Time-Scaled Stochastic Input to Biochemical Reaction Networks

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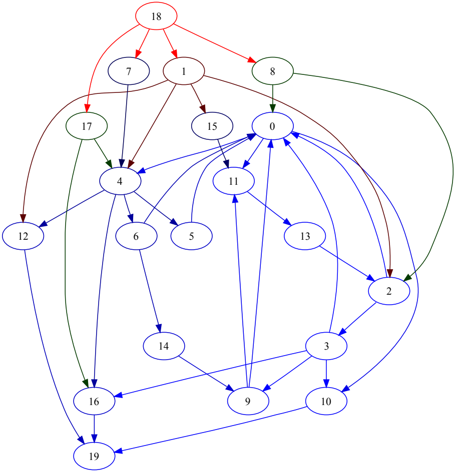
Multiple time scales

- Seconds or minutes, ex: hormonal and neural inputs
- Hours or days, ex: inputs from meals or circadian rhythms
- Years, ex: long term environment, diet, disease, pollution

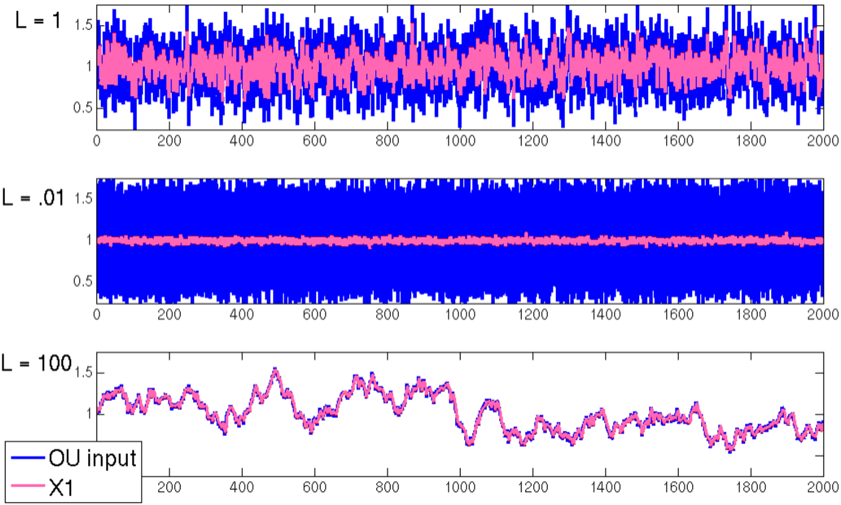
Question

How does the variance of reaction rates within a system compare to the variance of the input?

$$\xrightarrow{\mathtt{I}+\xi(t)} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{m-1}} X_m \xrightarrow{k_m}$$



Time Scale $\left(\frac{t}{L}\right)$ Affects Variance



Ways to study chemical reaction networks

- Continuous time Markov chains for small # of molecules
  - State of system is $x = (x_1, \ldots, x_n) \in \mathbb{Z}^n_{\geq 0}$.
  - Each reaction has a rate function $a(x)$ and a vector $v = (v_1, \ldots, v_n) \in \mathbb{Z}^n$.
  - State of system after reaction is $x + v$.

- Stochastic simulation algorithms
  - Fast and slow reactions.
  - Compute modified slow rates by simulating fast reactions.
  - Then simulate slow reactions.

Ways to study chemical reaction networks, cont...

- Averaging methods $$\begin{cases} \dfrac{dx}{dt} &= f(x,y) \\ \dfrac{dy}{dt} &= \dfrac{1}{\epsilon}g(x,y) + \dfrac{1}{\sqrt{\epsilon}}\beta(x,y)\dfrac{dW}{dt} \end{cases}$$

