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Probabilistic Methods for Biochemical Reaction Networks

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LECTURE II

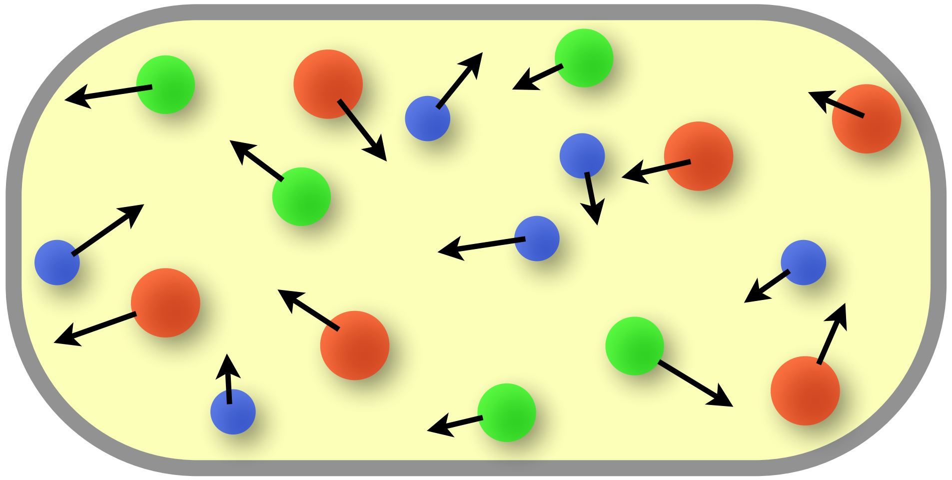
Outline

- A probabilistic modeling framework for chemical kinetics
- Generating sample paths: Monte Carlo methods
- Computing the probability density: the Chemical Master Equation
- Computing statistical moments
- Stochastic differential equation approximations

Stochastic Chemical Kinetics

A General 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 $\frac{d\Omega}{\Omega}$.

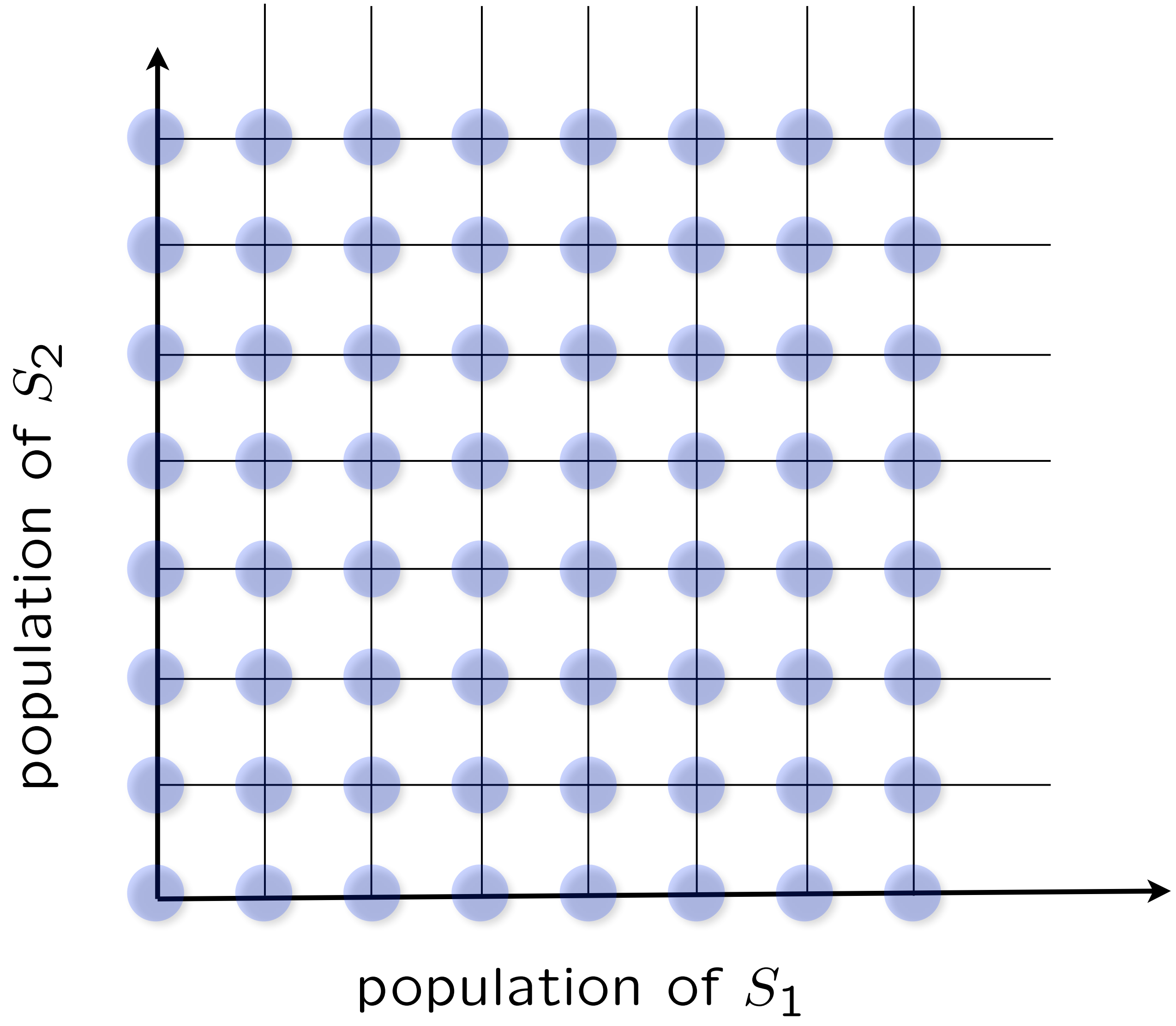
(**Thermal Equilibrium**) The molecules move due to the thermal energy. The reaction volume is at a constant temperature T. The velocity of a molecule is determined according to a Boltzman distribution:

