
0
200
400
600
800
1000
Time(s)

The Relationship of Deterministic to Stochastic Biochemical Processes.

Relationship of Stochastic and Deterministic Descriptions

Given N species $X_1, \ldots, X_N$ and M elementary reactions. Let $\Phi_i := [X_i]$.

A deterministic description can be obtained from mass-action kinetics:

$$\frac{d\Phi}{dt} = Sf(\Phi)$$

where $f(\cdot)$ is at most a second order monomial. It depends on the type of reactions and their rates.

Example:

$$\begin{aligned} A + B &\xrightarrow{k_1} C \\ A &\xrightarrow{k_2} B \end{aligned}$$

$$\begin{aligned} \frac{d\Phi_A}{dt} &= -k_1\Phi_A\Phi_B - k_2\Phi_A \\ \frac{d\Phi_B}{dt} &= -k_1\Phi_A\Phi_B + k_2\Phi_A \\ \frac{d\Phi_C}{dt} &= k_1\Phi_A\Phi_B \end{aligned}$$

or

$\frac{d\Phi}{dt} = Sf(\Phi)$ where

$$S = \begin{bmatrix} -1 & -1 \\ -1 & 1 \\ 1 & 0 \end{bmatrix}, \quad f(\Phi) = \begin{bmatrix} k_1\Phi_A\Phi_B \\ k_2\Phi_A \end{bmatrix}$$

Relationship of Stochastic and Deterministic Descriptions

Define $X^{\Omega}(t) = \frac{X(t)}{\Omega}$.

Question: How does $X^{\Omega}(t)$ relate to $\Phi(t)$?

Fact: Let $\Phi(t)$ be the deterministic solution to the reaction rate equations

$$\frac{d\Phi}{dt} = Sf(\Phi), \ \Phi(0) = \Phi_0.$$

Let $X^{\Omega}(t)$ be the stochastic representation of the same chemical systems with $X^{\Omega}(0) = \Phi_0$. Then for every $t \geq 0$:

$$\lim_{\Omega \to \infty} \sup_{s \leq t} \left| X^{\Omega}(s) - \Phi(s) \right| = 0 \ a.s.$$

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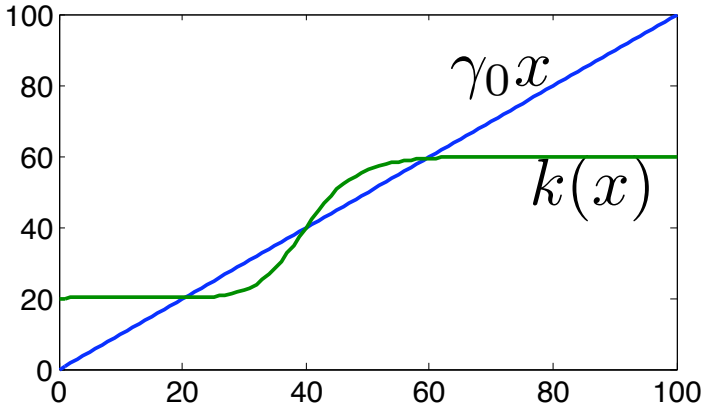
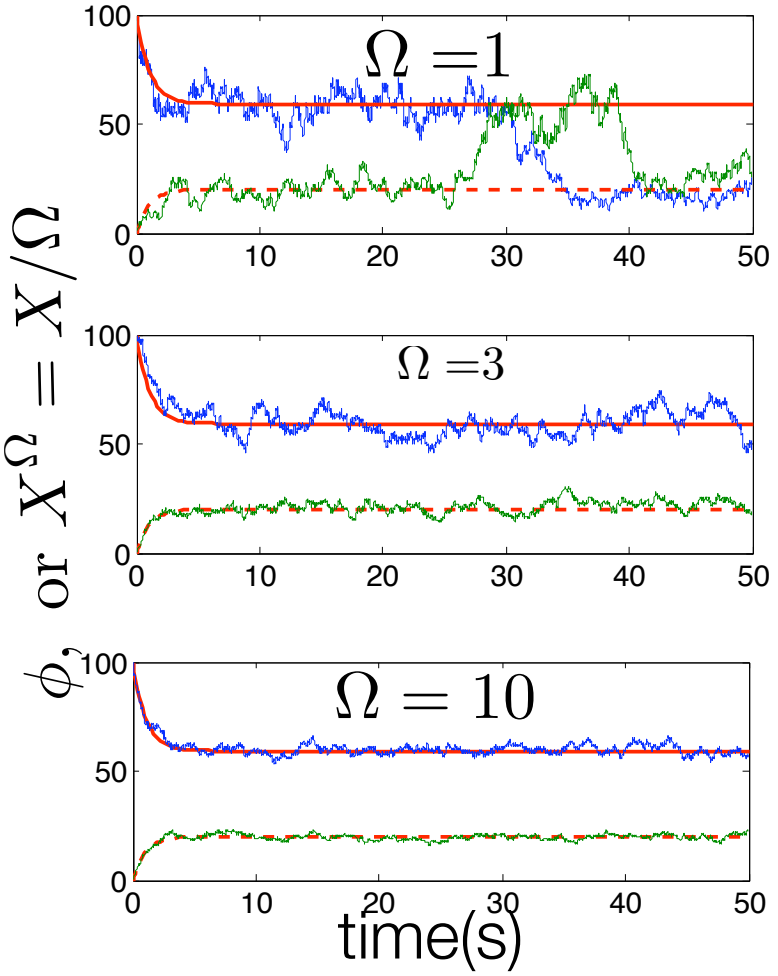
x produced with rate $k(x)$
and degraded with rate $\gamma_0 x$.