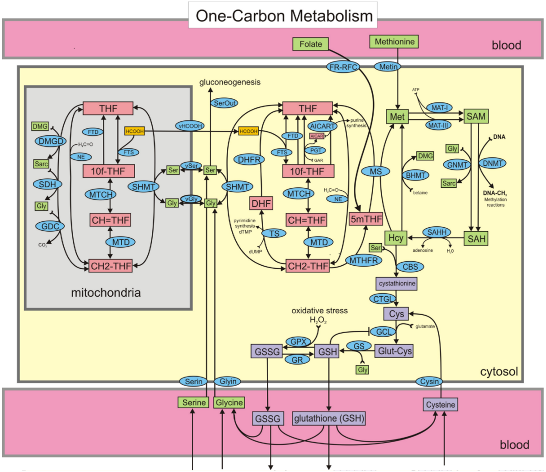
- Classic metabolic control analysis

  A given steady state is compared with a new one after slightly perurbing one parameter:

$$\text{Control Coefficient } = \frac{J'}{J}\Big/\frac{v'}{v}$$

Ways to study chemical reaction networks, cont...

- Computer models of specific networks



Reed MC, Thomas RL, Pavisic J, James SJ, Ulrich CM, & Nijhout HF (2008).

A Mathematical Model of Glutathione Metabolism. *Theo Biol & Med Modeling*: **8**, 8.

Simple Chains

$$\xrightarrow{\mathtt{I}+\xi(t)} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{n-1}} X_n \xrightarrow{k_n}$$

$$\begin{aligned}
dX_1 &= (\mathtt{I}+\xi(t))dt - k_1 X_1 dt \\
dX_2 &= k_1 X_1 dt - k_2 X_2 dt \\
&\cdots \\
dX_n &= k_{n-1} X_{n-1} dt - k_n X_n dt
\end{aligned}$$

Chains

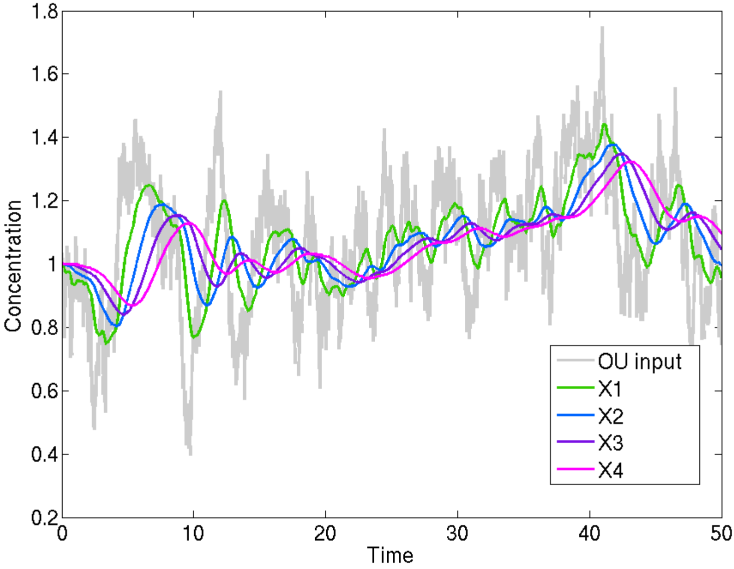
Variance decreases down a chain (Anderson)

$$\xrightarrow{\mathtt{I}+\xi(t)} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{m-1}} X_m \xrightarrow{k_m}$$

For a non-reversible chain and stationary stochastic process $\xi(t)$ with finite variance, mean zero, and $\xi(t) \geq -\mathtt{I}$,

$$\begin{aligned} Var(k_i x_i^*) &< Var(\xi) \\ Var(k_{i+1} x_{i+1}^*) &< Var(k_i x_i^*) \end{aligned}$$