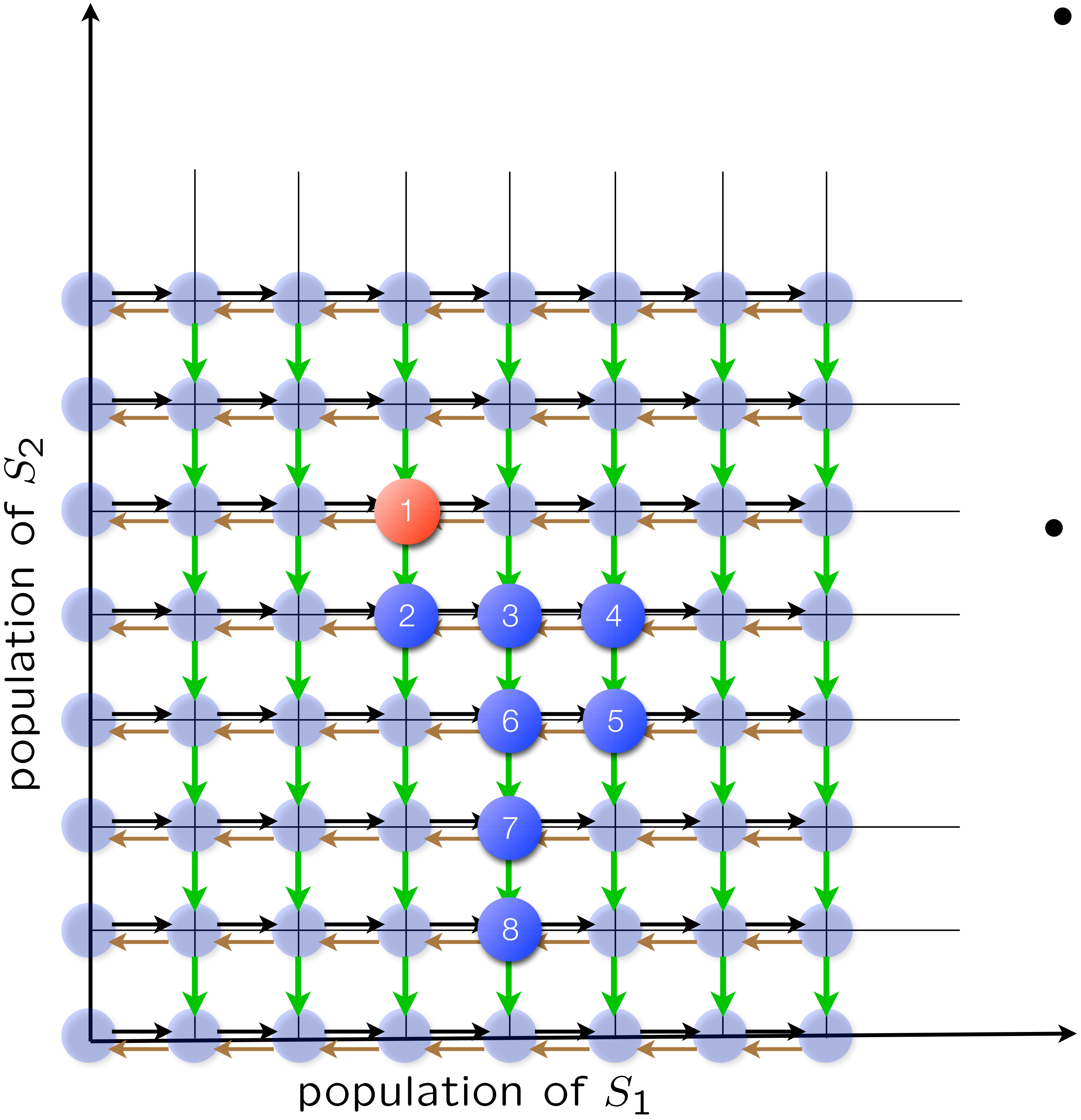
$$f_{v_x}(v) = f_{v_y}(v) = f_{v_z}(v) = \sqrt{\frac{m}{2\pi k_B T}}\; e^{-\frac{m}{2k_B T}v^2}$$

Stochastic Chemical Kinetics

- **(N-species)** Start with a chemically reacting system containig N distinct reacting species $\{\mathcal{S}_1, \ldots, \mathcal{S}_N\}$.

- The state of the system is described by the integer random variable $X(t) = [X_1(t), \ldots, X_N(t)]$; $X_i(t)$ is the population of $\mathcal{S}_i$ at time t.





Sequence: R_2 R_1 R_1 R_2 R_3 R_2 R_2

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

Example:	R_1	$\phi \rightarrow S_1$
	R_2	$S_1 + S_2 \rightarrow S_1$
	R_3	$S_1 \rightarrow \phi$

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

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

Stoichiometry matrix:

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

- **(Transition Probability)** Suppose the system is in state $X(t) = \mathbf{x}$.

The probability that R_k is the next reaction and that it occurs within the next dt time units is given by $\underbrace{w_k(\mathbf{x})}_{\textbf{propensity function}} dt$.

If R_k is the zeroth order reaction $\phi \rightarrow$ products, then $w_k(\mathbf{x}) = c_k$, for some constant c_k.

If R_k is the monomolecular reaction $S_i \rightarrow$ products, then $w_k(\mathbf{x}) = c_k \mathbf{x}_i$, for some constant c_k.

If R_k is the bimolecular reaction $S_i + S_j \rightarrow$ products, then

$$w_k(\mathbf{x}) = \left\{ \begin{array}{ll} c_k \mathbf{x}_i \mathbf{x}_j, & i \neq j \\ c_k \dfrac{\mathbf{x}_i(\mathbf{x}_i - 1)}{2}, & i = j \end{array} \right\}, \text{ for some constant } c_k.$$

Sample Path Representations

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

Counting Process Representation:

$$X(t) = X(0) + \sum_{K=1}^{M} s_k N_k(t)$$

$N_k(t)$ is a counting process representing # of firings of R_k in $[0, t]$.

N_k has a state-dependent intensity:

$$P\{N_k(t + \Delta t) - N_k(t) = 1\} \approx w_k(X(t)) \cdot \Delta t$$

Sample Path Representation

If the counting process $N(t)$ has intensity $w(t)$, there exists a unit Poisson process $Y(\cdot)$ such that

$$N(t) = Y\left[\int_0^t w(s)ds\right].$$

Applying to the counting process representation: $X(t) = X(0) + \sum_{k=1}^{M} s_k N_k$

we get

Random Time Change 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

Generator of X(t)

Generator: The generator of a stochastic process is defined as:

$$(\mathcal{A}f)(x) \;\equiv\; \lim_{t\downarrow 0} \frac{1}{t} E\{f(X(s+t) - f(X(s)) \,|X(s) = x\}$$

$\mathcal{A}$ is an operator that maps functions $f : \mathbb{R}^N \to \mathbb{R}$ in its domain into functions $\mathcal{A}f : \mathbb{R}^N \to \mathbb{R}$.

The generator of a stochastic process encodes a great deal of information about the process.

For the Markov process describing our chemical system:

$$(\mathcal{A}f)(x) \;=\; \sum_{k=0}^{N} w_k(x)(f(x+s_k) - f(x))$$

From Stochastic to Deterministic

Given N species $\mathcal{S}_1, \ldots, \mathcal{S}_N$ and M elementary reactions. Let $\Phi_i := [\mathcal{S}_i]$.

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

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

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 $t \geq 0$:

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

T. Kurtz

Simulating Sample Paths

Monte Carlo Methods

Generating Sample Paths

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)

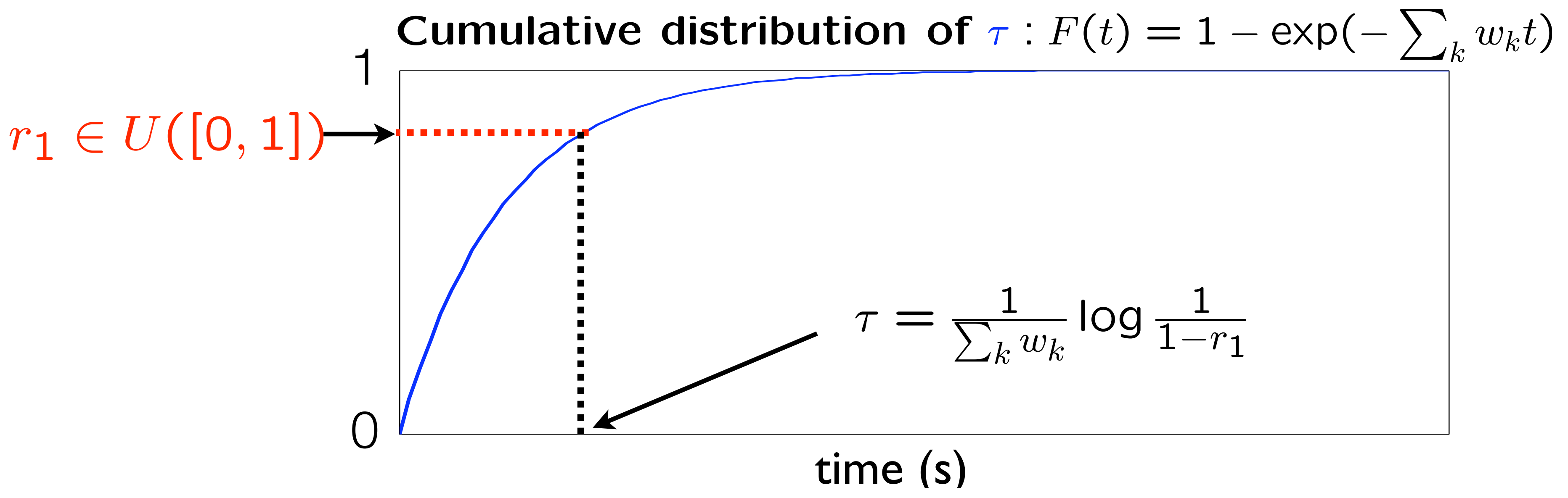
$\mu = \arg\min_i\{\tau_i\}$ (Index of the next reaction)