$$w_1(\phi) = \gamma\phi$$

$$w_2(\phi) = \left(20 + 40\frac{\phi^{10}}{40^{10} + \phi^{10}}\right)$$

Deterministic

$$w_1(X) = \Omega\gamma_0 X/\Omega = \gamma_0 X$$

$$w_2(X) = \Omega\left(20 + 40\frac{(X/\Omega)^{10}}{40^{10} + (X/\Omega)^{10}}\right)$$

Stochastic

Moment Computations

- Affine Propensity
- Moment Closures

Moment Computations

For the first moment $E[X_i]$, multiply the CME by x_i and sum over all $(x_1, \ldots, x_N) \in \mathbb{N}^N$

For the second moment $E[X_i X_j]$, multiply the CME by $x_i x_j$ and sum over all $(x_1, \ldots, x_N) \in \mathbb{N}^N$

$$\frac{dE[X_i]}{dt} = \sum_{k=1}^{M} s_{ik} E[w_k(X)]$$

$$\frac{dE[X_i X_j]}{dt} = \sum_{k=1}^{M} (s_{ik} E[X_j w_k(X)] + E[X_i w_k(X)] s_{jk} + s_{ik} s_{jk} E[w_k(X)])$$

Let $w(x) = [w_1(x), \ldots, w_M(x)]^T$

In matrix notation:

$$\frac{dE[X]}{dt} = SE[w(X)]$$

$$\frac{dE[XX^T]}{dt} = SE[w(X)X^T] + E[w(X)X^T]^T S^T + S\{diagE[w(X)]\}S^T$$

Affine Propensity

Suppose the propensity function is affine:

$$w(x) = Wx + w_0, \qquad (W \text{ is } N \times N,\ w_0 \text{ is } N \times 1)$$

Then $E[w(X)] = WE[X] + w_0$, and $E[w(X)X^T] = WE[XX^T] + w_0 E[X^T]$.

This gives us the moment equations:

$$\begin{aligned} \frac{d}{dt}E[X] &= SWE[X] + Sw_0 && \text{First Moment} \\ \frac{d}{dt}E[XX^T] &= SWE[XX^T] + E[XX^T]W^T S^T + S\ diag(WE[X] + w_0)S^T \\ &+ Sw_0 E[X^T] + E[X]w_0^T S^T && \text{Second Moment} \end{aligned}$$

These are linear ordinary differential equations and can be easily solved!

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Affine Propensity (cont.)

Define the covariance matrix $\Sigma = E[(X - E[X])(X - E(X)]^T]$.
We can also compute covariance equations:

$$\frac{d}{dt}\Sigma = SW\Sigma + \Sigma W^T S^T + S\ diag(WE[X] + w_0)S^T$$

Steady-state Case

The steady-state moments and covariances can be obtained by solving linear algebraic equations:

Let $\bar{X} = \lim_{t\to\infty} E[X(t)]$ and $\bar{\Sigma} = \lim_{t\to\infty} \Sigma(t)$.

Then

$$SW\bar{X} = -Sw_0$$

$$SW\bar{\Sigma} + \bar{\Sigma}W^T S^T + S\ diag(W\bar{X} + w_0)S^T = 0$$

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Fluctuations Arise from Noise Driven Dynamics

Define $A = SW$, and $B = S\sqrt{diag(W\bar{X} + w_0)}$.

