Stochastic Gene Expression: Modeling, Analysis, and Identification

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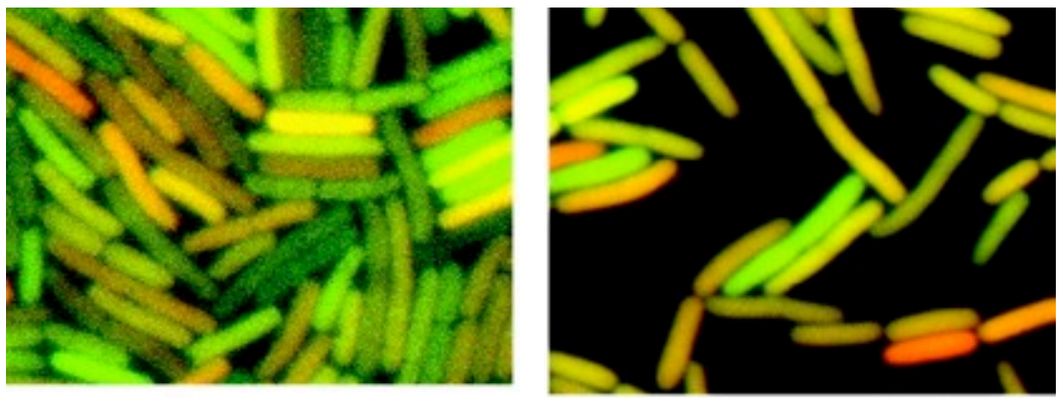
Stochastic Influences on Phenotype

Fingerprints of identical twins

J. Raser and E. O'Shea, Science, 1995.

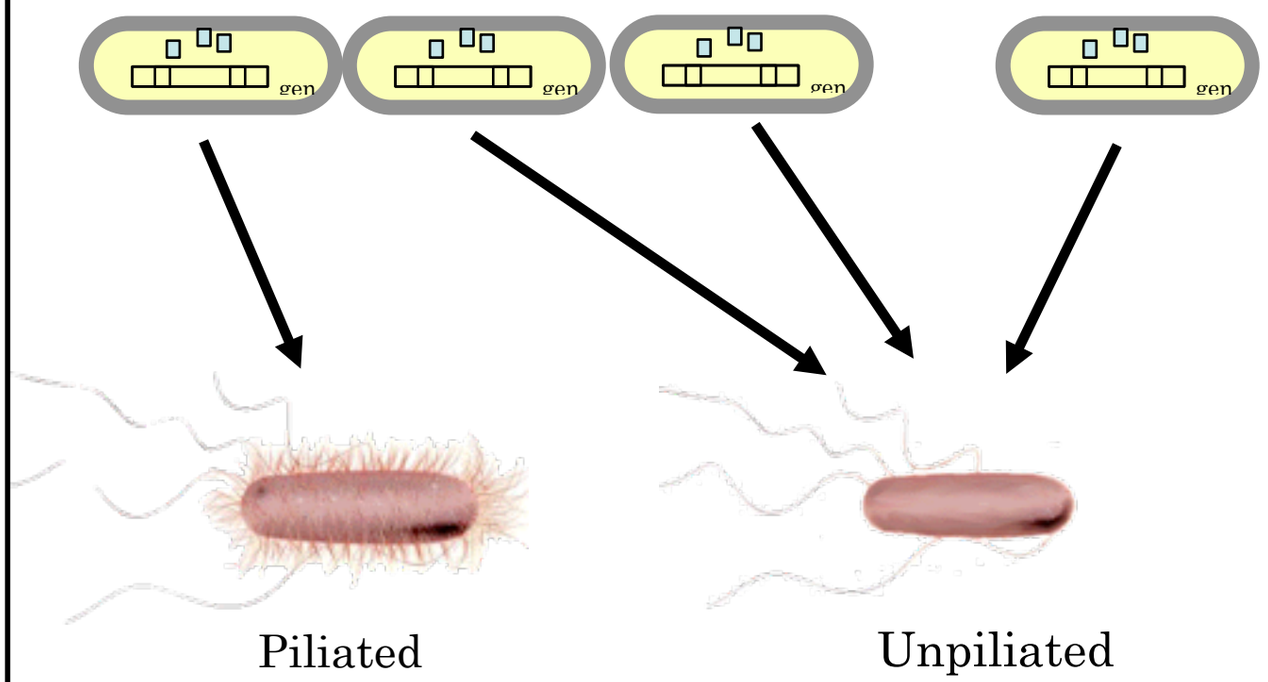
Cc, the first cloned cat and her genetic mother

J. Raser and E. O'Shea, Science, 1995.

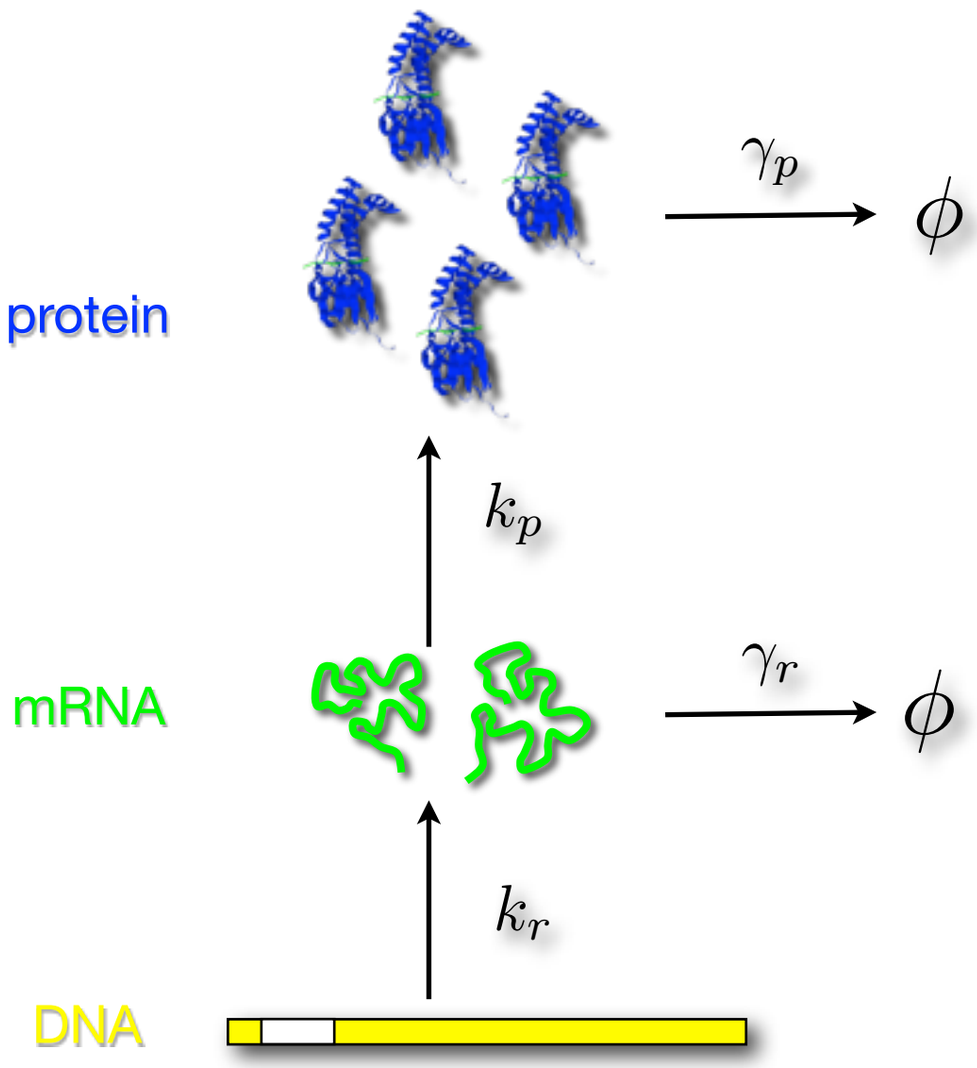


variability in gene expression

Elowitz et al, Science 2002



Modeling Gene Expression

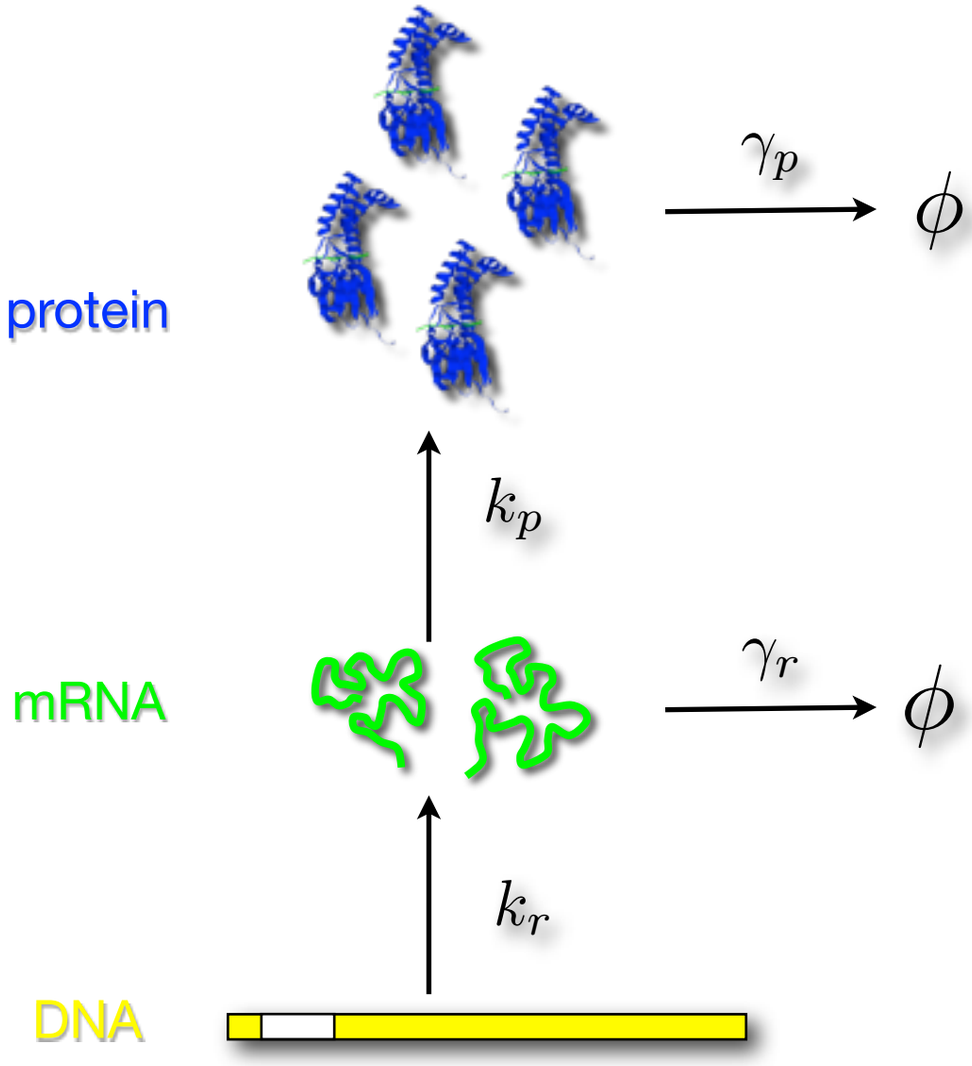


Deterministic model

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

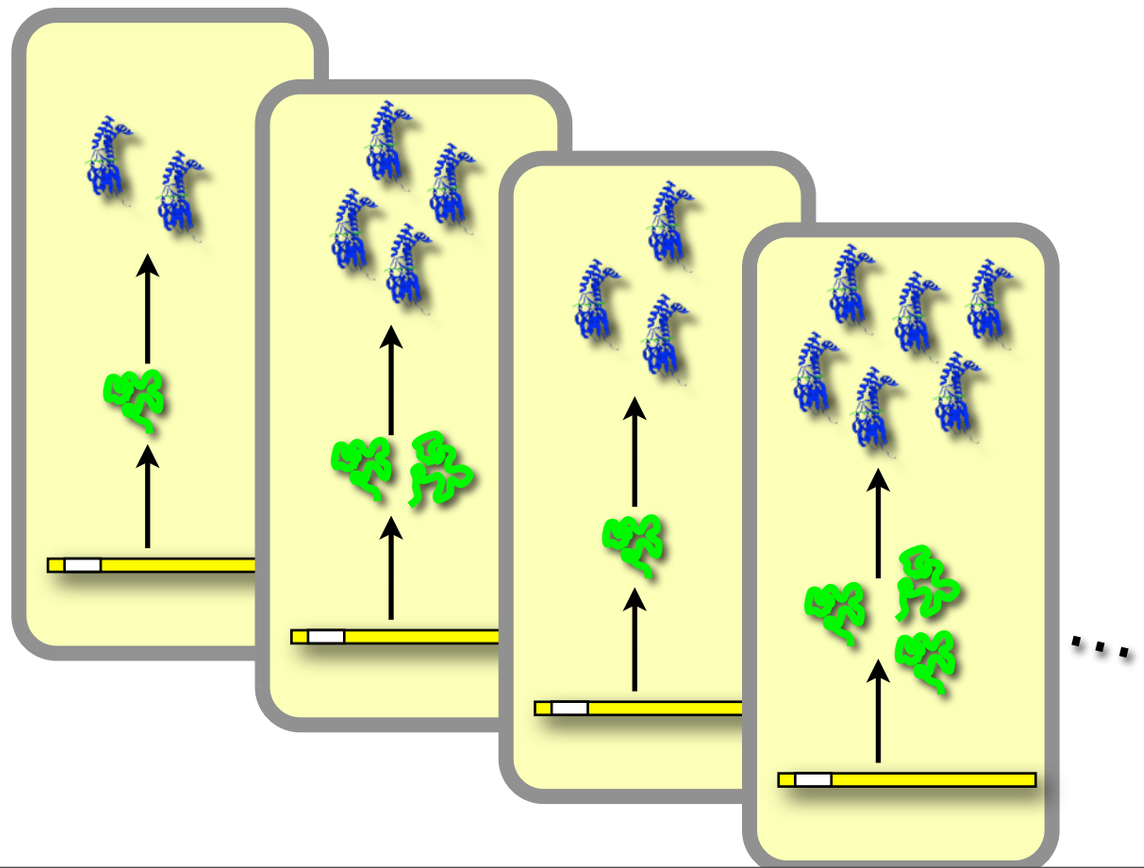
$$\frac{d[protein]}{dt} = -\gamma_p[protein] + k_p[mRNA]$$