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

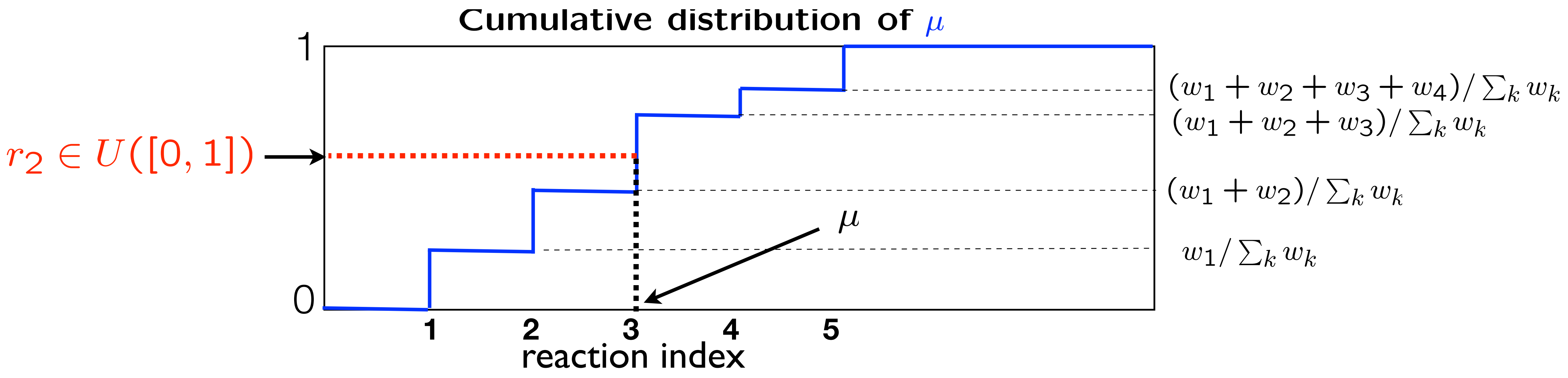
Fact 2: $P(\mu = k) = \frac{w_k}{\sum_i w_i}$

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: $x \leftarrow x + s_\mu$.

Stochastic Simulation Algorithm: Matlab code

```
clear all
t=0;tstop = 2000;                                  %%specify initial and final times
x = [0; 0];                                        %% Specify initial conditions
S = [1 -1 0  0; 0  0 1 -1];                        %% Specify stoichiometry
w = inline('[10, 1*x(1), 10*x(1), 1*x(2)]','x');   %% Specify Propensity functions
while t<tstop
    a = w(x);                                       % compute the prop. functions
    w0 = sum(a);                                 % compute the sum of the prop. functions
    t = t+1/w0*log(1/rand);                         % update time of next reaction
    if t<=tstop
      r2w0=rand*w0;                   % generate second random number and multiply by prop. sum
      i=1;                                          % initialize reaction counter
      while sum(a(1:i))<r2w0           % increment counter until sum(a(1:i)) exceeds r2w0
         i=i+1;
      end
      x = x+S(:,i);                                  % update the configuration
   end
end
```

Generating Sample Paths

Gibson-Bruck Next Reaction Method

The Gibson-Bruck method is an exact stochastic simulation algorithm

It is based on the random time change representation:

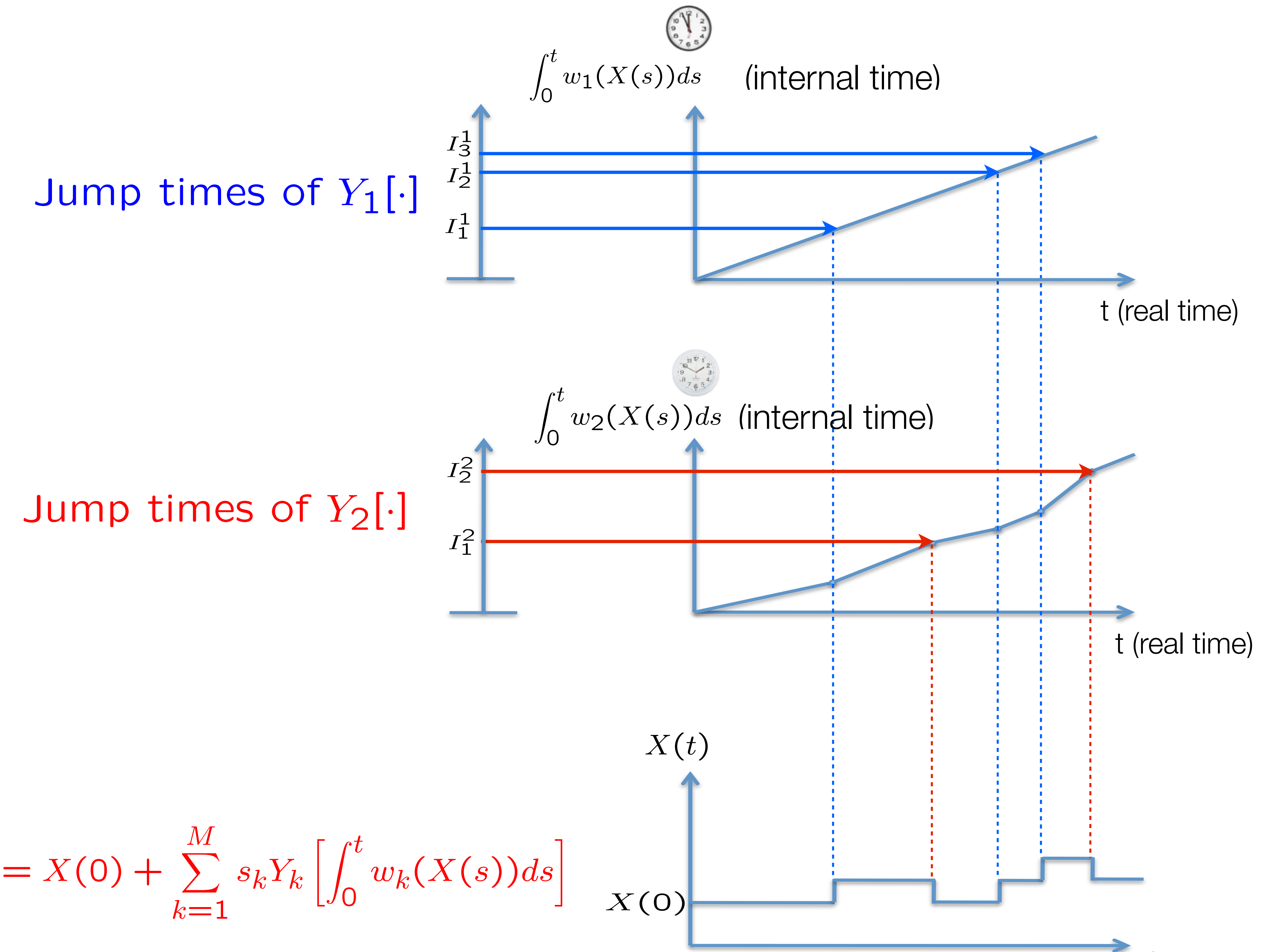
$$X(t) = X(0) + \sum_{k=1}^{M} s_k Y_k \left[\int_0^t w_k(X(s)) ds \right]$$