Variance Decreases Down a Chain



Side Reactions

$$\begin{tikzcd} \arrow[r, "\mathtt{I}+\xi(t)"] & X_1 \arrow[r, "k_1"] \arrow[d, shift right, "k_2"'] & {} \\ & \boxed{\text{Side System}} \arrow[u, shift right, "k_3"'] & \end{tikzcd}$$

$$\xrightarrow{\mathtt{I}+\xi(t)} \tilde{X}_1 \xrightarrow{k_1}$$

Assume: for $s < t$, $\mathbf{E}\xi(t)\xi(s) > 0$ and $\mathbf{E}\xi(t)\xi(s)$ is increasing in s. (Anderson) Then a side reaction system lowers variance:

$$Var(k_1 x_1^*) < Var(k_1 \tilde{x}_1^*)$$

Feedback Loops

Feedback loops lower variance (Anderson)

$$\begin{tikzcd}
{} \arrow[r, "\mathtt{I}+\xi(t)"] & X_1 \arrow[r, "k_1"] & \cdots \arrow[r, "k_{n-1}"] & X_n \arrow[r, "k_n"] \arrow[dl, "c"] & {} \\
& & \boxed{\text{Subsystem}} \arrow[ul, "f_1(t)"] & &
\end{tikzcd}$$

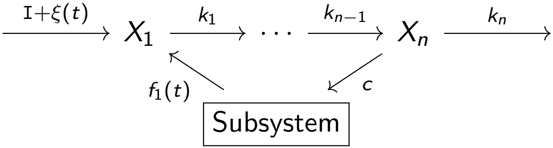
$$\xrightarrow{\mathtt{I}+\xi(t)} \tilde{X}_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{n-1}} \tilde{X}_n \xrightarrow{k_n}$$

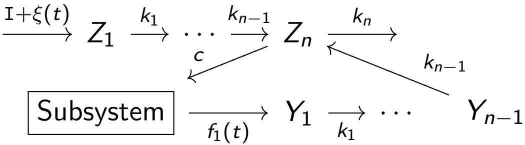
With the same hypotheses on $\xi(t)$ and $\mathbf{E}\xi(t)\xi(s)$ as before, then

$$Var(k_n x_n^*) < Var(k_n \tilde{x}_n^*)$$

Feedback Loops

Proof:



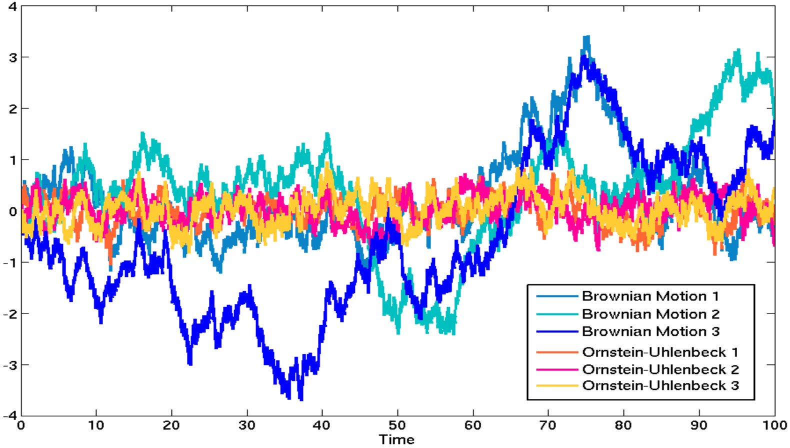


$$
\begin{aligned}
X_i &= Y_i + Z_i \text{ for } 1 \leq i \leq n-1 \\
X_n &= Z_n
\end{aligned}
$$

Assumptions

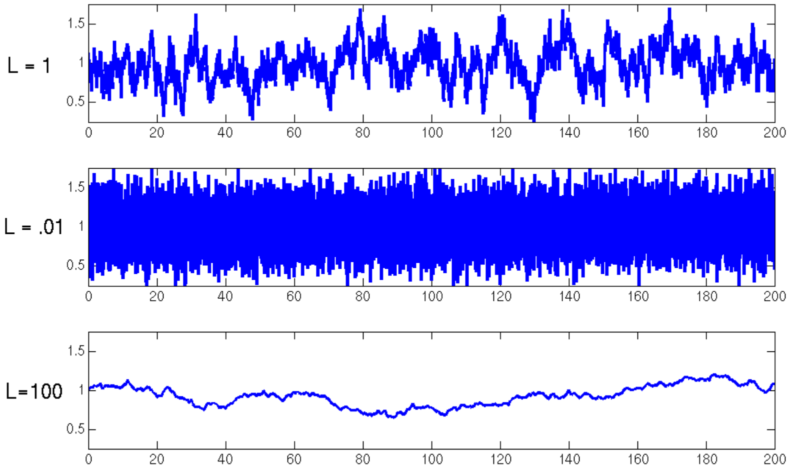
Let ξ be a stochastic process such that:

- $\xi_t \geq -\mathtt{I}$ and $\mathbb{E}\xi = 0$
- $\mathbb{E}(\xi_t \xi_s) = f(|t-s|)$ where $f \geq 0$ is measurable and decreasing with $\lim_{x\to\infty} f(x) = 0$.



	Variance	Covariance
Std BM	$\text{Var } B_t = t$	$\mathbb{E}[B_t B_s] = \min(s, t)$
Std OU	$\text{Var } Z_t = \frac{1}{2}$	$\mathbb{E}[Z_t Z_s] = \frac{1}{2} e^{-\lvert s-t \rvert}$

Time-Scaled Ornstein-Uhlenbeck Process $\xi_{t/L}$



Theorem:

Consider a chain

$$\xrightarrow{\mathtt{I}+\xi(t)} X_1 \xrightarrow{k_1} \dots \xrightarrow{k_{m-1}} X_m \xrightarrow{k_m}$$

Let $\xi(t)$ be a stationary stochastic process with

- finite variance and mean zero
- $\mathbb{E}[\xi(t)\xi(s)] = f(|t-s|)$ where $f \geq 0$ is measurable, decreasing with $\lim_{x\to\infty} f(x) = 0$.

Then

$$\begin{aligned} \lim_{L\to\infty} \text{Var } k_i X_{i,\frac{t}{L}} &= f(0) = \text{Var } \xi \\ \lim_{L\to 0} \text{Var } k_i X_{i,\frac{t}{L}} &= 0 \end{aligned}$$

$$\xrightarrow{\mathtt{I}+\xi(t)} X \xrightarrow{k}$$

Sketch of proof:

$$\begin{aligned}
\text{Var } X_{t,L} &= \mathbb{E}\left[\int_{-\infty}^{t} e^{-k(t-s)}\xi_{s/L}ds\right]^2 \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t} e^{k(-2t+s+r)}\mathbb{E}[\xi_{s/L}\xi_{r/L}]dsdr \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t} e^{k(-2t+s+r)}f\left(\frac{1}{L}|s-r|\right)dsdr \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t-r} e^{k(-2t+v+2r)}f\left(\frac{v}{L}\right)dvdr \\
&= \frac{1}{k}\int_{0}^{\infty} e^{-kv}f\left(\frac{v}{L}\right)dv
\end{aligned}$$

Proof cont...

$$
\begin{aligned}
\lim_{L\to 0} \operatorname{Var} X_t^L &= \lim_{L\to 0} \frac{1}{k} \int_0^\infty e^{-kv} f\left(\frac{v}{L}\right) dv \\
&= \lim_{L\to 0} \frac{1}{k} \int_0^\epsilon e^{-kv} f\left(\frac{v}{L}\right) dv + \frac{1}{k} \int_\epsilon^\infty \lim_{L\to 0} e^{-kv} f\left(\frac{v}{L}\right) dv \\
&\leq \lim_{L\to 0} \frac{1}{k} \int_0^\epsilon e^{-kv} M dv + 0 \\
&= \frac{M}{k^2}(1 - e^{-\epsilon k})
\end{aligned}
$$

Down the chain

$$\xrightarrow{\mathtt{I}+\xi_{t/L}} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{i-1}} X_i \xrightarrow{k_i}$$

We will use induction. We must show that the input $k_1 X_1$ has the same form as the original input $\mathtt{I} + \xi_{t/L}$.

Note that $X_{1,t} = \dfrac{\mathtt{I}}{k_1} + \displaystyle\int_{-\infty}^{t} e^{-k_1(t-s)}\xi_s ds$.