Modeling Gene Expression

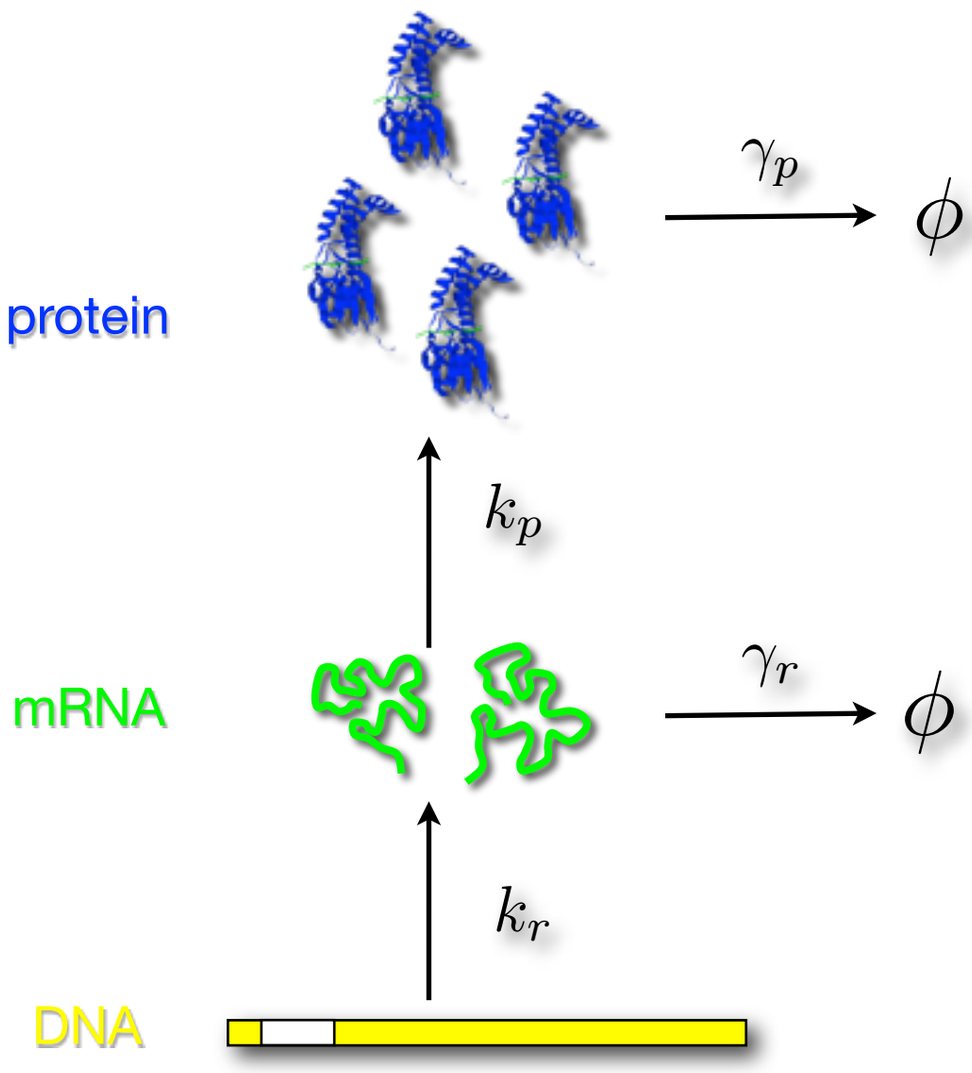


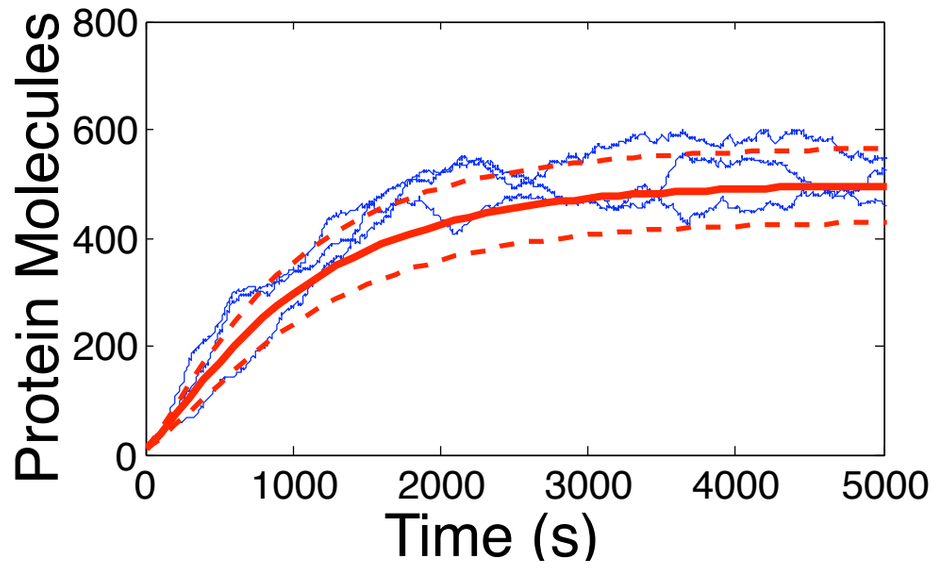
Stochastic model

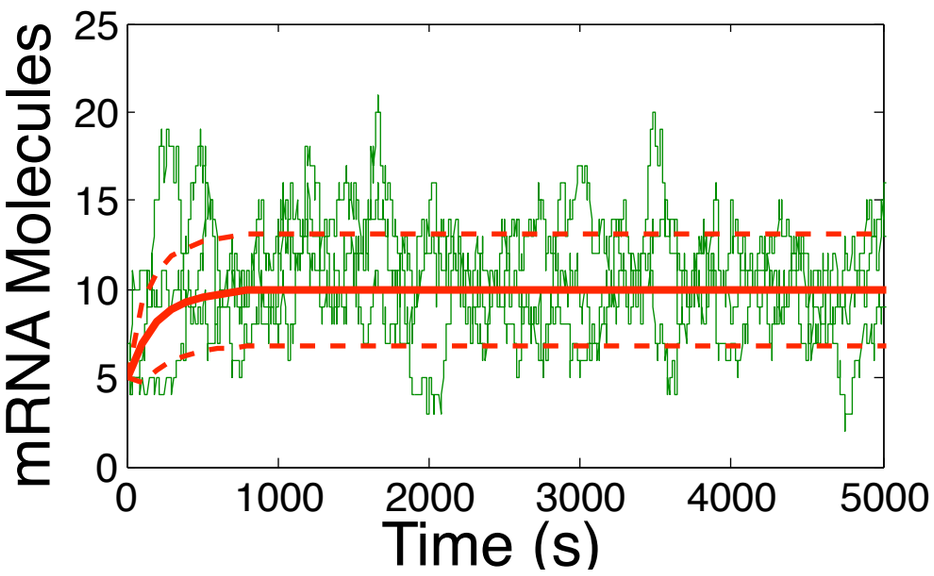
- Probability a single mRNA is transcribed in time dt is $k_r dt$.
- Probability a single mRNA is degraded in time dt is $(\#mRNA) \cdot \gamma_r dt$



Fluctuations at Small Copy Numbers







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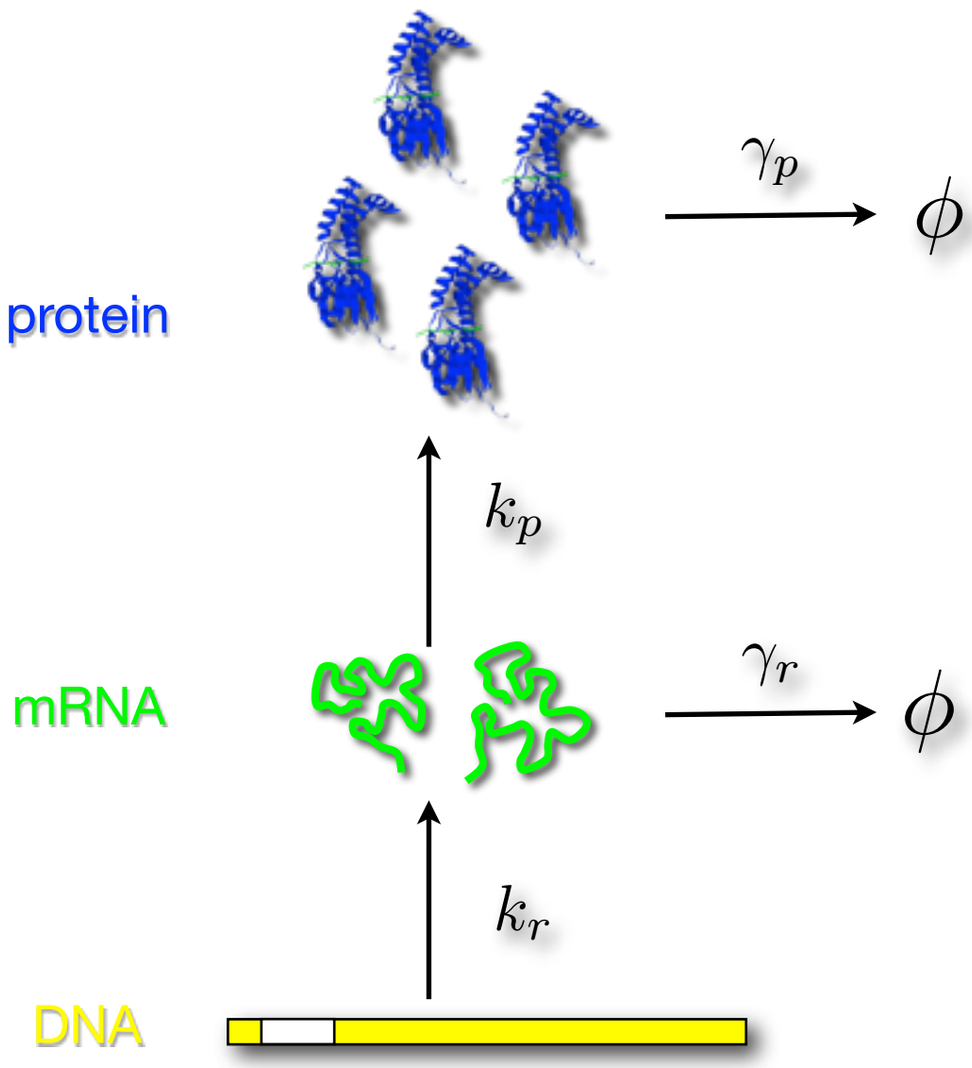


$$E(p) = \frac{k_r k_p}{\gamma_r \gamma_p}$$

$$\eta(p) = \frac{1}{\sqrt{E(p)}}\left(1 + \frac{kp}{\gamma_p + \gamma_r}\right)^{1/2} \qquad \text{(protein)}$$