It is more efficient that Gillespie's SSA

Uses one random number per reaction event

Generating Sample Paths

Example: Birth-Death Process $\phi \xrightarrow{c_1} \mathcal{S} \xrightarrow{c_2 X} \phi$ $X =$ Species $\mathcal{S}$ count



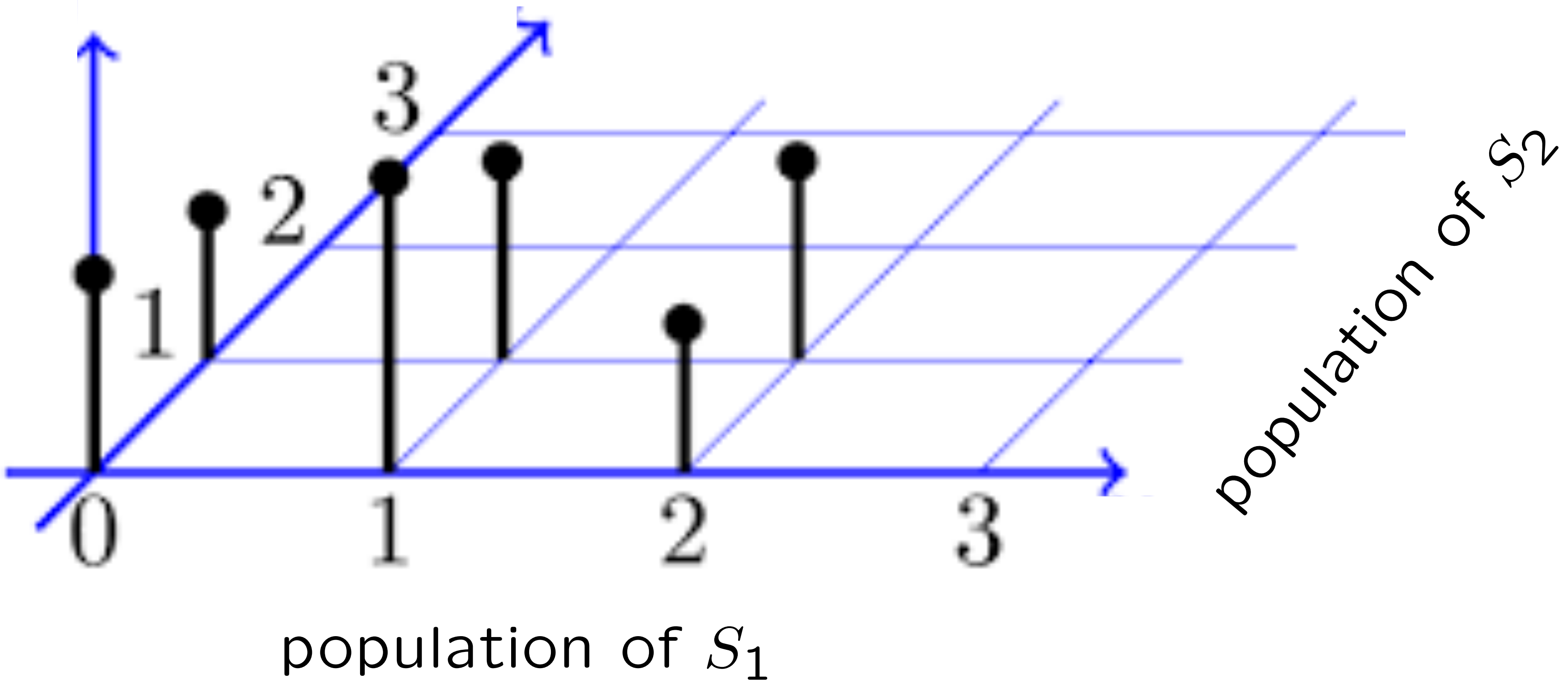
$$X(t) = X(0) + \sum_{k=1}^{M} s_k Y_k\left[\int_0^t w_k(X(s))ds\right]$$

The Probability Density Function of X

The Chemical Master Equation

The Chemical Master Equation

Given a system state x, we would like to find $P(X(t) = x)$



Notation: $p(x, t) := P(X(t) = x)$

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

$$p(x, t+dt) = \overset{\text{at } x}{p(x,t)} \overset{\text{No reaction fires}}{\left(1 - \sum_k w_k(x)dt + \mathcal{O}(dt^2)\right)}$$

$$+ \sum_k \underset{\text{R_k reaction away from x}}{p(x - s_k, t)} \underset{\text{R_k fires once}}{\left(\sum_k w_k(x)dt + \mathcal{O}(dt^2)\right)} + \underset{\text{more than one reaction in dt}}{\mathcal{O}(dt^2)}$$

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

The Chemical Master Equation

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

Dynkins Formula

Dynkins Formula

Given $f:\mathbb{R}^N \to \mathbb{R}$ and $t \geq 0$. Then

$$\mathbb{E}(f(X(t))) = \mathbb{E}(f(X(0))) + \mathbb{E}\left(\int_0^t \mathcal{A}f(X(s))ds\right).$$

Can be thought of as a stochastic generalization of the Fundamental Theorem of Calculus.

Using Dynkin's Formula to Derive the CME

For a state $x \in \mathbb{N}_0^N$, let $f(y) = \mathbb{1}_{\{x\}}(y)$ be the indicator function of $\{x\}$.

Note that for any $g : \mathbb{R}^N \to \mathbb{R}$ we have

$$\mathbb{E}\left(g(X(t))f(X(t))\right) = g(x)p(x,t) \tag{1}$$

$$\text{and } \mathbb{E}\left(g(X(t))f(X(t)+s_k)\right) = g(x-s_k)p(x-s_k,t), \tag{2}$$

Applying the Dynkin's formula on f we obtain

$$p(x,t) = p(x,0) + \sum_{k=1}^{M} \int_0^t \mathbb{E}\left(w_k(X(s))(f(X(s)+s_k) - f(X(s)))\right) ds$$

Using (1) and (2) we get

$$\boxed{p(x,t) = p(x,0) + \sum_{k=1}^{M} w_k(x-s_k) \int_0^t p(s,x-s_k)ds - \sum_{k=1}^{M} w_k(x) \int_0^t p(s,x)ds.}$$

Statistical Moments

Using Dynkin's Formula to Derive the Statistical Moments

We derive the differential equations for the first and second moment.

Let $f : \mathbb{R}^N \to \mathbb{R}$ be given by $f(x_1, \ldots, x_N) = x_i$. By Dynkin's formula

$$\mathbb{E}\left(f(X(t))\right) = \mathbb{E}\left(f(X(0))\right) + \sum_{k=1}^{M} \mathbb{E}\Big(\int_0^t w_k(X(s))(f(X(s)+s_k) - f(X(s))$$

But $\mathbb{E}\left(f(X(t))\right) = \mathbb{E}(X_i(t))$ and $(f(X(s)+s_k) - f(X(s))) = s_{ik}$.