Covariance of $X_{1,t}$

We calculate the covariance by using a change of variable and switching the order of integration.

$$
\begin{aligned}
\mathrm{Cov}(X_{1,t}X_{1,r}) &= \mathbb{E}\Big[\int_{-\infty}^{t} e^{-k(t-s)}\xi_s ds \int_{-\infty}^{r} e^{-k(r-u)}\xi_u du\Big] \\
&= \int_{-\infty}^{r}\int_{-\infty}^{t} e^{-k(t+r-s-u)} f(|s-u|) dsdu \\
&= \int_{-\infty}^{r}\int_{-\infty}^{t-u} e^{-k(t+r-v-2u)} f(v) dvdu \\
&= \int_{-\infty}^{t-r}\int_{-\infty}^{r} e^{-k(t+r-v-2u)} f(v) dudv \\
&\quad + \int_{t-r}^{\infty}\int_{-\infty}^{-v+t} e^{-k(t+r-v-2u)} f(v) dudv
\end{aligned}
$$

Proof cont...

Evaluating the integrals, we simplify:

$$\begin{aligned}
\mathrm{Cov}(X_t X_r) &= \frac{1}{2k}\int_{-\infty}^{t-r} e^{-k(t-r-v)} f(v)dv \\
&\quad + \frac{1}{2k}\int_{t-r}^{\infty} e^{-k(-t+r+v)} f(v)dv \\
&= \frac{1}{2k} e^{k(r-t)} \int_{r-t}^{\infty} e^{-kv} f(v)dv \\
&\quad + \frac{1}{2k} e^{k(t-r)} \int_{t-r}^{\infty} e^{-kv} f(v)dv
\end{aligned}$$

Proof cont...

The covariance equation of X_1 can be defined

$$
\begin{aligned}
\tilde{f}(|t-r|) &= \frac{1}{2k} e^{k|t-r|} \int_{|t-r|}^{\infty} e^{-kv} f(v)dv \\
&\quad + \frac{1}{2k} e^{-k|t-r|} \int_{-|t-r|}^{\infty} e^{-kv} f(v)dv \\
\tilde{f}(x) &= \frac{1}{2k} e^{kx} \int_{x}^{\infty} e^{-kv} f(v)dv \\
&\quad + \frac{1}{2k} e^{-kx} \int_{-x}^{\infty} e^{-kv} f(v)dv
\end{aligned}
$$

Check that $\lim_{x\longrightarrow\infty} \tilde{f}(x) = 0$

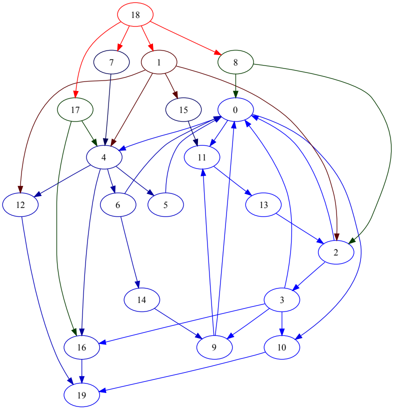
Fix a y such that $0 < y < x$.

$$
\begin{aligned}
&\lim_{x\longrightarrow\infty} \tilde{f}(x) \\
&= \lim_{x\longrightarrow\infty} \left[\frac{1}{2k} e^{kx} \int_x^{\infty} e^{-kv} f(v) dv + \frac{1}{2k} e^{-kx} \int_{-x}^{\infty} e^{-kv} f(v) dv \right] \\
&\leq \lim_{x\longrightarrow\infty} \left[\frac{f(x)}{2k} e^{kx} \int_x^{\infty} e^{-kv} dv + \frac{f(y)}{2k} e^{-kx} \int_{-x}^{-y} e^{-kv} dv + \right. \\
&\qquad \left. \frac{f(0)}{2k} e^{-kx} \int_{-y}^{0} e^{-kv} dv + \frac{f(0)}{2k} e^{-kx} \int_0^{\infty} e^{-kv} dv \right] \\
&\leq \lim_{x\longrightarrow\infty} \left[\frac{f(x)}{2k^2} + \frac{f(y)}{2k^2} \left(1 - e^{-k(x-y)}\right) \right. \\
&\qquad \left. + \frac{f(0)}{2k^2} \left(e^{-kx} - e^{-k(x-y)}\right) + \frac{f(0)}{2k^2} e^{-kx} \right] \\
&= \frac{f(y)}{2k^2}
\end{aligned}
$$

Check that $\lim_{x\to\infty} \tilde{f}(x) = 0$ continued...