$$E(r) = \frac{k_r}{\gamma_r}$$

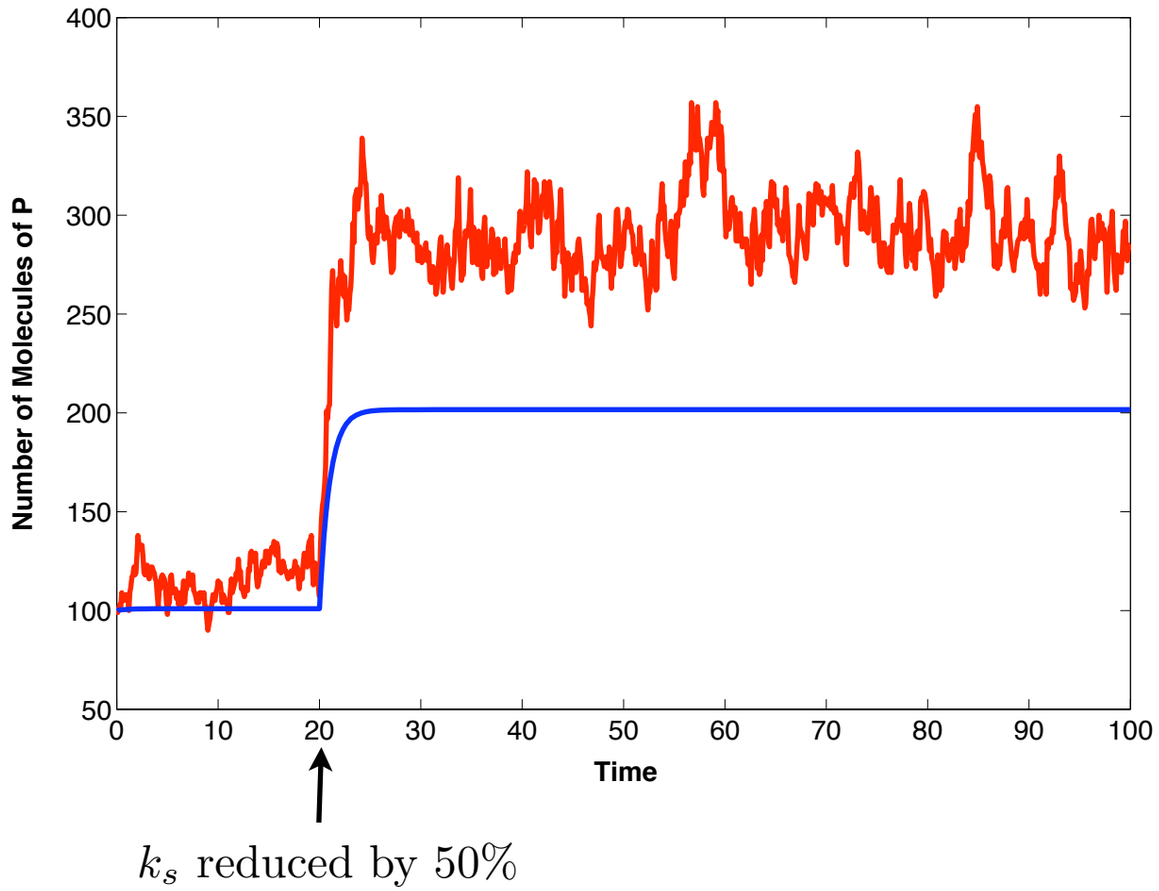
$$\eta(r) = \frac{1}{\sqrt{E(r)}} \qquad \text{(mRNA)}$$

C_v = coefficient of variation = $\dfrac{\text{standard deviation}}{\text{mean}}$

Mass-Action Models Are Inadequate

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

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

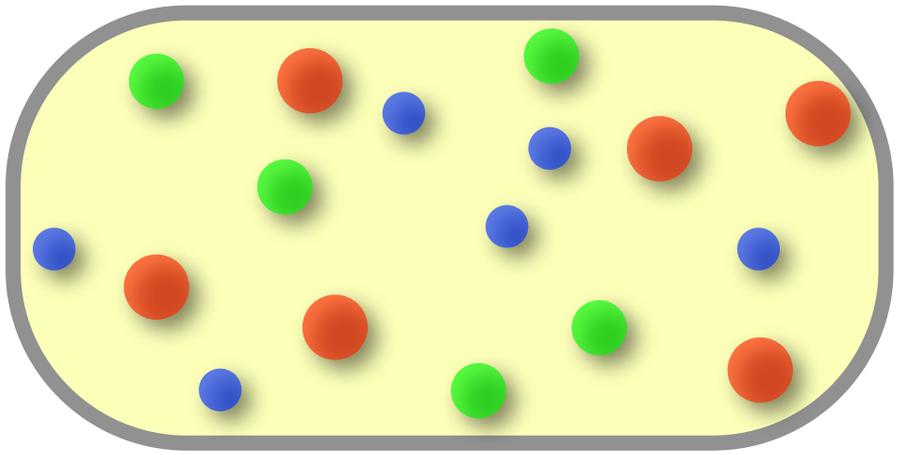


- Stochastic mean value different from deterministic steady state
- Noise *enhances* signal!

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

Formulation of Stochastic Chemical Kinetics

Reaction volume=Ω



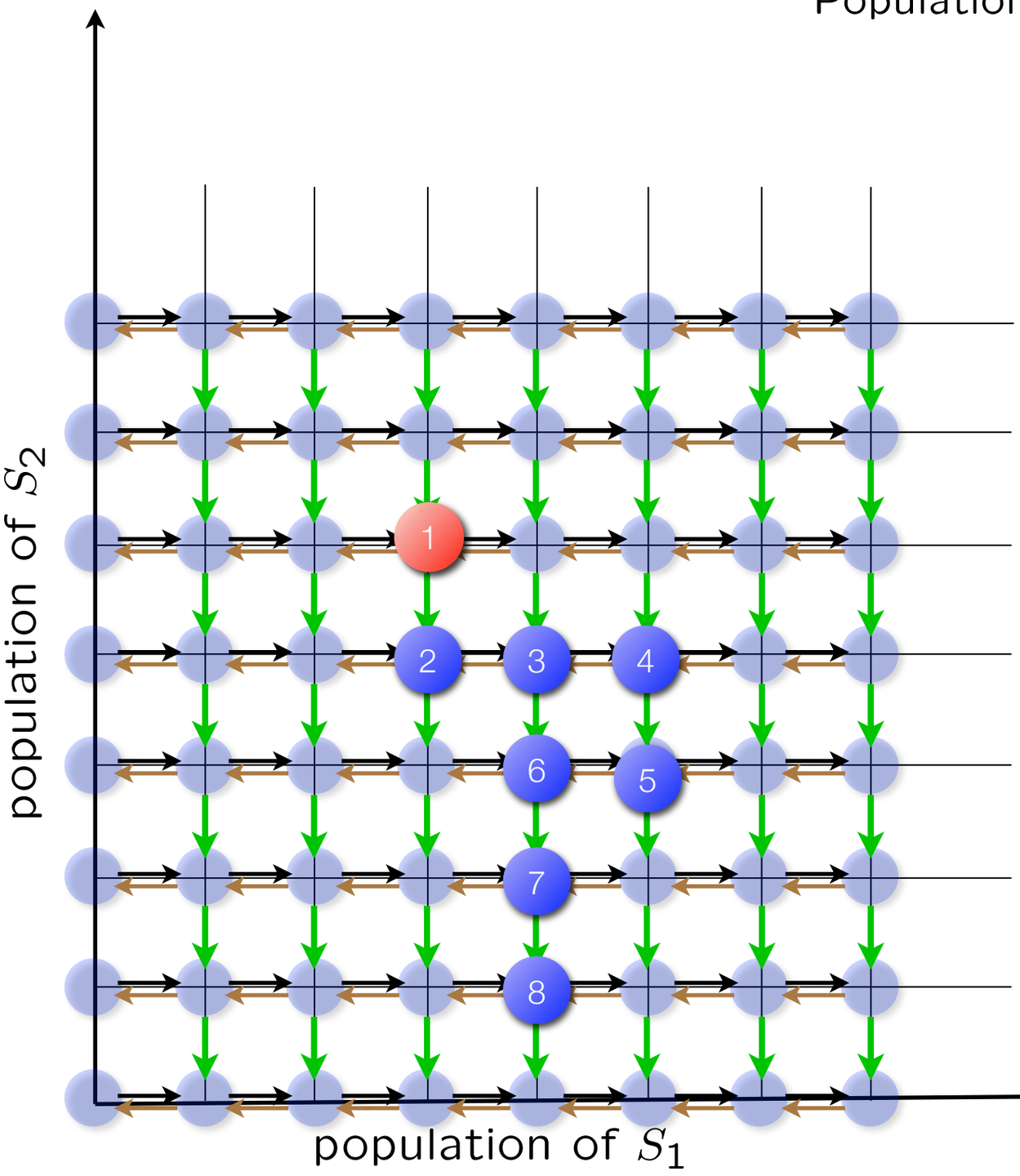
Key Assumptions

(**Well-Mixed**) The probability of finding any molecule in a region $d\Omega$ is given by $\frac{d\Omega}{\Omega}$.

(**Thermal Equilibrium**) The molecules move due to the thermal energy. The reaction volume is at a constant temperature T. The velocity of a molecule is determined according to a Boltzman distribution:

$$f_{v_x}(v) = f_{v_y}(v) = f_{v_z}(v) = \sqrt{\frac{m}{2\pi k_B T}}\, e^{-\frac{m}{2k_B T}v^2}$$

Population: $X(t) = [X_1(t), \ldots, X_N(t)]^T$ (integer r.v.)



- **(M-reactions)** The system's state can change through any one of M reaction: $R_\mu : \mu \in \{1, 2, \ldots, M\}$..

  Example: R_1 $\quad \phi \to S_1$

  R_2 $\quad S_1 + S_2 \to S_1$

  R_3 $\quad S_1 \to \phi$

- **(State transition)** An R_μ reaction causes a state transition from $\mathbf{x}$ to $\mathbf{x} + s_\mu$.

$$s_1 = \begin{pmatrix} 1 \\ 0 \end{pmatrix}; \quad s_2 = \begin{pmatrix} 0 \\ -1 \end{pmatrix}; \quad s_3 = \begin{pmatrix} -1 \\ 0 \end{pmatrix}$$

Stoichiometry matrix:

$$S = \begin{bmatrix} s_1 & s_2 & \cdots & s_M \end{bmatrix}$$

- **(Transition Probability)** Probability that R_μ reaction will occur in the next dt time units is: $w_\mu(x)dt$

Example: $w_1(x) = c_1$; $w_2(x) = c_2 \cdot x_1 x_2$; $w_3(x) = c_3 x_1$;

Characterizing X(t)

$X(t)$ is Continuous-time discrete-state Markov Chain

Sample Path Representation:

$$X(t) = X(0) + \sum_{k=1}^{M} s_k Y_k \left[\int_0^t w_k(X(s)) ds \right]$$

$Y_k[\cdot]$ are independent unit Poisson

The Chemical Master Equation (Forward Kolmogorov Equation)

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

$$p(x,t) := prob(X(t) = x)$$

From Stochastic to Deterministic

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 $t \geq 0$:

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

Simulation and Analysis Tools

- Sample Paths Computations
- Moment Computation
- SDE Approximation
- Density Computations

1. Sample Paths Computation

Gillespie's Stochastic Simulation Algorithm:

To each of the reactions $\{R_1, \ldots, R_M\}$ we associate a RV τ_i:

τ_i is the time to the next firing of reaction R_i

Fact 0: τ_i is exponentially distributed with parameter w_i

We define two new RVs:

$\tau = \min_i\{\tau_i\}$ (Time to the next reaction)

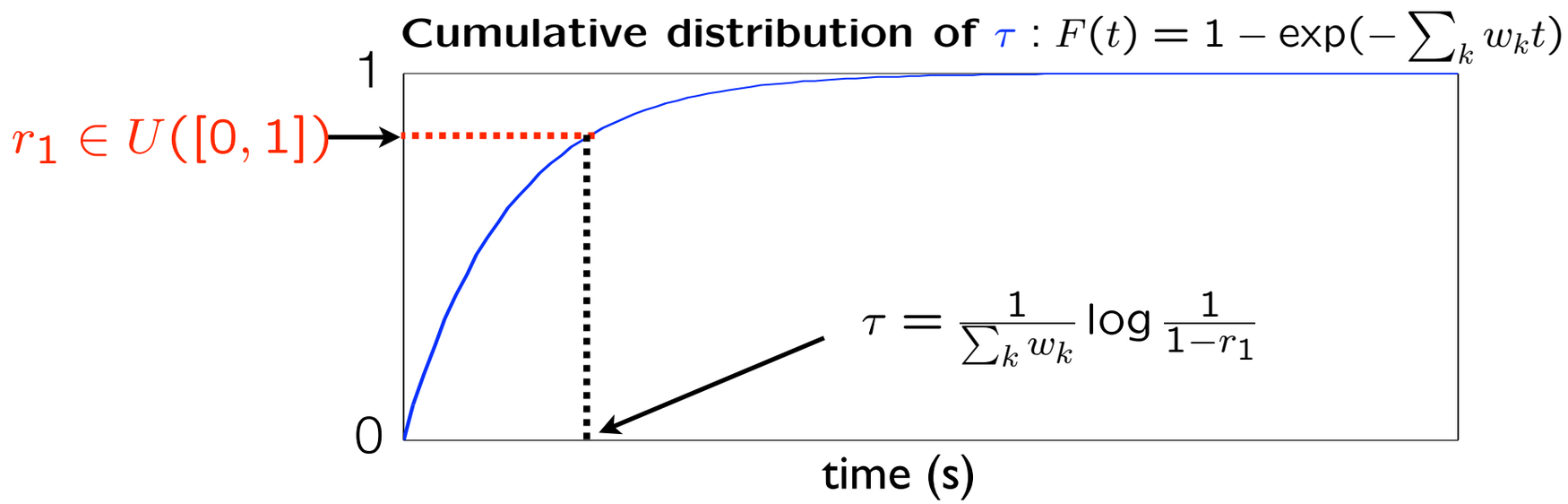
$\mu = \arg\min_i\{\tau_i\}$ (Index of the next reaction)