The steady-state covariances equation

$$SW\bar{\Sigma} + \bar{\Sigma}W^T S^T + S\ diag(W\bar{X} + w_0)S^T = 0$$

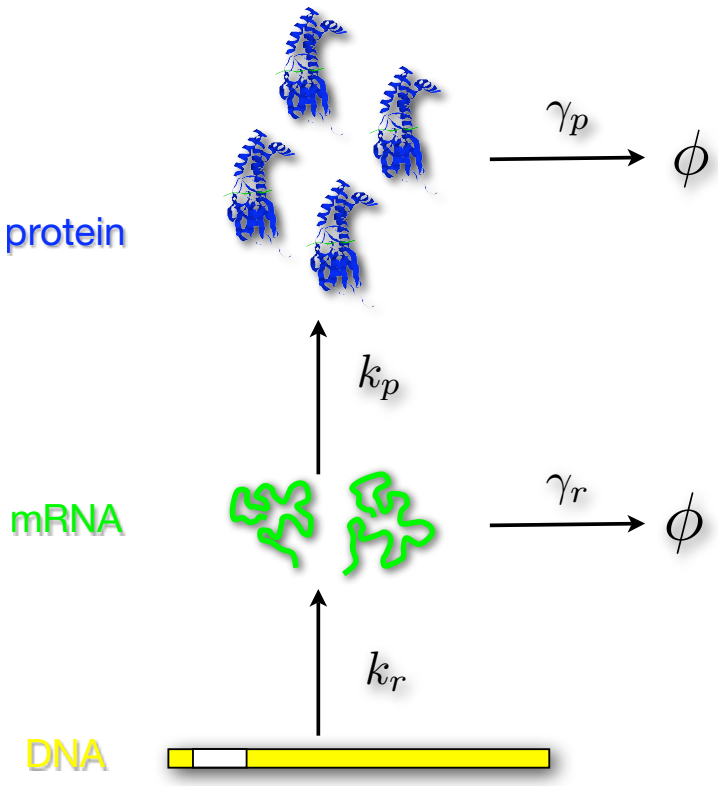
becomes

$$A\bar{\Sigma} + \bar{\Sigma}A^T + BB^T = 0 \qquad \text{Lyapunov Equation}$$

Slide Contributed by Mustafa Khammash

Example: Gene Expression

Application to Gene Expression



Reactants

$X_1(t)$ is # of mRNA; $X_2(t)$ is # of protein

Reactions

$$R_1 : \phi \xrightarrow{k_r} mRNA$$

$$R_2 : mRNA \xrightarrow{\gamma_r} \phi$$

$$R_3 : mRNA \xrightarrow{k_p} protein + mRNA$$

$$R_4 : protein \xrightarrow{\gamma_p} \phi$$

Stoichiometry and Propensity

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

$$w(X) = \begin{bmatrix} k_r \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & 0 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_{W} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_r \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

Steady-State Moments

$$A = SW = \begin{bmatrix} -\gamma_r & 0 \\ k_p & -\gamma_p \end{bmatrix}, \qquad Sw_0 = \begin{bmatrix} k_r \\ 0 \end{bmatrix}$$

$$\bar{X} = -A^{-1} S w_0 = \begin{bmatrix} \frac{k_r}{\gamma_r} \\ \\ \frac{k_p k_r}{\gamma_p \gamma_r} \end{bmatrix}$$

Steady-State Covariance

$$BB^T = S\ diag(W\bar{X} + w_0) S^T = \begin{bmatrix} 2k_r & 0 \\ 0 & \frac{2k_p k_r}{\gamma_r} \end{bmatrix}$$

The steady-state covariances equation

$$A\bar{\Sigma} + \bar{\Sigma} A^T + BB^T = 0 \qquad \text{Lyapunov Equation}$$

can be solved algebraically for $\bar{\Sigma}$.

$$\bar{\Sigma} = \begin{bmatrix} \frac{k_r}{\gamma_r} & \frac{k_p k_r}{\gamma_r(\gamma_r+\gamma_p)} \\ \\ \frac{k_p k_r}{\gamma_r(\gamma_r+\gamma_p)} & \frac{k_p k_r}{\gamma_p \gamma_r}(1 + \frac{k_p}{\gamma_r+\gamma_p}) \end{bmatrix}$$

Coefficients of Variation

$$C_{vr}^2 = \frac{1}{\frac{k_r}{\gamma_r}} = \frac{1}{\bar{X}_1}$$

$$C_{vp}^2 = \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left(1 + \frac{k_p}{\gamma_r + \gamma_p}\right) = \frac{1}{\bar{X}_2} \left(1 + \frac{k_p}{\gamma_r + \gamma_p}\right)$$

Question: Does a large $\bar{X}_2$ imply a small C_{vp}?

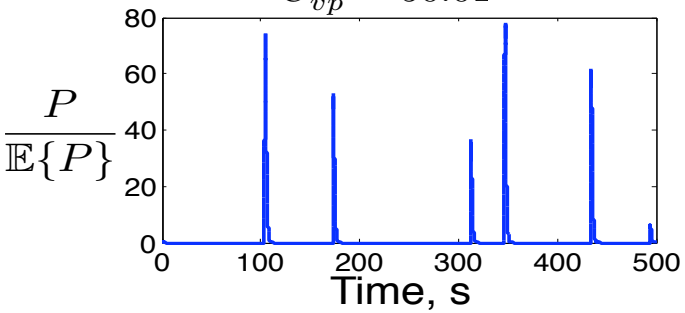
$$\begin{aligned} C_{vp}^2 &= \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left(1 + \frac{k_p}{\gamma_r + \gamma_p}\right) \\ &\geq \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left(\frac{k_p}{\gamma_r + \gamma_p}\right) = \frac{\gamma_r \gamma_p}{k_r} \cdot \frac{1}{\gamma_r + \gamma_p} \end{aligned}$$

$\bar{X}_2 = \frac{k_r k_p}{\gamma_r \gamma_p}$, which can be chosen *independently* from C_{vp}.