Hence we get

$$\mathbb{E}(X_i(t)) = \mathbb{E}(X_i(0)) + \sum_{k=1}^{M} s_{ik} \int_0^t \mathbb{E}\left(w_k(X(s))\right) ds.$$

Using Dynkin's Formula to Derive the Statistical Moments (cont.)

$$\mathbb{E}(X_i(t)) = \mathbb{E}(X_i(0)) + \sum_{k=1}^{M} s_{ik} \int_0^t \mathbb{E}\left(w_k(X(s))\right) ds \tag{3}$$

Let S be the stoichiometry matrix and let $w(x)$ be the propensity vector

$$w(x) = (w_1(x), \ldots, w_M(x))^T.$$

Since (3) holds for each i, we can write the equation for the first moment $\mathbb{E}(X(t)) = (\mathbb{E}(X_1(t)), \ldots, \mathbb{E}(X_N(t)))$ as

$$\mathbb{E}(X(t)) = \mathbb{E}(X(0)) + \int_0^t S\mathbb{E}(w(X(s)))ds.$$

This equation in differential form becomes

$$\frac{d\mathbb{E}(X(t))}{dt} = S\mathbb{E}(w(X(t))).$$

Using Dynkin's Formula to Derive the Statistical Moments (cont.)

Now consider the function $f : \mathbb{R}^N \to \mathbb{R}$ given by $f(x) = x_i x_j$.

For any $x \in \mathbb{N}_0^N$ we get

$$\begin{aligned}\sum_{k=1}^{M} w_k(x)\left(f(x+s_k) - f(x)\right) &= \sum_{k=1}^{M} w_k(x)\left((x_i + s_{ik})(x_j + s_{jk}) - x_i x_j\right)\\ &= \sum_{k=1}^{M} w_k(x)\left(x_i s_{jk} + x_j s_{ik} + s_{ik} s_{jk}\right)\\ &= [x w^T(x) S^T]_{ij} + [S w(x) x^T]_{ij} + [S W(x) S^T]\end{aligned}$$

where $W(x)$ is $M \times M$ diagonal matrix with entries $w_1(x), \ldots, w_M(x)$.

Applying the Dynkin's formula with f we get

$$\begin{aligned}\mathbb{E}\left(X_i(t) X_j(t)\right) = \mathbb{E}\left(X_i(0) X_j(0)\right) &+ \\ \int_0^t \mathbb{E}\left([X(s) w^T(X(s)) S^T]_{ij} + [S w(X(s)) X^T(s)]_{ij} + [S W(X(s)) S^T]_{ij}\right) ds.\end{aligned}$$

Using Dynkin's Formula to Derive the Statistical Moments (cont.)

$$\mathbb{E}\left(X_i(t)X_j(t)\right) = \mathbb{E}\left(X_i(0)X_j(0)\right) + \int_0^t \mathbb{E}\left([X(s)w^T(X(s))S^T]_{ij} + [Sw(X(s))X^T(s)]_{ij} + [SW(X(s))S^T]_{ij}\right) ds.$$

Since this holds for each i and j, we can write the equation for the second moment (covariance matrix) $\mathbb{E}(X(t)X^T(t))$ as

$$\mathbb{E}\left(X(t)X^T(t)\right) = \mathbb{E}\left(X(0)X^T(0)\right) + \int_0^t \left(\mathbb{E}(X(s)w^T(X(s))S^T) + \mathbb{E}(Sw(X(s))X^T(s)) + \mathbb{E}(SW(X(s))S^T)\right) ds.$$

This equation in differential form becomes

$$\boxed{\frac{d\mathbb{E}(X(t)X^T(t))}{dt} = \mathbb{E}(X(t)w^T(X(t))S^T) + \mathbb{E}(Sw(X(t))X^T(t)) + \mathbb{E}(SW(X(t))S^T).}$$

To Sum Up

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

Moment Dynamics

$$\begin{aligned} \frac{d\mathbb{E}[X]}{dt} &= S\ \mathbb{E}[w(X)] \\ \frac{d\mathbb{E}[XX^T]}{dt} &= S\mathbb{E}[w(X)X^T] + \mathbb{E}[Xw^T(X)]S^T + S\ \mathbb{E}[W(X)])\ S^T \end{aligned}$$

Affine Propensity

Suppose the propensity function is affine:

$$w(x) = W_0 x + w_0, \qquad (W_0 \text{ is } N \times N,\ w_0 \text{ is } N \times 1)$$

Then $\mathbb{E}[w(X)] = W_0\mathbb{E}[X] + w_0$, and $\mathbb{E}[w(X)X^T] = W_0\mathbb{E}[XX^T] + w_0\mathbb{E}[X^T]$.

This gives us the moment equations:

$$\begin{aligned} \frac{d}{dt}\mathbb{E}[X] &= SW_0\mathbb{E}[X] + Sw_0 && \text{First Moment} \\ \frac{d}{dt}\mathbb{E}[XX^T] &= SW_0\mathbb{E}[XX^T] + \mathbb{E}[XX^T]W_0^T S^T + S\ diag(W_0\mathbb{E}[X] + w_0)S^T \\ &+ Sw_0\mathbb{E}[X^T] + \mathbb{E}[X]w_0^T S^T && \text{Second Moment} \end{aligned}$$

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

Affine Propensity (cont.)

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

$$\boxed{\frac{d}{dt}\Sigma = SW\Sigma + \Sigma W_0^T S^T + S\ diag(W_0\mathbb{E}[X] + w_0)S^T}$$

Stationary Case

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

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

Then

$$\boxed{\begin{gathered} SW_0\bar{X} = -Sw_0 \\ SW_0\bar{\Sigma} + \bar{\Sigma}W_0^T S^T + S\ diag(W_0\bar{X} + w_0)S^T = 0 \end{gathered}}$$

Fluctuations Arise from Noise Driven Dynamics

Define $A = SW_0$, and $B = S\sqrt{diag(W_0\bar{X} + w_0)}$.
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

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

The Lyapunov equation characterizes the steady-state covariance of a output of the linear dynamical system

$$\dot{y} = Ay + B\omega$$

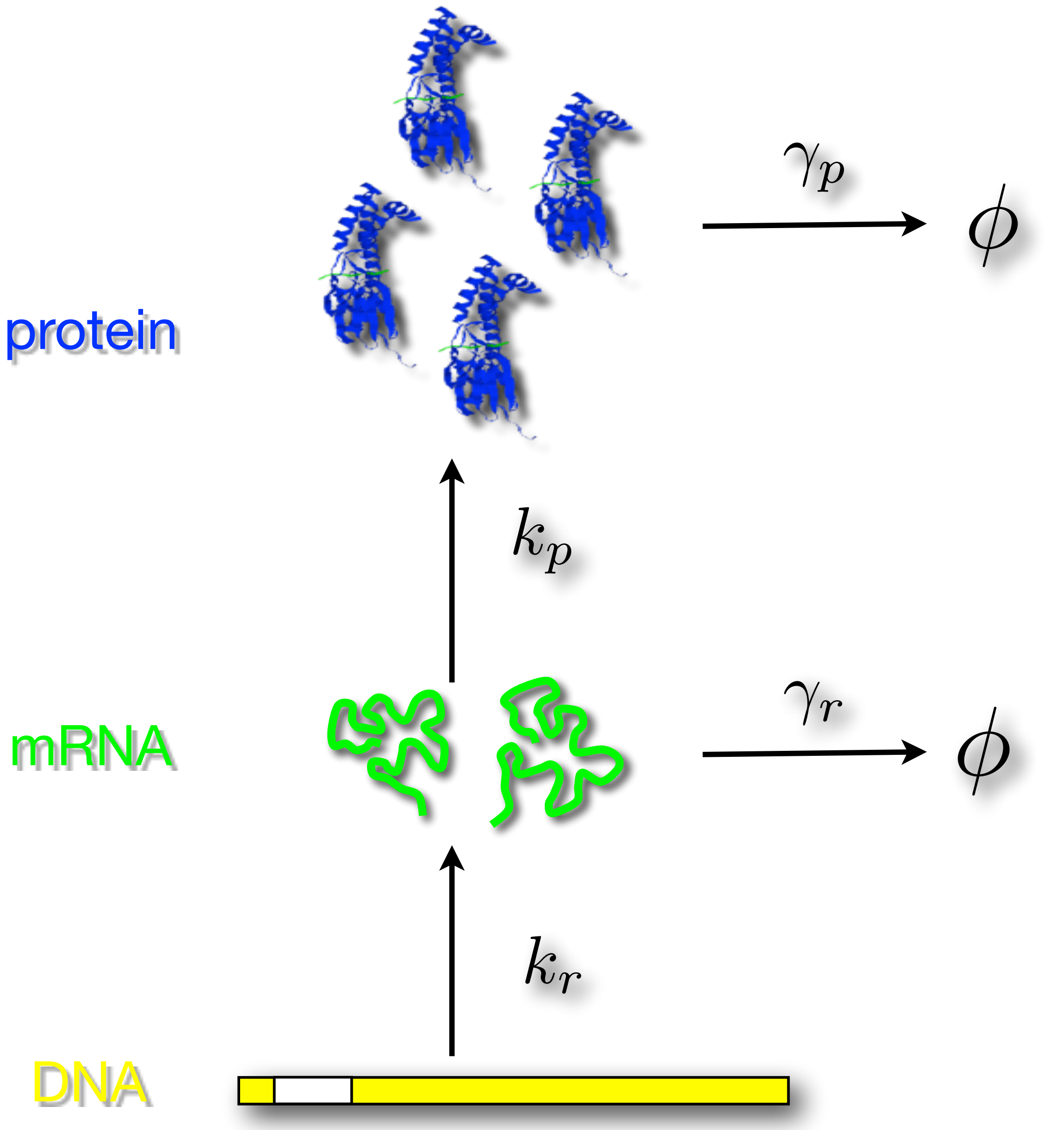
where ω is a unit intensity white Gaussian noise!