Fact 1: τ is exponentially distributed with parameter $\sum_i w_i$

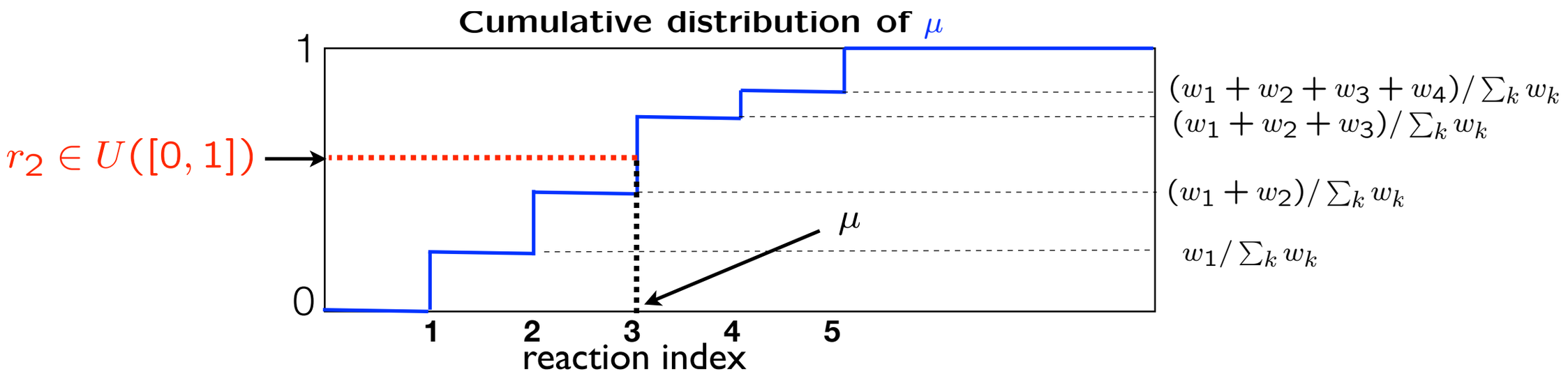
Fact 2: $P(\mu = k) = \dfrac{w_k}{\sum_i w_i}$

Stochastic Simulation Algorithm

- **Step 0** Initialize time t and state population x
- **Step 1** Draw a sample τ from the distribution of τ



- **Step 2** Draw a sample μ from the distribution of μ



- **Step 3** Update time: $t \leftarrow t + \tau$. Update state: $x \leftarrow x + s_\mu$.

2. Moment Computations

Let $w(x) = [w_1(x), \ldots, w_M(x)]^T$ be the vector of propensity functions

Moment Dynamics

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

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

- Affine propensity. Closed moment equations.
- Quadratic propensity. Not generally closed.
  - *Mass Fluctuation Kinetics* (Gomez-Uribe, Verghese)
  - *Derivative Matching* (Singh, Hespanha)

Affine Propensity

Suppose the propensity function is affine:

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

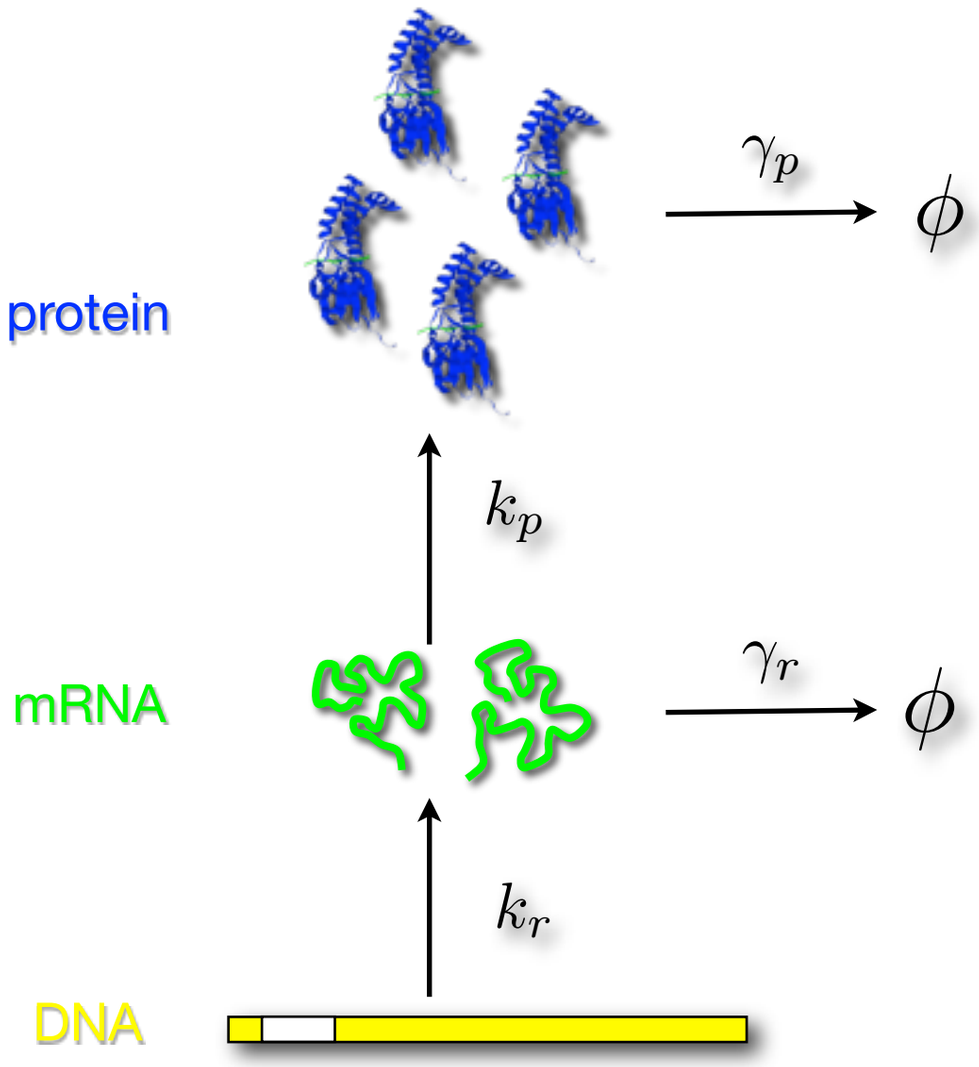
Then $E[w(X)] = WE[X] + w_0$, and $E[w(X)X^T] = WE[XX^T] + w_0 E[X^T]$.

This gives us the moment equations:

$$\begin{aligned} \frac{d}{dt}E[X] &= SWE[X] + Sw_0 && \text{First Moment} \\ \frac{d}{dt}E[XX^T] &= SWE[XX^T] + E[XX^T]W^T S^T + S\ diag(WE[X] + w_0)S^T \\ &+ Sw_0E[X^T] + E[X]w_0^T S^T && \text{Second Moment} \end{aligned}$$

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

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

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

$$\bar{X} = -A^{-1} Sw_0 = \begin{bmatrix} \frac{k_r}{\gamma_r} \\ \\ \frac{k_p k_r}{\gamma_p \gamma_r} \end{bmatrix}$$

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 $\bar{\Sigma}$.

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

3. SDE Approximation

Let $X^{\Omega}(t) := \frac{X(t)}{\Omega}$

Write $X^{\Omega} = \Phi_0(t) + \frac{1}{\sqrt{\Omega}} V^{\Omega}$ where $\Phi_0(t)$ solves the deterministic RRE

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

Linear Noise Approximation

$V^{\Omega}(t) \to V(t)$ as $\Omega \to \infty$, where $dV(t) = A(t)V(t)dt + B(t)dW_t$

$$A(t) = \frac{d[Sf(\Phi)]}{d\Phi}(\Phi_0(t)), \qquad B(t) := S\sqrt{diag[f(\Phi_0(t))]}$$

Linear Noise Approximation: $X^{\Omega}(t) \approx \Phi(t) + \frac{1}{\sqrt{\Omega}} V(t)$

Linear Noise Approximation: Stationary Case

Multiplying $X^{\Omega}(t) \approx \bar{\Phi} + \frac{1}{\sqrt{\Omega}} V(t)$ by Ω, we get

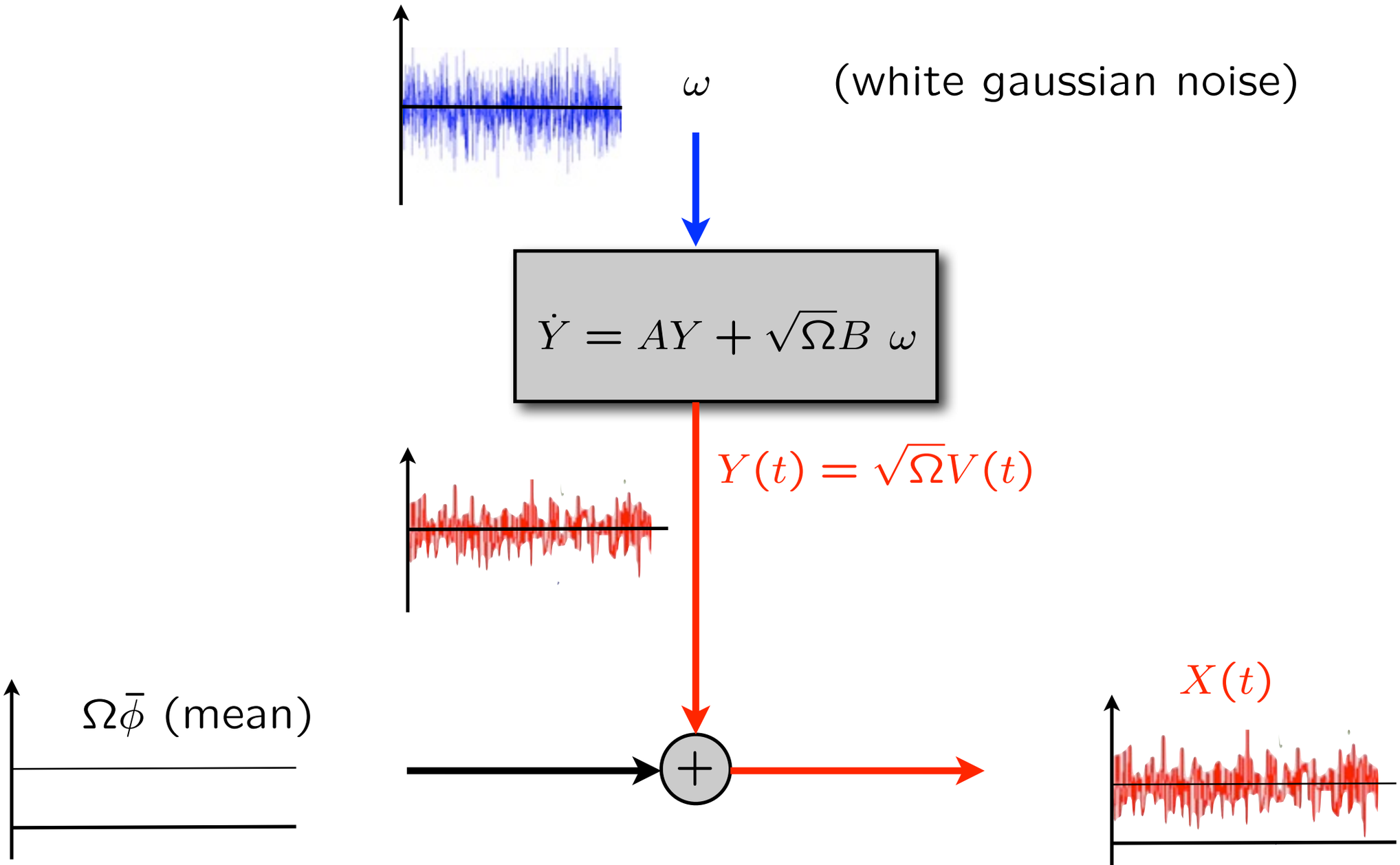
$$X(t) \approx \Omega\bar{\Phi} + \sqrt{\Omega} V(t)$$

deterministic **zero mean stochastic**

$$E[X(t)] = \Omega\bar{\Phi}$$

Let $\bar{\Sigma}$ be the steady-state covariance matrix of $\sqrt{\Omega} \cdot V(t)$. Then

$$A\bar{\Sigma} + \bar{\Sigma}A^T + \Omega BB^T = 0$$


ω
(white gaussian noise)
$\dot{Y} = AY + \sqrt{\Omega}B\ \omega$
$Y(t) = \sqrt{\Omega}V(t)$
$\Omega\bar{\phi}$ (mean)
$X(t)$

4. Density Computation

We are interested in $p(\mathbf{x}, t)$, the probability that the chemical system will be in state $\mathbf{x}$ at time, t.