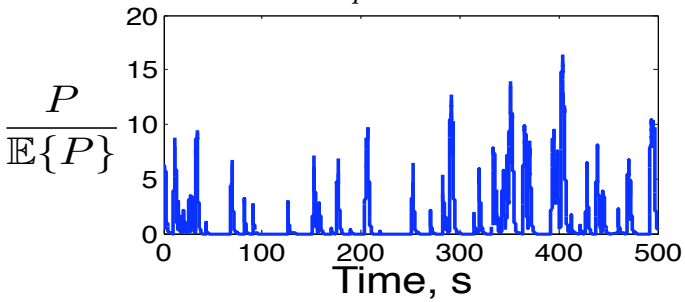
Large mean does not imply small fluctuations!

$$\mathbb{E}\{P\} = 100, \quad \gamma_r = \gamma_p = 1$$

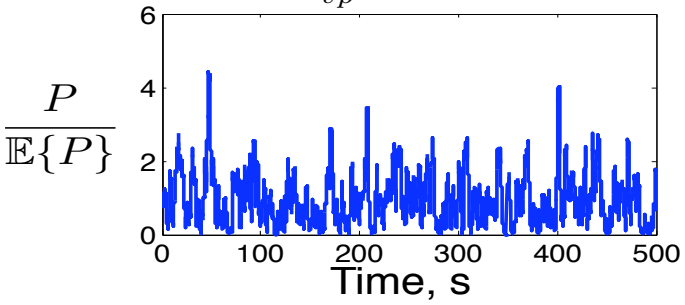
$k_r = 0.01 \quad k_p = 10,000$
$C_{vp}^2 = 50.01$



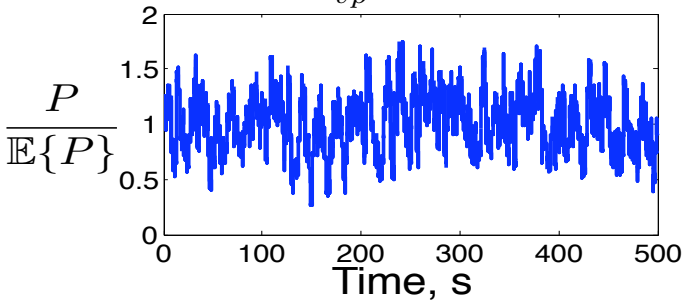
$k_r = 0.1 \quad k_p = 1000$
$C_{vp}^2 = 5.01$



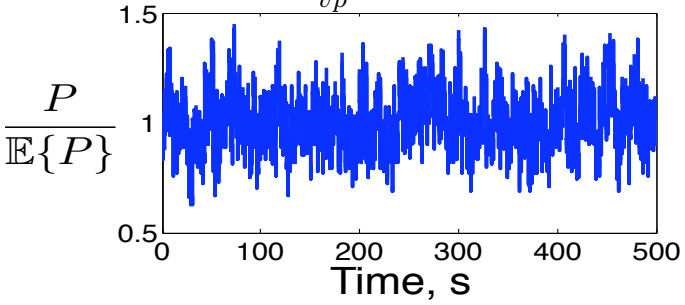
$k_r = 1 \quad k_p = 100$
$C_{vp}^2 = 0.51$



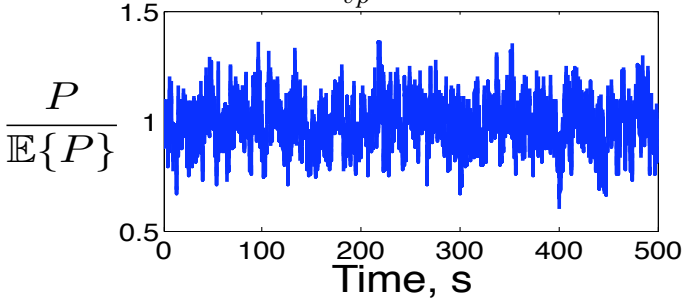
$k_r = 10 \quad k_p = 10$
$C_{vp}^2 = 0.06$



$k_r = 100 \quad k_p = 1$
$C_{vp}^2 = 0.015$



$k_r = 1000 \quad k_p = 0.1$
$C_{vp}^2 = 0.0105$



Moment Computations

- Affine Propensity
- Moment Closures

Moment Closures.