More precisely, the solution of the vector SDE:

$$dy = Ay\ dt + B\ dW_t$$

where W_t is Brownian motion. This is also called **Ornstein-Uhlenbeck**

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

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

$$w(X) = \begin{bmatrix} k_r \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & 0 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_{W_0} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_r \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

Steady-State Moments

$$A = SW_0 = \begin{bmatrix} -\gamma_r & 0 \\ k_p & -\gamma_p \end{bmatrix}, \qquad Sw_0 = \begin{bmatrix} k_r \\ 0 \end{bmatrix}$$

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

Steady-State Covariance

$$BB^T = S\ diag(W_0\bar{X} + w_0)S^T = \begin{bmatrix} 2k_r & 0 \\ 0 & \frac{2k_p k_r}{\gamma_r} \end{bmatrix}$$

The steady-state covariances equation

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

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

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

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}?

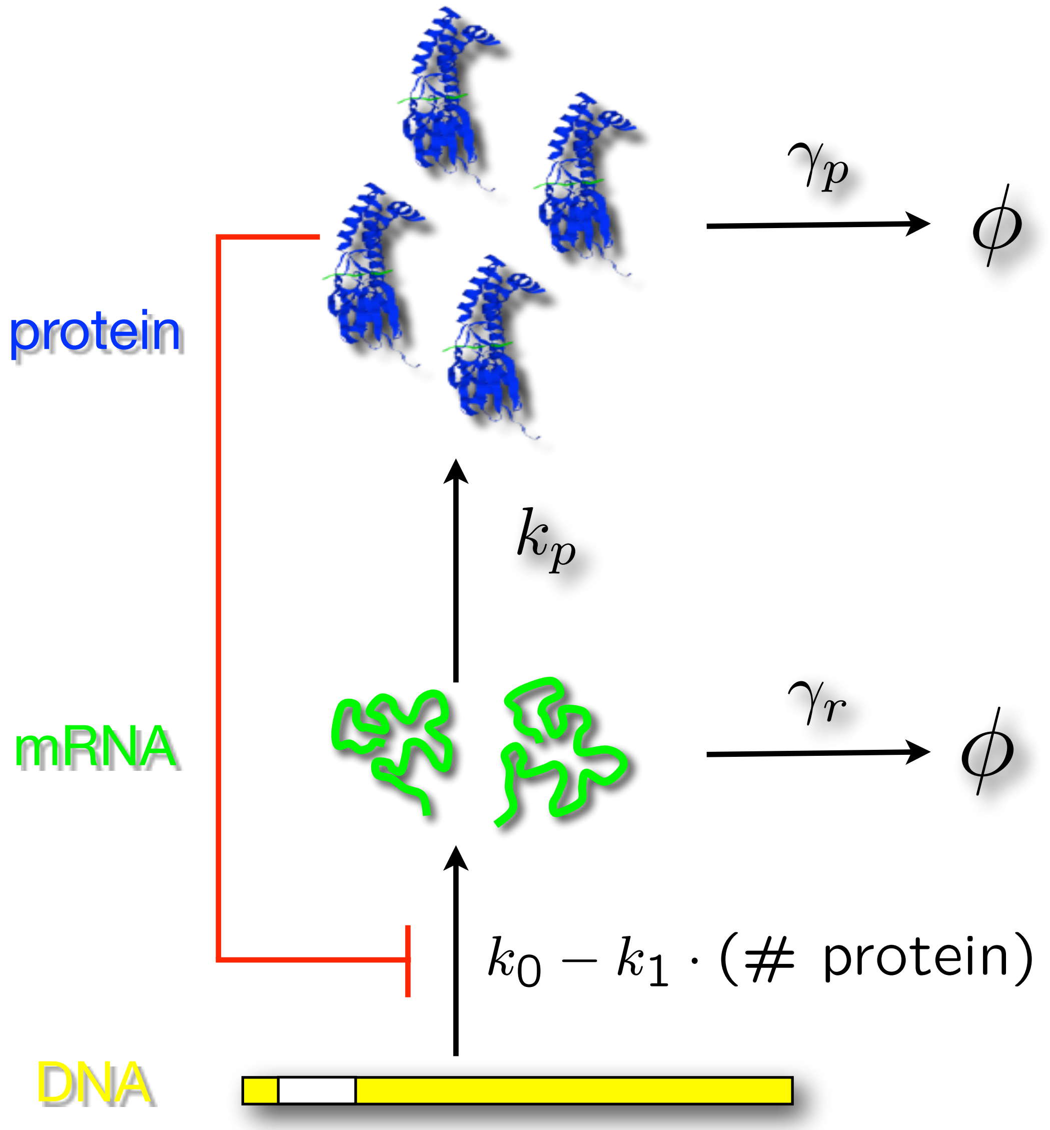
$$\begin{aligned} C_{vp}^2 &= \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left(1 + \frac{k_p}{\gamma_r + \gamma_p}\right) \\ &\geq \frac{1}{\frac{k_r k_p}{\gamma_r \gamma_p}} \left(\frac{k_p}{\gamma_r + \gamma_p}\right) = \frac{\gamma_r \gamma_p}{k_r} \cdot \frac{1}{\gamma_r + \gamma_p} \end{aligned}$$

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

Large mean does not imply small fluctuations!