Since y can be arbitrarily large and $\lim_{x\to\infty} f(x) = 0$, we have that $\lim_{x\to\infty} \tilde{f}(x) \leq \frac{f(y)}{2k^2} \to 0$.

Single Species Complex Networks



- Each complex is a single substrate
- Weakly reversible
- Mass action kinetics (linear ODEs)
- Single linkage class

A Simple Example

$$\begin{tikzcd} {} \arrow[r, "\mathtt{I}+\xi"] & X_1 \arrow[r, "k_3"] \arrow[d, shift right, "k_1"'] & X_3 \arrow[r, "k_4"] & {} \\ & X_2 \arrow[u, shift right, "k_2"'] & & \end{tikzcd}$$

$$\begin{aligned} \dot{x}(t) &= Ax(t) + \mathtt{I} + \xi(t) \\ x(0) &= x_0 \end{aligned}$$

$$A = \begin{pmatrix} -(k_1 + k_3) & k_2 & 0 \\ k_1 & -k_2 & 0 \\ k_3 & 0 & -k_4 \end{pmatrix}$$

Key Properties of SSC systems

Lemma to Feinberg's Deficiency Zero Theorem:

- Unique equlibrium that is globally asymptotically stable and in $\mathbb{R}^m_{>0}$
- Eigenvalues of A have strictly negative real parts
- For all $v \in \mathbb{R}^m_{\geq 0}$, $e^{At}v \cdot e_j \geq 0$ for all j.

The Equations

$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & Ax(t) + \mathtt{I} + \xi(t) \\ x(0) & = & x_0 \end{array} \right.$$

$$x^*(t, \xi) = \int_{-\infty}^{t} e^{A(t-s)} \mathtt{I} ds + \int_{-\infty}^{t} e^{A(t-s)} \xi(s) ds$$

$$m_i = \mathbb{E}(x_i) = \mathtt{I} \int_{-\infty}^{t} e^{A(t-s)} e_1 \cdot e_i ds$$

Variance Lowers

Theorem: (Anderson) Let $x^*(t)$ be the solution of an SSC system with one input $\mathtt{I} + \xi(t)$, where $\xi(t)$ is a stationary stochastic process with finite variance, mean zero, and $\xi(t) \geq -\mathtt{I}$. Let m_i be the mean of species x_i. Then

$$var(x_i^*) < \left(\frac{m_i}{\mathtt{I}}\right)^2 Var(\xi)$$

Assumptions

Let ξ be a stochastic process such that:

- $\xi_t \geq -\mathtt{I}$ and $\mathbb{E}\xi = 0$
- $\mathbb{E}(\xi_t \xi_s) = f(|t-s|)$ where $f \geq 0$ is measurable and bounded

$$\text{with } \lim_{x \to \infty} f(x) = 0$$

Time-Scaled Result

Theorem: For any species $X_{i,t}^L$ in an SSC system with input $\mathtt{I} + \xi$, let $m_i = \mathbb{E}X_i$. Given the assumption on the previous slide,

$$\begin{aligned} \lim_{L\to\infty} \text{Var } X_{i,t}^L &= \left(\frac{m_i}{\mathtt{I}}\right)^2 f(0) = \left(\frac{m_i}{\mathtt{I}}\right)^2 \text{Var } \xi \\ \lim_{L\to 0} \text{Var } X_{i,t}^L &= 0 \end{aligned}$$

Outline of proof

$$\begin{aligned} \text{Var } X_i^L &= \mathbb{E}\left[\int_{-\infty}^{t} \xi_{s/L} e^{A(t-s)} ds\right]^2 \\ &= \int_{-\infty}^{t}\int_{-\infty}^{t} f\left(\frac{1}{L}|s-r|\right)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)dsdr \end{aligned}$$