From before, the mean level changes as:

$$\frac{dE[X]}{dt} = SE[w(X)]$$

- When Second and Higher order terms exist in the propensity functions, each moment depends upon higher moments.
  - For example, if $w(X) = \mathbf{u}X^T X\mathbf{v}$, then

$$\frac{dE[X]}{dt} = S\mathbf{u}E[X^T X]\mathbf{v}$$

- The first moment depends upon the second; the second upon the third; and so on.

- Moment closures are approximations that attempt to remove this dependence.

Moment Closures.

$$\frac{dE[X_i]}{dt} = \sum_{k=1}^{M} s_{ik} E[w_k(X)]$$

$$\frac{dE[X_i X_j]}{dt} = \sum_{k=1}^{M} (s_{ik} E[X_j w_k(X)] + E[X_i w_k(X)] s_{jk} + s_{ik} s_{jk} E[w_k(X)])$$

$$\frac{d}{dt}\begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\},\{\sigma_{ij}\}) + u_1(\{\sigma_{ijk}\},\{\sigma_{ijkl}\},\ldots) \\ f_2(\{\mu_i\},\{\sigma_{ij}\}) + u_2(\{\sigma_{ijk}\},\{\sigma_{ijkl}\},\ldots) \end{bmatrix},$$

$$\frac{d}{dt}\begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\},\{\sigma_{ij}\}) + \widehat{u}_1(\{\mu_i\},\{\sigma_{ij}\}) \\ f_2(\{\mu_i\},\{\sigma_{ij}\}) + \widehat{u}_2(\{\mu_i\},\{\sigma_{ij}\}) \end{bmatrix},$$

where the choice of $\widehat{u}_1$ and $\widehat{u}_2$
depends upon the chosen moment closure.

Gaussian Moment Closure

- If one assumes that the distributions are Gaussian, then the closure is simple:

$$\sigma_{ijk} = \mathbb{E}\{(X_i - \mathbb{E}\{X_i\})(X_j - \mathbb{E}\{X_j\})(X_k - \mathbb{E}\{X_k\})\} = 0$$

- which yields:

$$\begin{aligned}\mathbb{E}\{(X_i X_j X_k\} = &-\mathbb{E}\{X_i X_j\}\mathbb{E}\{X_k\} - \mathbb{E}\{X_j X_k\}\mathbb{E}\{X_i\} \\ &-\mathbb{E}\{X_k X_i\}\mathbb{E}\{X_j\} + 2\mathbb{E}\{X_i\}\mathbb{E}\{X_j\}\mathbb{E}\{X_k\}\end{aligned}$$

- Higher moments are easy to derive with a moment generating function:

$$M_{\mathbf{x}}(\mathbf{t}) = \exp\left(\mu^T \mathbf{t} + 1/2 \mathbf{t}^T \mathbf{\Sigma} \mathbf{t}\right),$$

$$\mathbb{E}\{x_1^{n_1} \dots x_4^{n_4}\} = \left. \frac{d^{n_1+\dots+n_4}}{dx_1^{n_1} \dots dx_4^{n_4}} M_x(\mathbf{t}) \right|_{\mathbf{t}=\mathbf{0}}.$$

Many other closures are possible:

- If one assumes that the distributions are Log-Normal, a different closure is used:

$$\mathbb{E}[X_i X_j X_k] = \frac{\mathbb{E}[X_i X_j]\mathbb{E}[X_j X_k]\mathbb{E}[X_i X_k]}{\mathbb{E}[X_i]\mathbb{E}[X_j]\mathbb{E}[X_k]}.$$

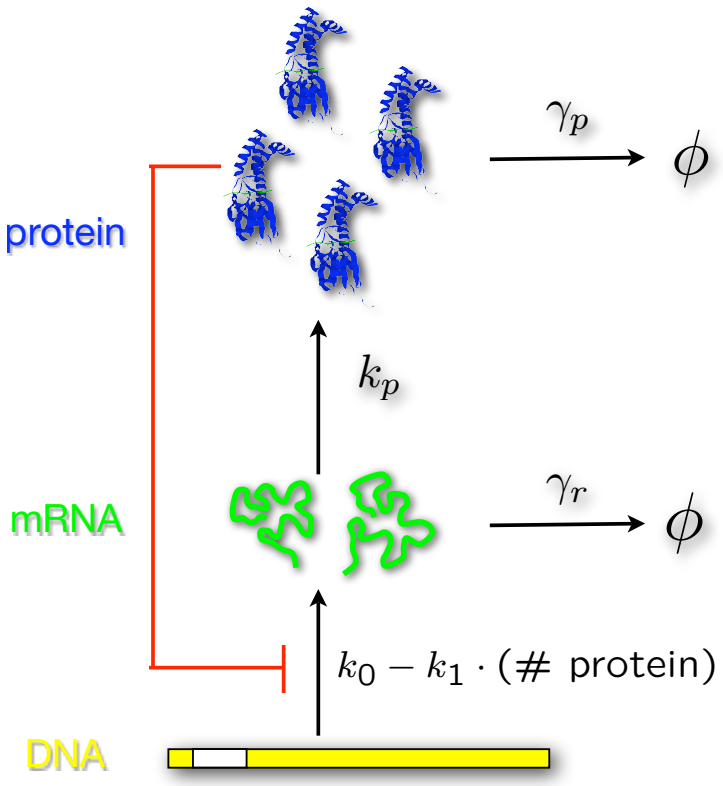
- One of the most common closures is the Linear Noise Approximation.
- In this, all moments are written in terms of themselves and lower moments:
  - the mean is set equal to the deterministic process.
  - the second moments are assumed to be gaussian, and depend upon the mean and itself.