Application: Noise Suppression

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

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

$$w(X) = \begin{bmatrix} k_0 - k_1 X_2 \\ \gamma_r X_1 \\ k_p X_1 \\ \gamma_p X_2 \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & -k_1 \\ \gamma_r & 0 \\ k_p & 0 \\ 0 & \gamma_p \end{bmatrix}}_{W_0} \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \underbrace{\begin{bmatrix} k_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}}_{w_0}$$

Steady-State Moments

$$A = SW_0 = \begin{bmatrix} -\gamma_r & -k_1 \\ k_p & -\gamma_p \end{bmatrix}, \qquad Sw_0 = \begin{bmatrix} k_0 \\ 0 \end{bmatrix}$$

$$\bar{X} = -A^{-1}Sw_0 = \begin{bmatrix} \frac{\frac{k_0}{\gamma_r}}{1+\frac{k_1 k_p}{\gamma_p \gamma_r}} \\ \\ \frac{\frac{k_0 k_p}{\gamma_r \gamma_p}}{1+\frac{k_1 k_p}{\gamma_p \gamma_r}} \end{bmatrix} =: \begin{bmatrix} \mu_r \\ \mu_p \end{bmatrix}$$

Steady-State Covariance

$$BB^T = S\ diag(W_0\bar{X} + w_0)S^T = \begin{bmatrix} k_0 + \gamma_r\mu_r - k_1\mu_p & 0 \\ 0 & k_p\mu_r + \gamma_p\mu_p \end{bmatrix}$$

The steady-state covariances equation

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

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

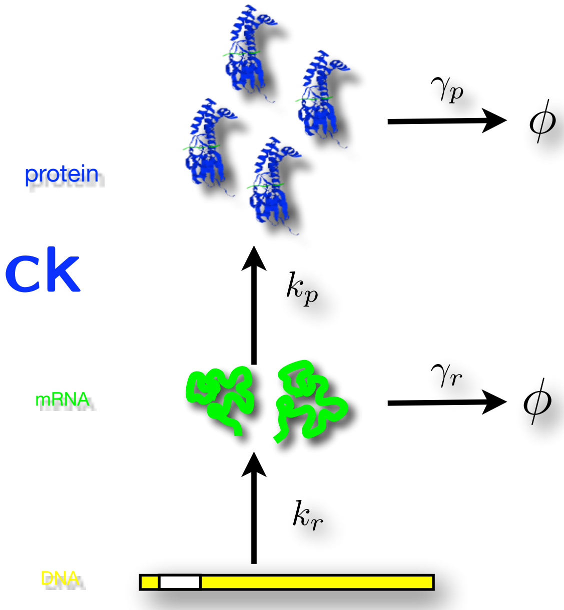
$$\bar{\Sigma}_{22} = \sigma_p^2 = \left[\frac{1-\phi}{1+b\phi} \cdot \frac{b}{1+\eta} + 1\right]\mu_p \qquad \text{where } \phi = \frac{k_1}{\gamma_p},\ b = \frac{k_p}{\gamma_r},\ \eta = \frac{\gamma_p}{\gamma_r}$$

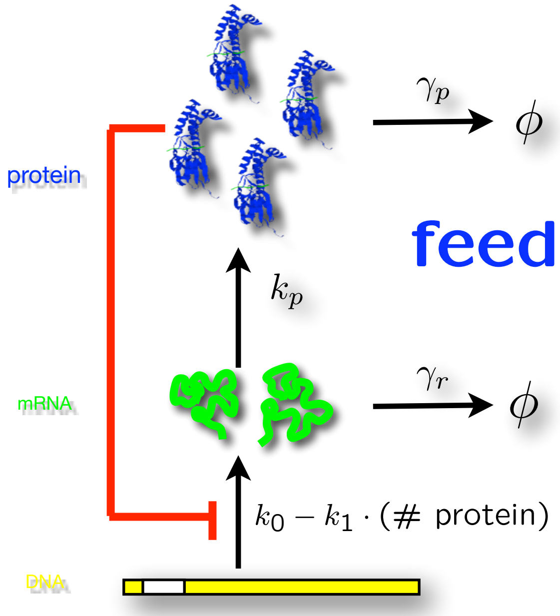
Feedback vs. No Feedback

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

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

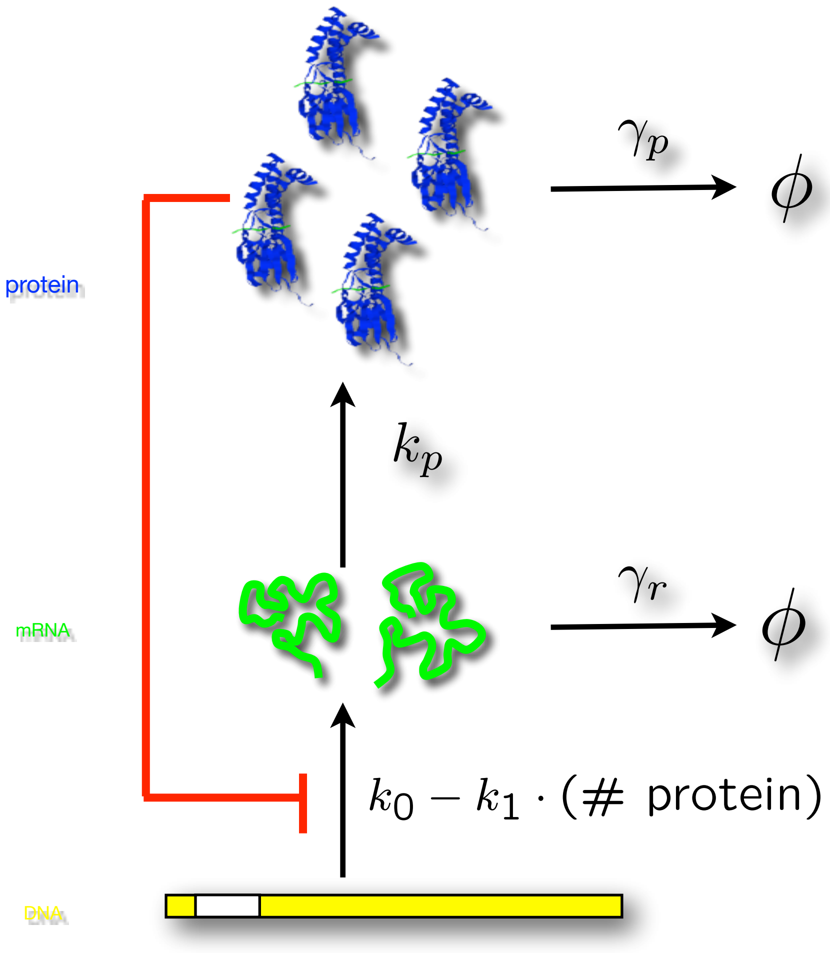
$$\left[\underbrace{\frac{1-\phi}{1+b\phi}}_{<1} \cdot \frac{b}{1+\eta} + 1\right]\mu_p^*$$