Form the *probability density state vector* $\mathbf{P}(\mathbf{X}, \cdot) : R \rightarrow \ell_1$:

$$\mathbf{P}(\mathbf{X}; t) := [p(\mathbf{x}_1; t) \quad p(\mathbf{x}_2; t) \quad p(\mathbf{x}_3; t) \quad \dots \quad]^T$$

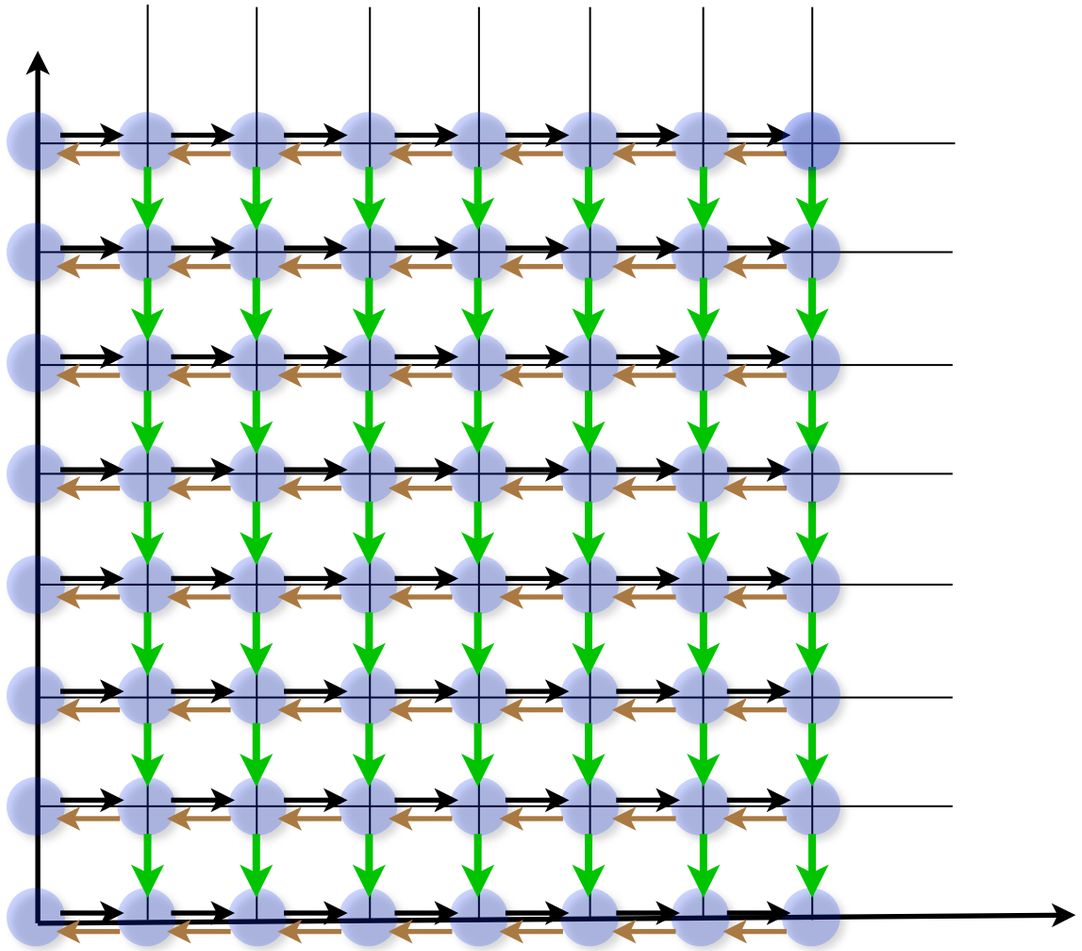
The Chemical Master Equation (CME):

$$\dot{p}(\mathbf{x}; t) = -p(\mathbf{x}; t) \sum_{\mu=1}^{M} a_\mu(\mathbf{x}) + \sum_{\mu=1}^{M} p(\mathbf{x} - \nu_\mu; t) a_\mu(\mathbf{x} - \nu_\mu)$$

can now be written in matrix form:

$$\dot{\mathbf{P}}(\mathbf{X}; t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}; t)$$

The Finite State Projection Approach



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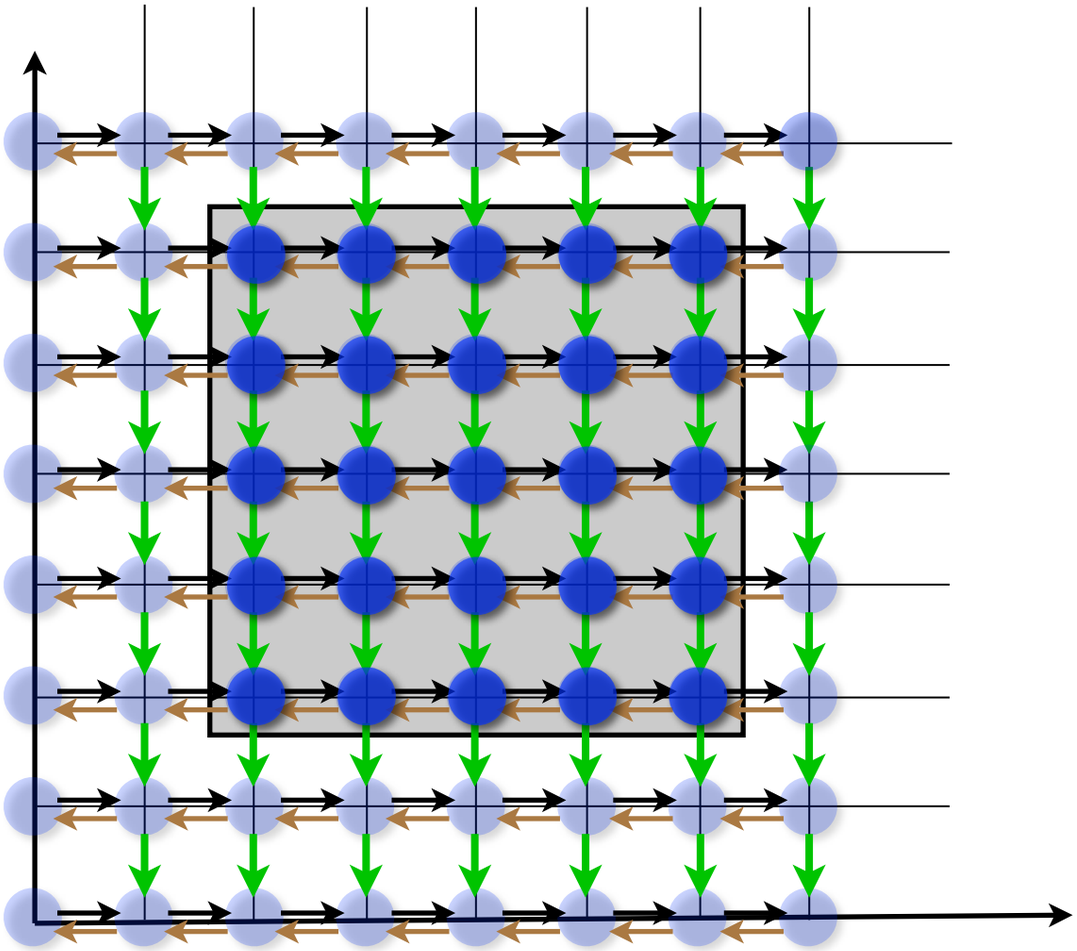
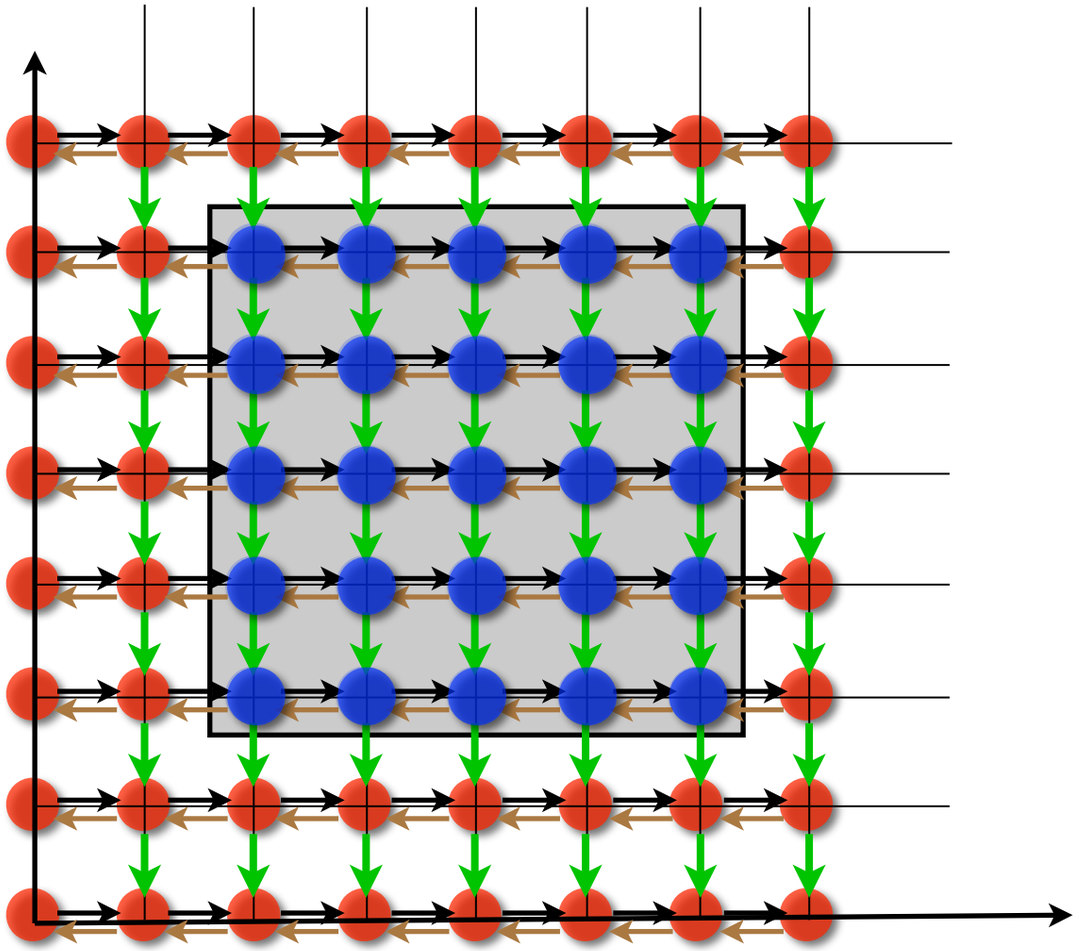


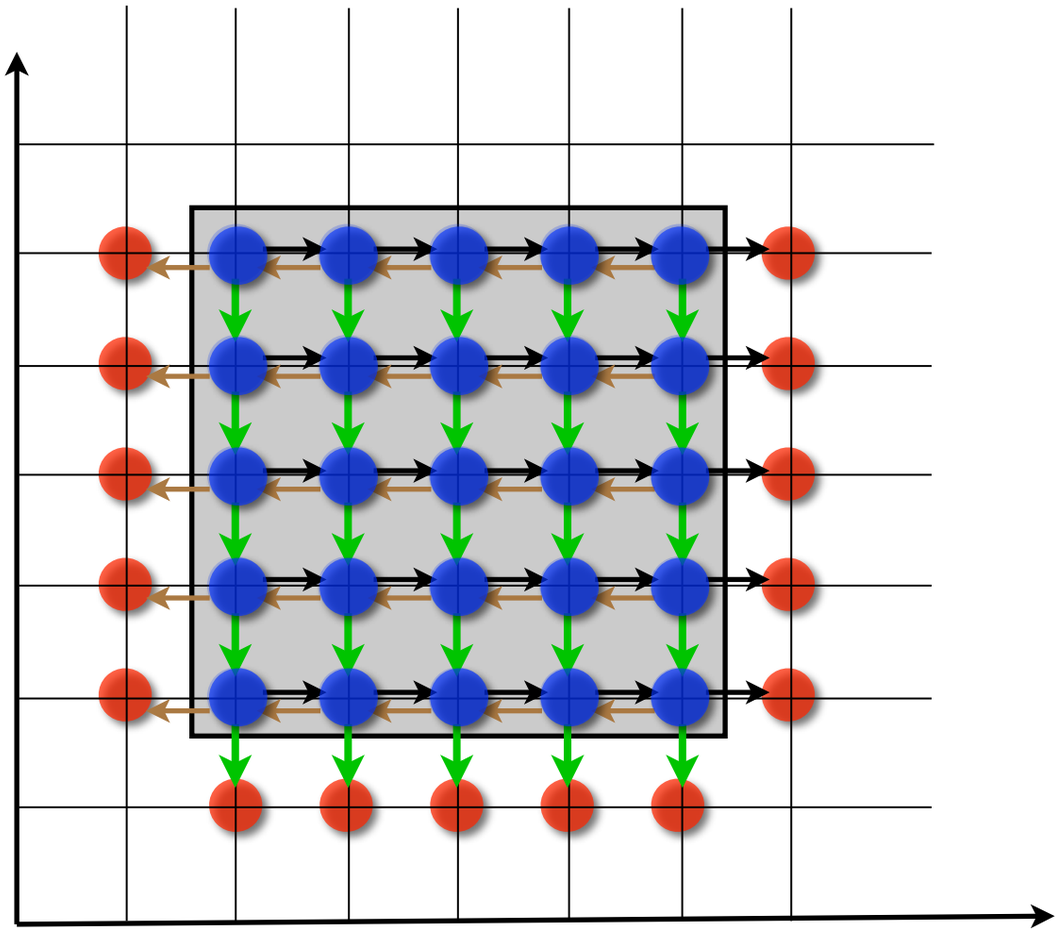
- A finite subset is appropriately chosen

The Finite State Projection Approach



- A finite subset is appropriately chosen
- The remaining (infinite) states are projected onto a single state (red)

The Finite State Projection Approach



- A finite subset is appropriately chosen
- The remaining (infinite) states are projected onto a single state (red)
- Only transitions into removed states are retained

The projected system can be solved exactly!