$$\frac{d}{dt}\begin{bmatrix} \{\mu_i\} \\ \{\sigma_{ij}\} \end{bmatrix} = \begin{bmatrix} f_1(\{\mu_i\}) \\ f_2(\{\mu_i, \{\sigma_{ij}\}) \end{bmatrix},$$

Noise Suppression and Exploitation (Examples)

- Feedback for Noise Suppression
- Stochastic Focussing
- Stochastic Switches

Noise Attenuation through Negative Feedback



Reactants

$X_1(t)$ is # of mRNA; $X_2(t)$ is # of protein

Reactions

$$R_1 : \phi \xrightarrow{k_r} mRNA \qquad k_r = k_0 - k_1 \cdot (\#\ \text{protein})$$

$$R_2 : mRNA \xrightarrow{\gamma_r} \phi$$

$$R_3 : mRNA \xrightarrow{k_p} protein + mRNA$$

$$R_4 : protein \xrightarrow{\gamma_p} \phi$$

Stoichiometry and Propensity

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

$$w(X) = \begin{bmatrix} k_0 - k_1 X_2 \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & -k_1 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_{W} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

Steady-State Moments

$$A = SW = \begin{bmatrix} -\gamma_r & -k_1 \\ k_p & -\gamma_p \end{bmatrix}, \qquad Sw_0 = \begin{bmatrix} k_0 \\ 0 \end{bmatrix}$$

$$\bar{X} = -A^{-1} S w_0 = \begin{bmatrix} \dfrac{\frac{k_0}{\gamma_r}}{1+\frac{k_1 k_p}{\gamma_p \gamma_r}} \\ \\ \dfrac{\frac{k_0 k_p}{\gamma_r \gamma_p}}{1+\frac{k_1 k_p}{\gamma_p \gamma_r}} \end{bmatrix} =: \begin{bmatrix} \mu_r \\ \mu_p \end{bmatrix}$$

Steady-State Covariance

$$BB^T = S\ diag(W\bar{X} + w_0)S^T = \begin{bmatrix} k_0 + \gamma_r \mu_r - k_1 \mu_p & 0 \\ 0 & k_p \mu_r + \gamma_p \mu_p \end{bmatrix}$$

The steady-state covariances equation

$$A\bar{\Sigma} + \bar{\Sigma} A^T + BB^T = 0 \qquad \text{Lyapunov Equation}$$

can be solved algebraically for $\bar{\Sigma}$.

$$\bar{\Sigma}_{22} = \sigma_p^2 = \left[\frac{1-\phi}{1+b\phi} \cdot \frac{b}{1+\eta} + 1 \right] \mu_p \qquad \text{where } \phi = \frac{k_1}{\gamma_p},\ b = \frac{k_p}{\gamma_r},\ \eta = \frac{\gamma_p}{\gamma_r}$$

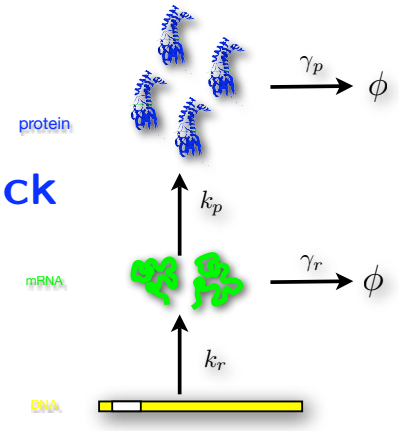
Feedback vs. No Feedback

In order to compare the noise in the two cases, we must ensure that both configuations have the same mean!