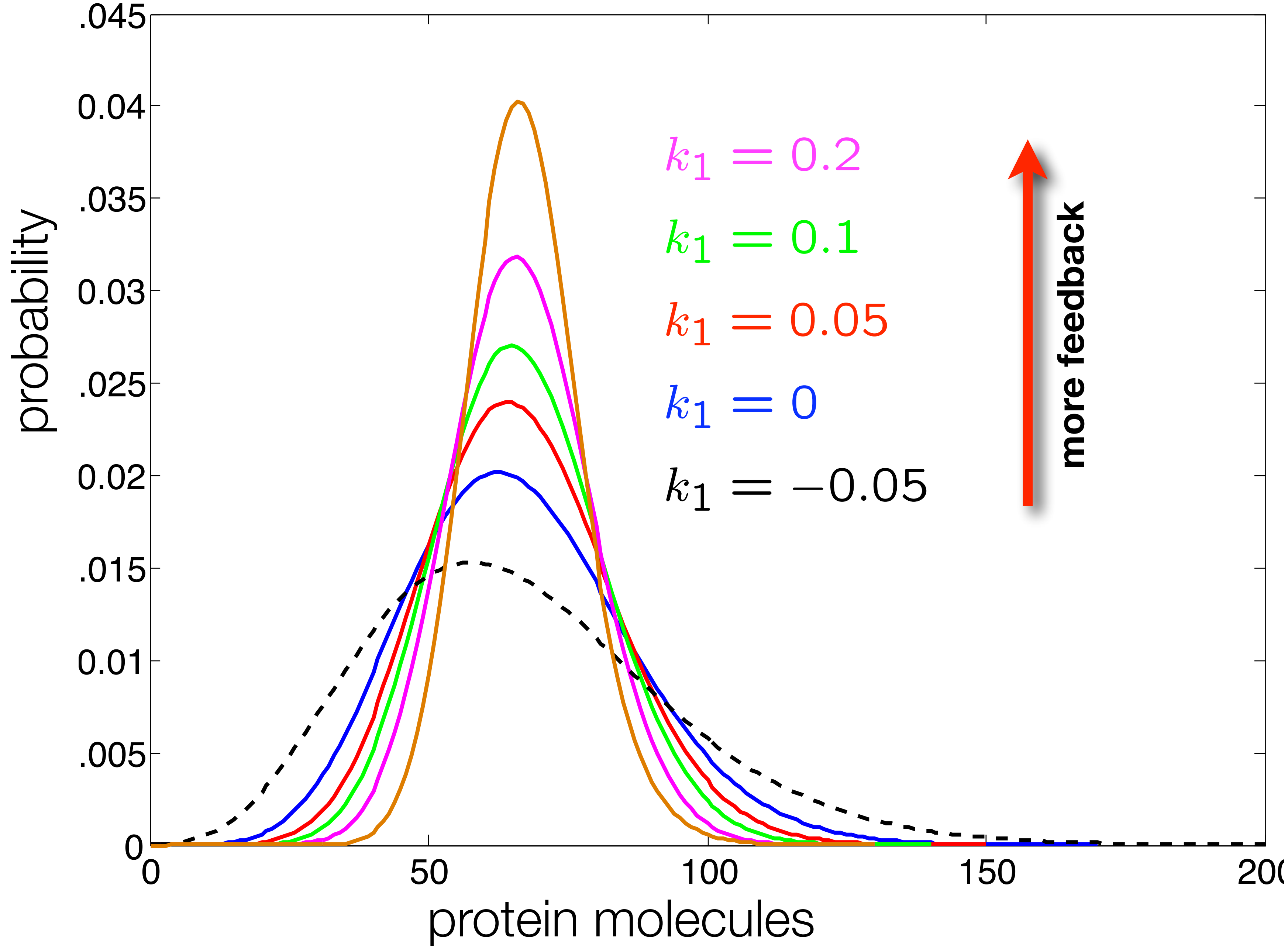
where $\phi = \frac{k_1}{\gamma_p}$

Protein variance is always smaller with negative feedback!

Example

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





SDE Approximations of X

The Linear Noise Approximation (LNA)

Linear Noise Approximation (LNA)

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

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

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

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

Linear Noise Approximation: Stationary Case

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

We look at the LNA around a stationary solution: $0 = Sf(\bar{\Phi})$.

Linear Noise Approximation

$$\boxed{X^{\Omega}(t) \approx \bar{\Phi} + \frac{1}{\sqrt{\Omega}} V(t)}$$

$$dV(t) = A \; V(t) dt + B \; dW_t$$

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

Linear Noise Approximation: Stationary Case

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

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

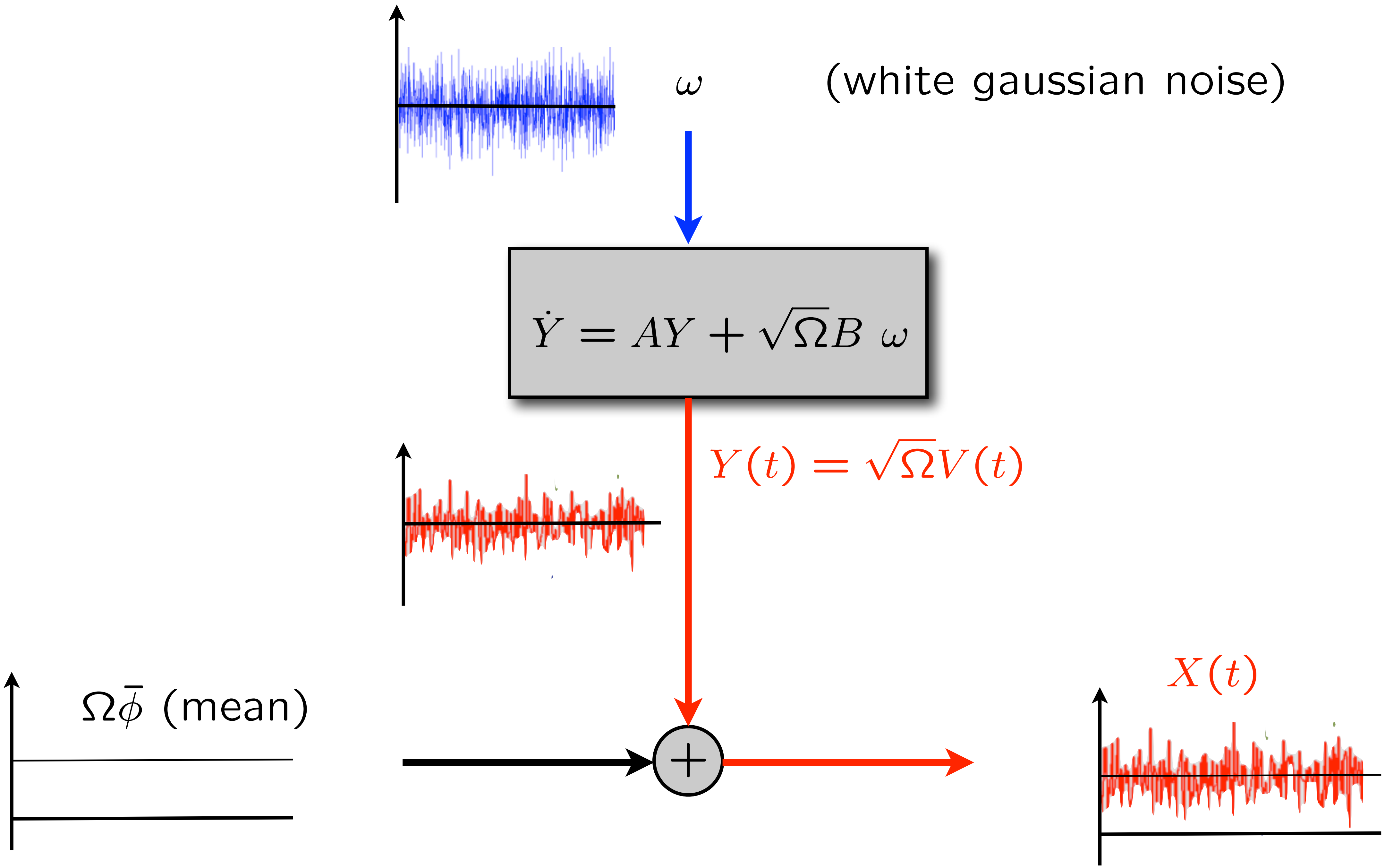
deterministic

zero mean stochastic

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

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)

$X(t)$

Summary

Random Time-Change Represenation

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

$Y_k[\cdot]$ independent unit Poisson

Statistical Moments

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

Density Dynamics (Chemical Master Equation)

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

$p(x,t) = \Pr\{X(t) = x\}$

Stochastic Diff. Eqn. Approximation

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

where $dV(t) = A(t)V(t)dt + B(t)dW_t$