Finite Projection Bounds

Let $J = [m_1 \dots m_N]$ be an indexing vector. We define $\mathbf{A}_J$ to be the principle submatrix of $\mathbf{A}$ defined by J.

Theorem [Projection Error Bounds] Consider any Markov process described by the Forward Kolmogorov Equation:

$$\dot{\mathbf{P}}(X_J; t) = A \cdot \mathbf{P}(X_J; t).$$

If for an indexing vector J: $\mathbf{1}^T \exp(A_J T)\mathbf{P}(X_J; 0) \geq 1 - \epsilon$, then

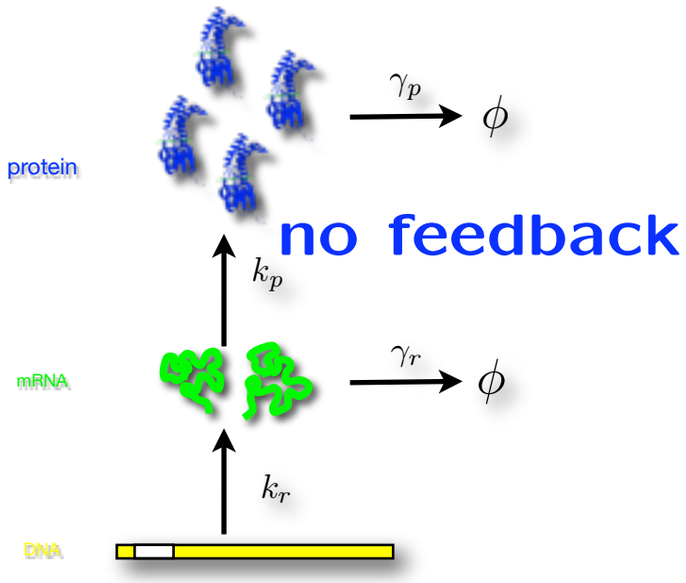
$$\left\| \begin{bmatrix} \mathbf{P}(X_J; t) \\ \mathbf{P}(X_{J'}; t) \end{bmatrix} - \begin{bmatrix} \exp(A_J t)\mathbf{P}(X_J; 0) \\ 0 \end{bmatrix} \right\|_1 < \epsilon \qquad t \in [0, T]$$

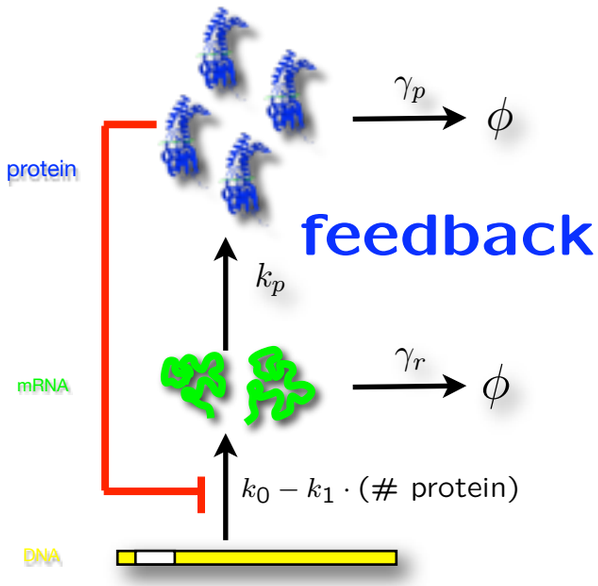
Munsky B. and Khammash M., Journal of Chemical Physics, 2006

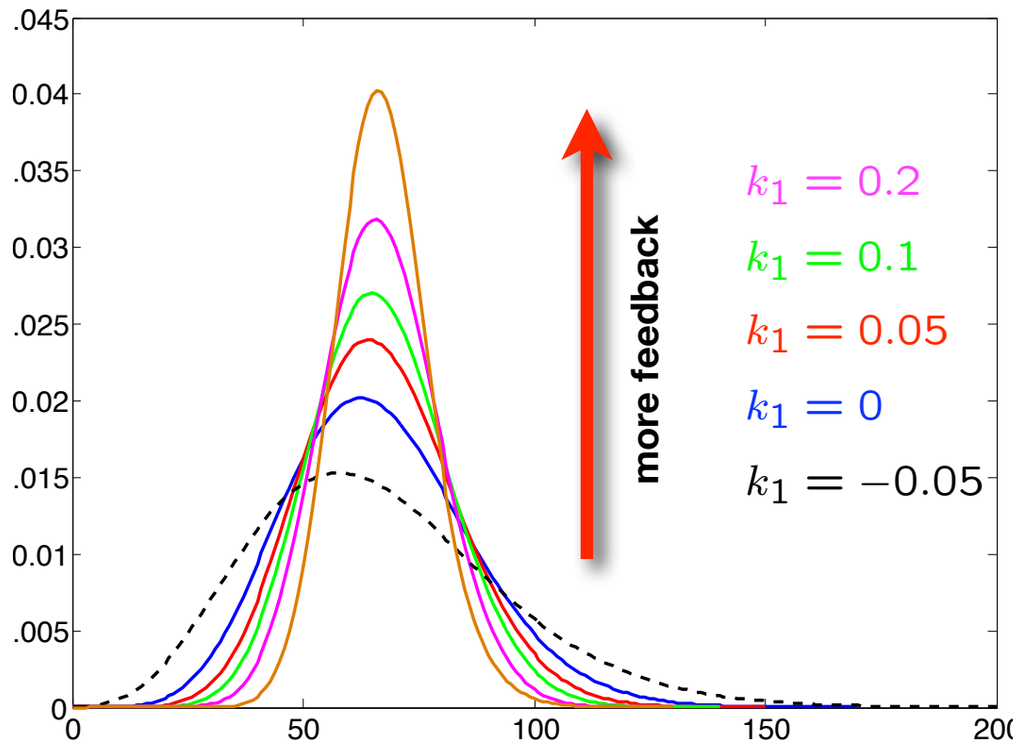
Applications of FSP

- Feedback Analysis
- Synthetic Switch Analysis
- Epigenetic Switch Analysis
- System Identification

Application: Noise Attenuation through Feedback







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

$\mu_p^* \quad = \quad \textbf{Mean} \quad = \quad \mu_p^*$

Variance

$$\left[\frac{b}{1+\eta} + 1\right] \mu_p^*$$

Variance

$$\left[\frac{1-\phi}{1+b\phi} \cdot \frac{b}{1+\eta} + 1\right] \mu_p^*$$

$$< 1$$

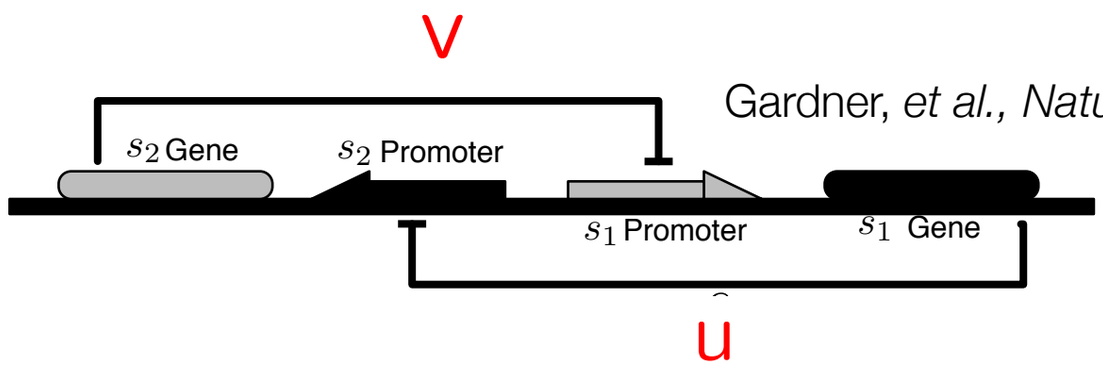
where $\phi = \dfrac{k_1}{\gamma_p},\ b = \dfrac{k_p}{\gamma_r},\ \eta = \dfrac{\gamma_p}{\gamma_r}$

Thattai, van Oudenaarden

Protein variance is always smaller with negative feedback!

Analysis of Stochastic Switchs

Two repressors, *u* and *v*.



Gardner, *et al., Nature* 403, 339-342 (2000)

v inhibits the production of *u:*

$$a_1(u,v) = \frac{\alpha_1}{1+v^\beta} \quad \nu_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

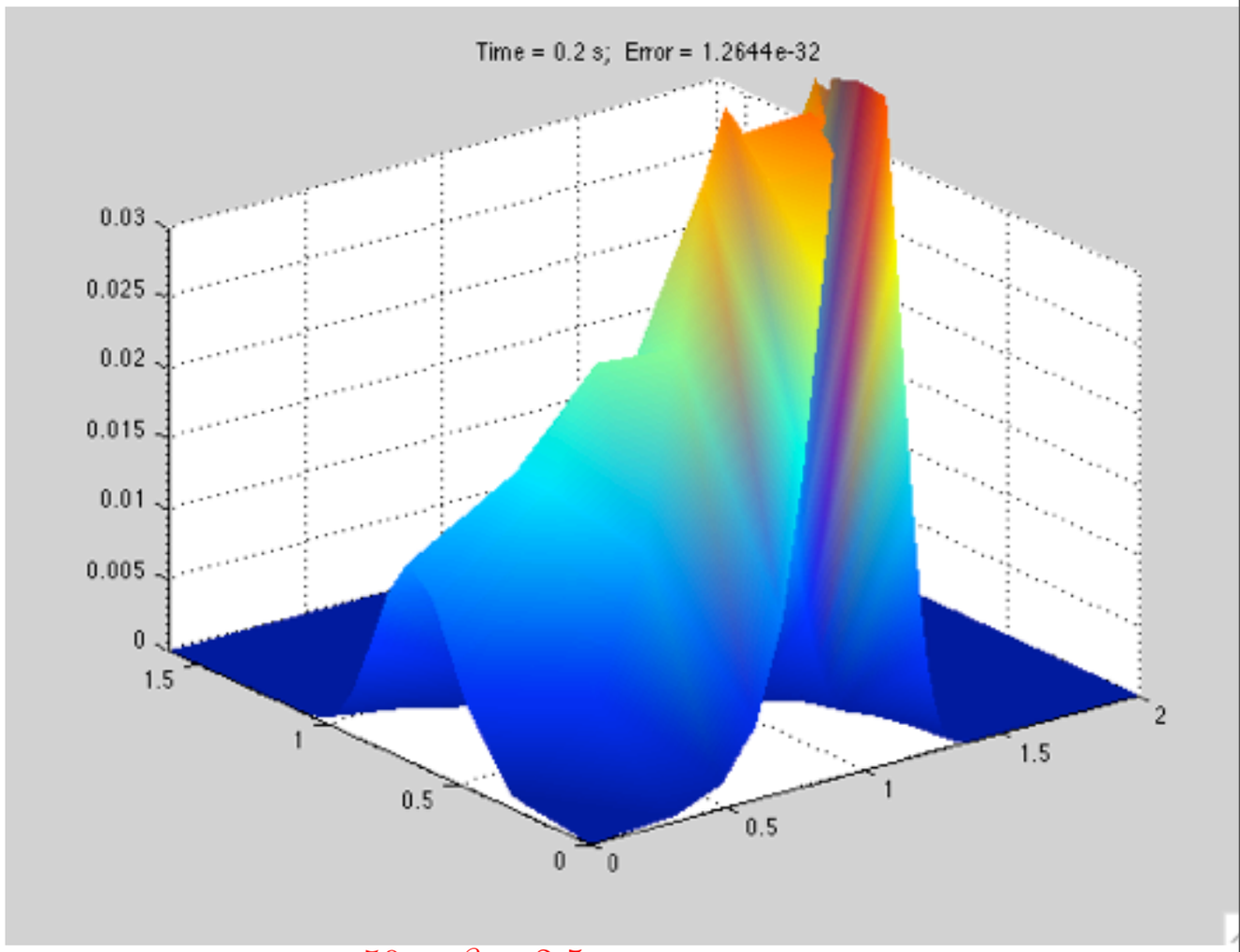
u inhibits the production of *v:*

$$a_3(u,v) = \frac{\alpha_2}{1+u^\gamma} \quad \nu_3 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