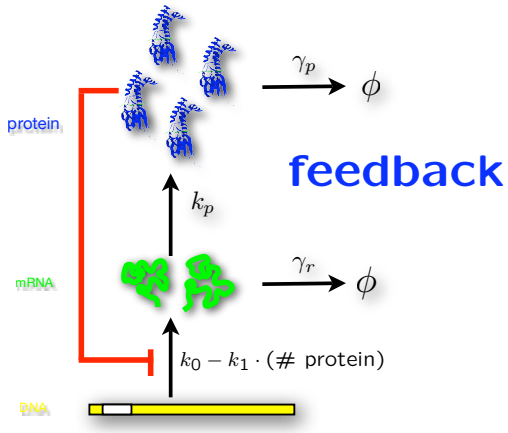
Impose the constraint: $\mu_p^{FB} = \mu_p^{NFB} =: \mu_p^*$

This may be achieved by choosing $k_0 = k_r + k_1 \mu_p^{NFB}$.

no feedback



feedback



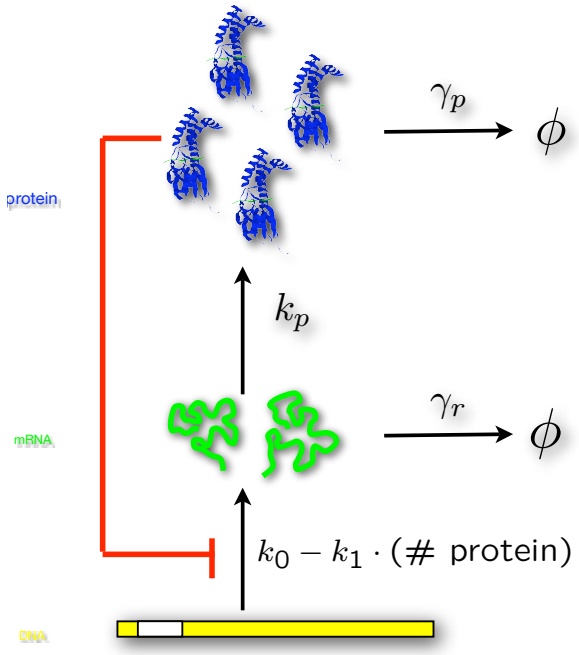
Mean μ_p^* μ_p^*

Variance $\left[\frac{b}{1+\eta} + 1\right] \mu_p^*$ $\left[\frac{1-\phi}{1+b\phi} \cdot \frac{b}{1+\eta} + 1\right] \mu_p^*$ where $\phi = \frac{k_1}{\gamma_p}$

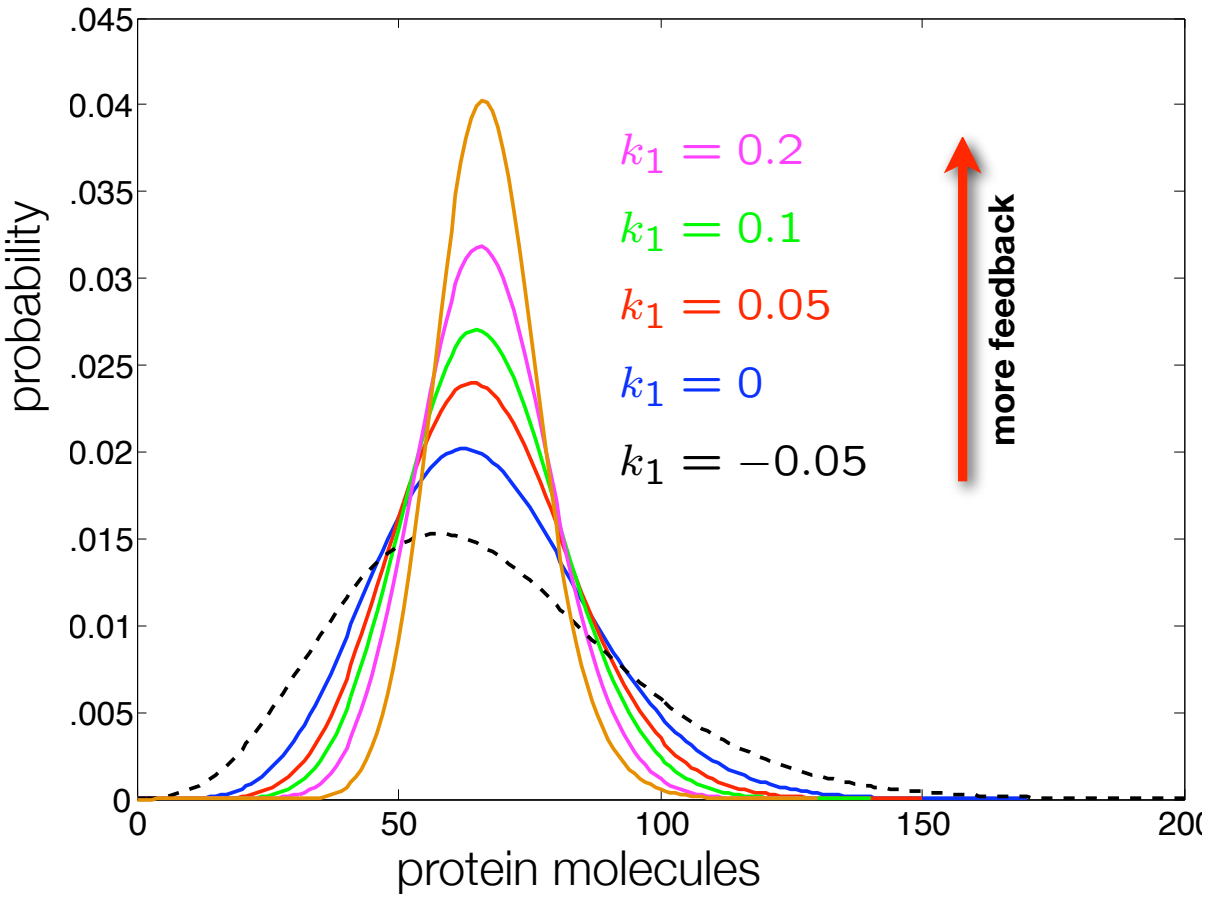
< 1

Protein variance is always smaller with negative feedback!

Example



$\gamma_p = \gamma_r = 1 \qquad k_p = 10;$



Note that these distributions are NOT Gaussian.

Exploiting the Noise:
Failure of the linear noise approximation

$$\phi \underset{k_a S}{\overset{k}{\rightleftharpoons}} I \xrightarrow{k_p} P \xrightarrow{1} \phi$$

$$\phi \underset{k_d}{\overset{k_s}{\rightleftharpoons}} S$$

may be approximated by

$$\phi \xrightarrow{kq} P \xrightarrow{1} \phi$$

$$q = \frac{1}{1 + \frac{n}{\Omega K}} \qquad K = k_p/k_a$$

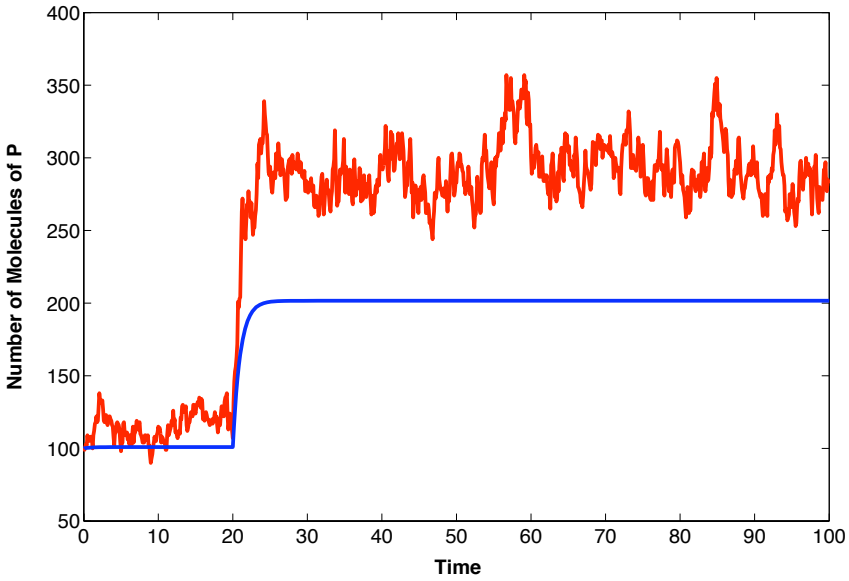
n is #S

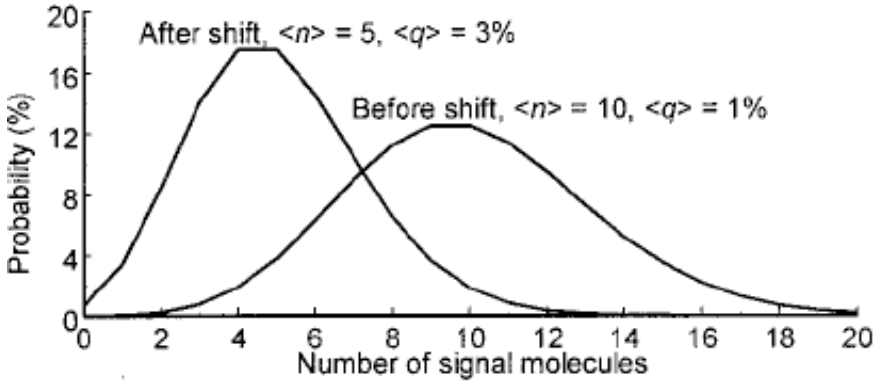
convex

From Jensen's Inequality:

$$E[q] = E\left[\frac{1}{1 + \frac{n}{\Omega K}}\right] \geq \frac{1}{1 + \frac{E[n]}{\Omega K}}$$

- Noise *enhances* signal!





Johan Paulsson , Otto G. Berg , and Måns Ehrenberg, PNAS 2000