u and *v* degrade exponentially:

$$a_2(u,v) = u \quad \nu_2 = \begin{bmatrix} -1 \\ 0 \end{bmatrix}$$

$$a_4(u,v) = v \quad \nu_4 = \begin{bmatrix} 0 \\ -1 \end{bmatrix}$$



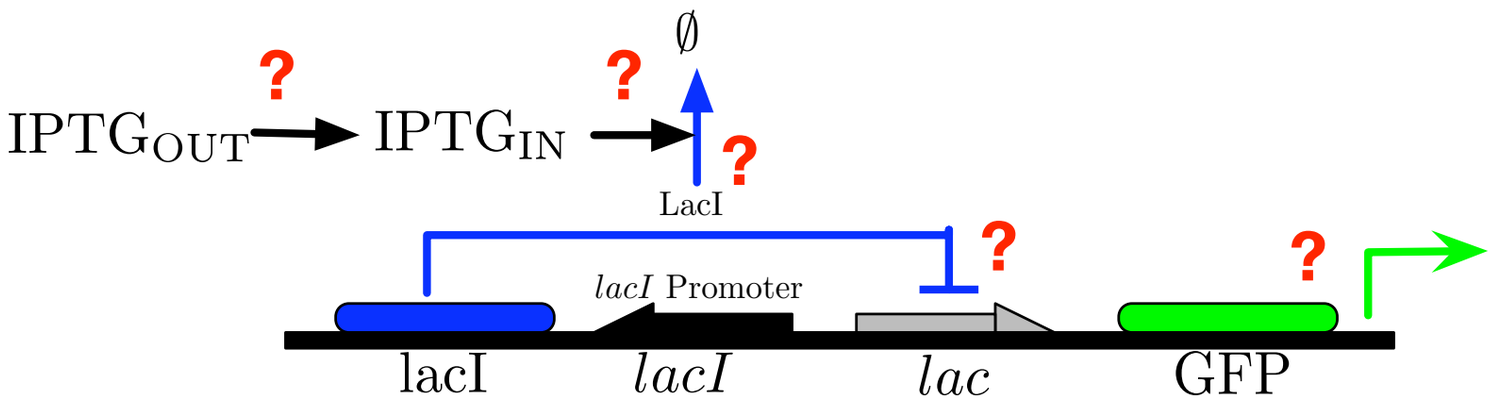
$\alpha_1 = 50 \quad \beta = 2.5$

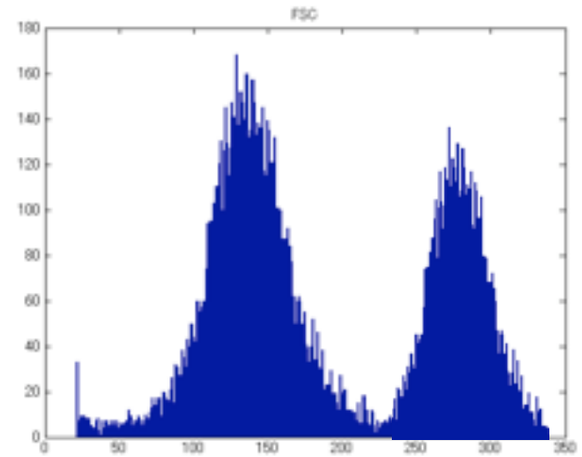
$\alpha_2 = 16 \quad \gamma = 1$

$u(0) = v(0) = 0$

Using Noise to Identify Model Parameters

Why use noise?

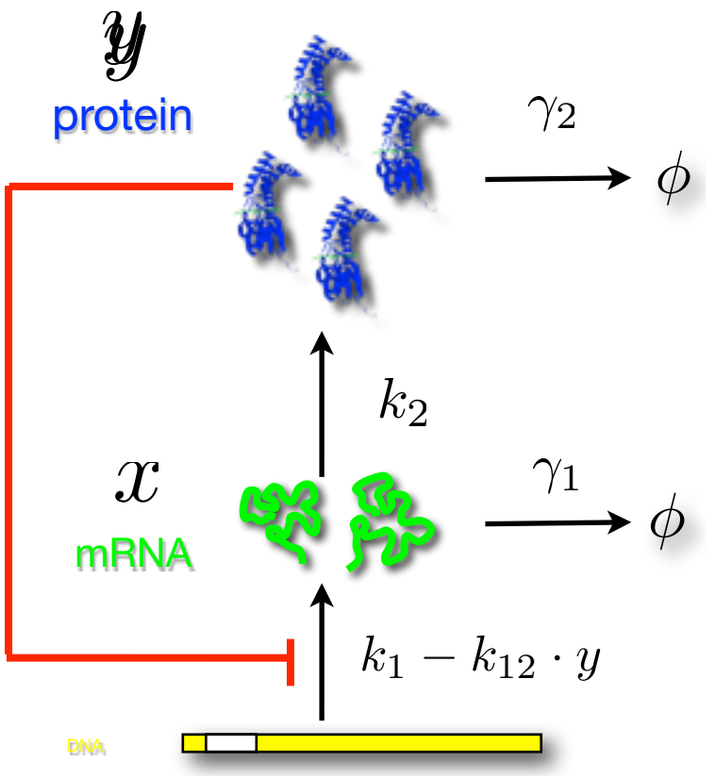




- Noise provides an excitation source for the network dynamics
- Resulting distributions of proteins can be measured
- Such distributions provide a lot of information about the dynamics
- Can they be used to identify model parameters?
- Noise has been used to discriminate among competing models

Dunlop et. al (2008). Nature Genetics. Regulatory activity revealed by dynamic correlations in gene expression noise.

Identification from Moment Information



$$\mathbf{v}(t) := \begin{bmatrix} E\{x\} & E\{x^2\} & E\{y\} & E\{y^2\} & E\{xy\} \end{bmatrix}^T$$

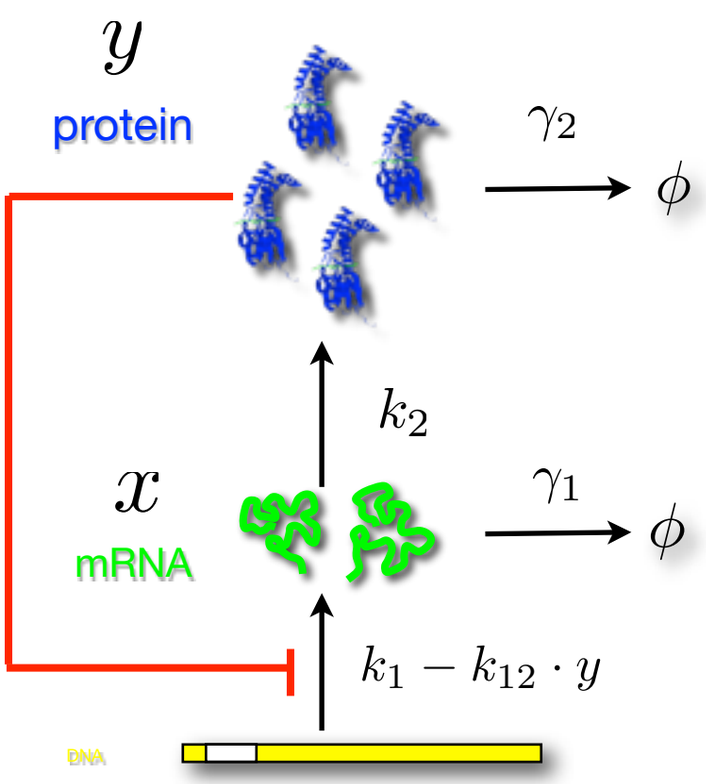
$$\dot{\mathbf{v}} = \begin{bmatrix} -\gamma_1 & 0 & k_{21} & 0 & 0 \\ \gamma_1 + 2k_1 & -2\gamma_1 & k_{21} & 0 & 2k_{21} \\ k_2 & 0 & -\gamma_2 & 0 & 0 \\ k_2 & 0 & \gamma_2 & -2\gamma_2 & 2k_2 \\ 0 & k_2 & k_1 & k_{21} & -\gamma_1 - \gamma_2 \end{bmatrix} \mathbf{v} + \begin{bmatrix} k_1 \\ k_1 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$= \mathbf{A}\mathbf{v} + \mathbf{b}$$

Identifiability

Can one identify the parameters $\lambda = \{k_1, \gamma_1, k_2, \gamma_2, k_{21}\}$ from measurements of the moments $\mathbf{v}(t)$?

Identifying Using Steady-State Moments



Can the stationary distribution be used to identify all the parameters?

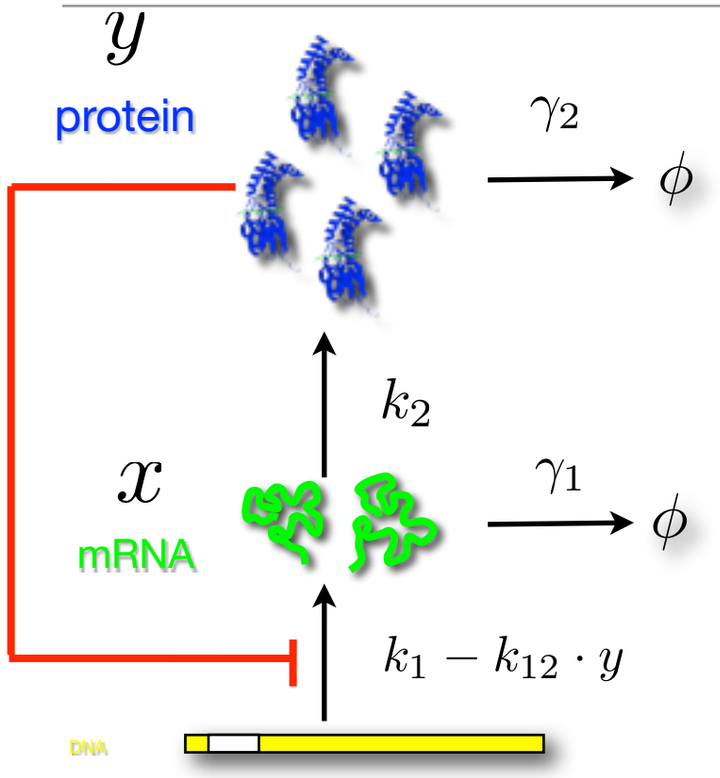
$$\mathbf{v}(t) := \begin{bmatrix} E\{x\} & E\{x^2\} & E\{y\} & E\{y^2\} & E\{xy\} \end{bmatrix}^T$$

$$\mathbf{v}_\infty = \lim_{t\to\infty} [v_1, v_2, v_3, v_4, v_5]^T.$$

Full Identifiability with Stationary Moments

Impossible!

Identifiability from Transient Time-Measurements



$$\mathbf{v}(t) := \left[\begin{array}{ccccc} E\{x\} & E\{x^2\} & E\{y\} & E\{y^2\} & E\{xy\} \end{array} \right]^T$$

Multiple Measurements

Suppose $\mathbf{v}_j := \mathbf{v}(t_j)$ has been measured at equally separated points in time $\{t_0, t_1, \ldots, t_m\}$

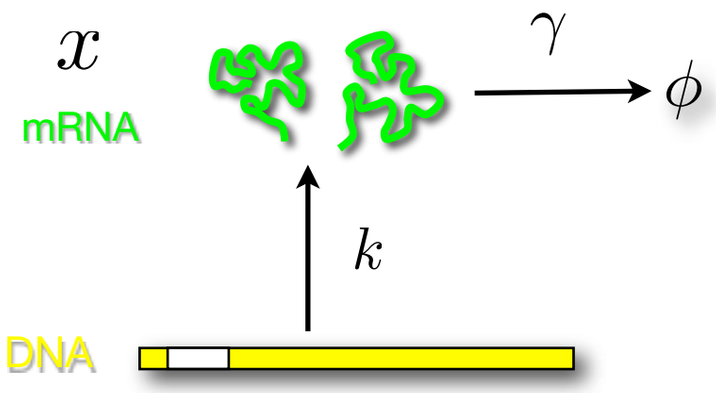
Identifiability with Multiple Moment Measurements

For $m = 6$ the model parameters are *identifiable*.

$$\mathbf{G} = \left[\begin{array}{ccc} \mathbf{v}_1 & \cdots & \mathbf{v}_6 \end{array} \right] \left[\begin{array}{ccc} \mathbf{v}_0 & \cdots & \mathbf{v}_5 \\ 1 & \cdots & 1 \end{array} \right]^{-1} \begin{bmatrix} I \\ 0 \end{bmatrix}$$

$$A = \frac{1}{\tau} \log(\mathbf{G}) \qquad \mathbf{b} = -(\mathbf{I} - \mathbf{G})^{-1} \mathbf{A}\mathbf{v}$$

Identification with Two Measurements

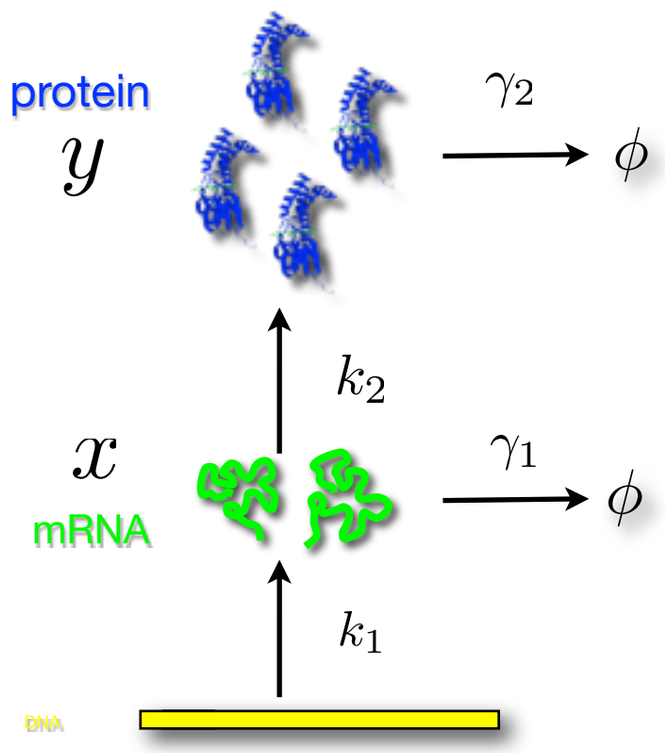


Identifiability of Transcription Parameters

Suppose the mean and variance are known at two times $t_0 < t_1 < \infty$, and define $(\mu_0, \sigma_0) := (\mu(t_0), \sigma(t_0))$ and $(\mu_1, \sigma_1) := (\mu(t_1), \sigma(t_1))$.

Then *the transcription parameters are identifiable*, and

$$\gamma = -\frac{1}{2\tau}\log\left(\frac{\sigma_1^2 - \mu_1}{\sigma_0^2 - \mu_0}\right) \qquad k = \gamma\frac{\mu_1 - \exp(-\gamma\tau)\mu_0}{1 - \exp(-\gamma\tau)}. \qquad (\tau := t_1 - t_0)$$



Identifiability of Transcription & Translation Parameters

$$\mathbf{v}(t) := \begin{bmatrix} E\{x\} & E\{x^2\} & E\{y\} & E\{y^2\} & E\{xy\} \end{bmatrix}^T$$

- Given $\mathbf{v}(t_0)$ and $\mathbf{v}(t_1)$, there is strong theoretical and numerical evidence that unique identifiability of all parameters $k_1, k_2, \gamma_1, \gamma_2$ is always possible.
- An analytic expression exists for finding the parameters.

$$\mathbf{A}_\lambda \mathbf{v}_1 = \mathbf{A}_\lambda e^{\mathbf{A}_\lambda \tau}\mathbf{v}_0 - (I - e^{\mathbf{A}_\lambda \tau})\mathbf{b}$$

Using Densities to Identify Network Parameters

- Moment equations can be written only in special cases.
- Densities (distributions) contain much more information than first two moments.
- Using the Chemical Master Equation, we propose to use density measurements for model identification.

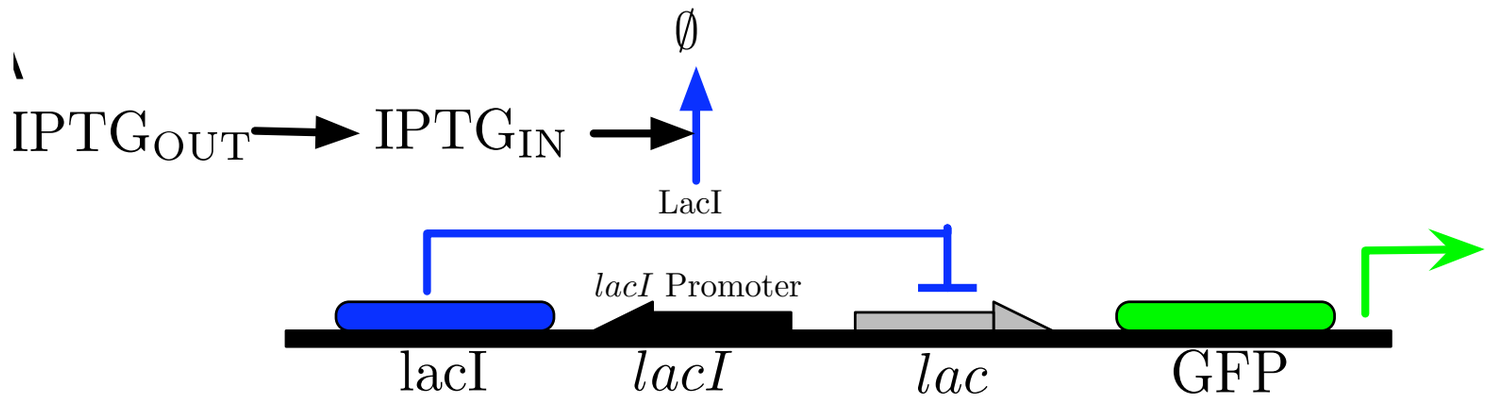
Using Density:

Suppose we measure $\mathbf{P}$ at different times: $\mathbf{P}(t_0), \mathbf{P}(t_1), \ldots, \mathbf{P}(t_{N-1})$

We can use these to identify unknown network parameters λ:

$$\begin{aligned} &\text{Find } \lambda \quad \text{subject to} \\ \dot{\mathbf{P}}^{FSP} &= A(\lambda)\mathbf{P}^{FSP} \\ \mathbf{P}^{FSP}(t_0) &= \mathbf{P}(t_0) \\ \mathbf{P}^{FSP}(t_1) &= \mathbf{P}(t_1) \\ &\vdots \\ \mathbf{P}^{FSP}(t_{N-1}) &= \mathbf{P}(t_{N-1}) \end{aligned}$$

Identification of *lac* Induction



Model

$$\phi \xrightarrow{k_L} \mathsf{LacI}$$

$$\mathsf{LacI} \xrightarrow{\delta_L} \phi \qquad \delta_L = \delta_L^{(0)} + \delta_L^{(1)}[\mathsf{IPTG}]_{\mathsf{IN}}$$

$$\phi \xrightarrow{w_G} \mathsf{GFP} \qquad w_G = \frac{k_G}{1 + \alpha[\mathsf{LacI}]^{\eta}},$$

$$\mathsf{GFP} \xrightarrow{\delta_G} \phi$$

$$\mathsf{IPTG}_{\mathsf{IN}} = \mathsf{IPTG}_{\mathsf{OUT}}(1 - e^{-rt})$$

9 unknown parameters!

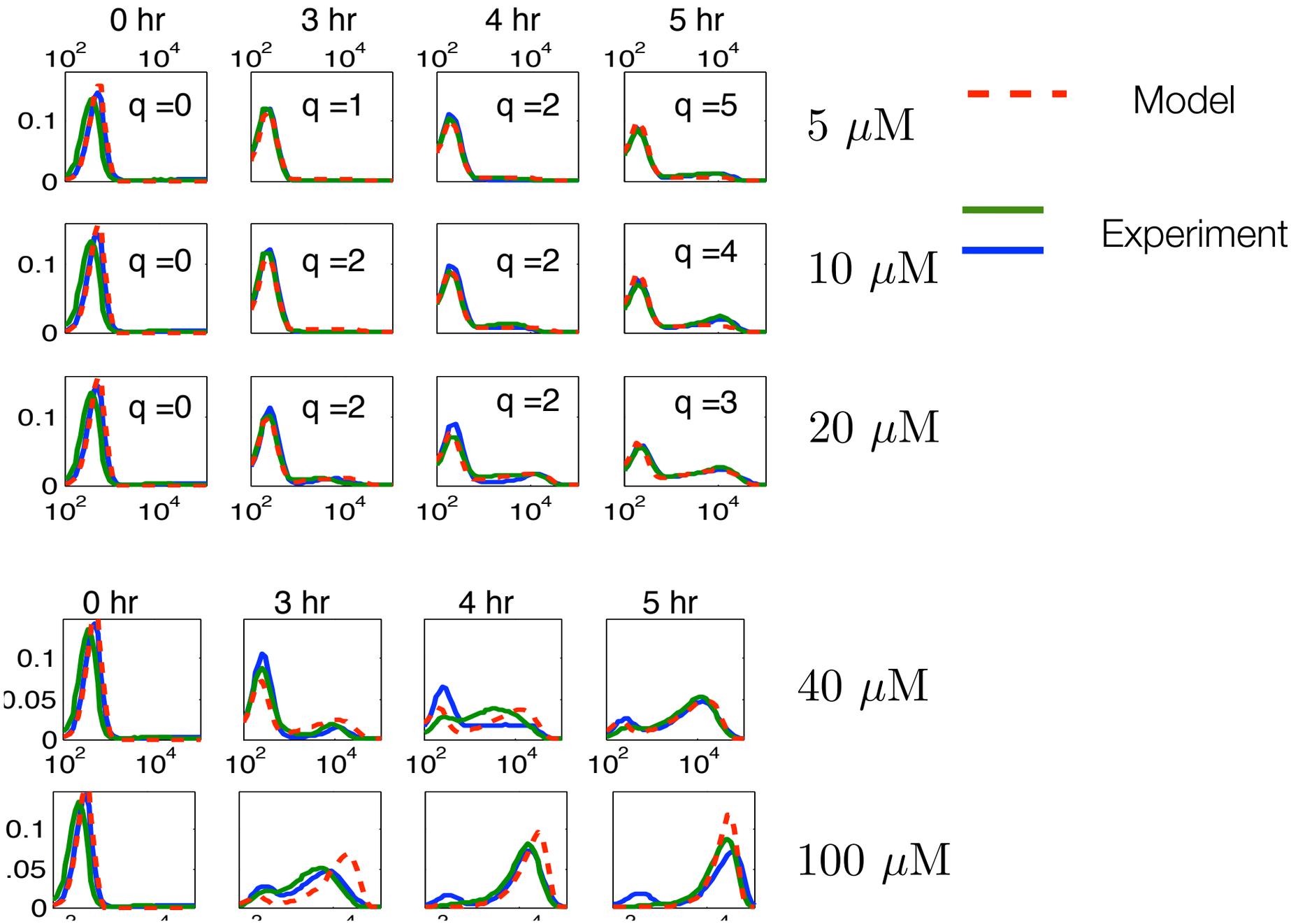
Experiment

- *E. coli* strain DL5905
- Induced with different IPTG concentrations: 5,10, 20, 40, 100 uM
- Induction times: 0, 1, 2, 3, 4, 5 hours before flow cytometry

Identified Parameters

$$\left\{ \begin{array}{lll} k_L = 1.7 \times 10^{-3}\ \mathrm{s}^{-1} & k_G = 1.0 \times 10^{-1}\ \mathrm{s}^{-1} & \eta = 2.1 \\ \delta_L^{(0)} = 3.1 \times 10^{-4}\ \mathrm{N}^{-1}\mathrm{s}^{-1} & \delta_L^{(1)} = 5.0 \times 10^{-2}\ (\mu\mathrm{M}\cdot\mathrm{N})^{-1}\mathrm{s}^{-1} & \alpha = 1.3 \times 10^{4}\ \mathrm{N}^{-\eta} \\ r = 2.8 \times 10^{-5}\ \mathrm{s}^{-1} & \mu_{\mathrm{GFP}} = 220\ \mathrm{AU} & \sigma_{\mathrm{GFP}} = 390\ \mathrm{AU} \end{array} \right\}$$

Identified Model vs. Experiment



Model Predictions

B. Munsky, B. Trinh, M. Khammash, *Nature Molecular Systems Biology*, in press.

Slides that describe unpublished work on osmoregulation identification have not been included

Conclusions

- Fluctuations may be very important
  - Cell variability
  - Cell fate decisions
- Some tools are available
  - Monte Carlo simulations (SSA and variants)
  - Moment approximation methods
  - Linear noise approximation (Van Kampen)
  - Finite State Projection
- Cellular noise reveals network parameters and enables model identification
  - Stationary moments are not sufficient for full identifiability
  - Small number of transient measurements of noise is sufficient for identifiability
  - Finite State Projection allows the use of master equation solution for identification
  - Cellular noise (process noise) vs. measurement noise (output noise)

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