Show $g(s,r) = M(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)$ is integrable

Apply Dominated Convergence Theorem

Proof continued... $L \to \infty$

$$\lim_{L\to\infty} \text{Var } X_i^L$$

$$= \lim_{L\to\infty} \int_{-\infty}^{t} \int_{-\infty}^{t} f\left(\frac{1}{L}|s-r|\right)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)dsdr$$

$$= f(0)\left(\int_{-\infty}^{t} (e^{A(t-s)}e_1 \cdot e_i)ds\right)^2$$

$$= f(0)\left(\frac{m_i}{\mathrm{I}}\right)^2$$

Proof continued... $L \to 0$

Break region into pieces: $(-\infty, r-\epsilon] \cup [r-\epsilon, r+\epsilon] \cup [r+\epsilon, t]$

Define $\lambda = \min |\text{Real}(\lambda_i)|$, where λ_i are the eigenvalues of A

$$\begin{aligned}
&\lim_{L\to 0} \text{Var } X_i^L \\
&\quad = \int_{-\infty}^{t} \int_{r-\epsilon}^{r+\epsilon} \lim_{L\to 0} f\left(\frac{1}{L}|s-r|\right)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)dsdr \\
&\quad \leq \int_{-\infty}^{t} \int_{r-\epsilon}^{r+\epsilon} Me^{-\lambda(t-s)}e^{-\lambda(t-r)}dsdr \\
&\quad \leq \frac{M}{2\lambda^2}\left(e^{\lambda\epsilon} - e^{-\lambda\epsilon}\right)
\end{aligned}$$

Reversible Chains

$$\xrightarrow{\mathtt{I}+\xi} X_1 \underset{b_1}{\overset{k_1}{\rightleftharpoons}} X_2 \underset{b_2}{\overset{k_2}{\rightleftharpoons}} \cdots \underset{b_{n-1}}{\overset{k_{n-1}}{\rightleftharpoons}} X_n \xrightarrow{k_n}$$

Define fluxes:

$$\begin{aligned} y_1 &= k_1 x_1 - b_1 x_2 \\ &\vdots \\ y_{n-1} &= k_{n-1} x_{n-1} - b_{n-1} x_n \\ y_n &= k_n x_n \end{aligned}$$

$$\begin{aligned} \dot{y}_1 &= k_1(\mathtt{I} + \xi - y_1) - b_1(y_1 - y_2) \\ \dot{y}_i &= k_i y_{i-1} - (k_i + b_i) y_i + b_i y_{i+1} \\ &\qquad \text{for } 1 < i < n \\ \dot{y}_n &= k_n(y_{n-1} - y_n) \end{aligned}$$

Reversible Chains

$$\xrightarrow{\mathtt{I}+\xi} X_1 \underset{b_1}{\overset{k_1}{\rightleftharpoons}} X_2 \underset{b_2}{\overset{k_2}{\rightleftharpoons}} \cdots \quad \underset{b_{n-1}}{\overset{k_{n-1}}{\rightleftharpoons}} X_n \xrightarrow{k_n}$$

Theorem:

$$\lim_{L\to\infty} \text{Var } y_{t,L} = \text{Var } \xi$$
$$\lim_{L\to 0} \text{Var } y_{t,L} = 0$$

Two Lemmas

Let A be the matrix of rate coefficients:

$$A = \begin{pmatrix} -(k_1 + b_1) & b_1 & & & & \\ k_2 & -(k_2 + b_2) & b_2 & & & \\ & & & \ddots & & \\ & & & k_{n-1} & -(k_{n-1} + b_{n-1}) & b_{n-1} \\ & & & & k_n & -k_n \end{pmatrix}$$

Lemma: All eigenvalues of A have negative real parts.

Lemma: Det $A = (-1)^n \prod_{i=1}^{n} k_{n-i+1}$

Lemma:

$$\text{Det } (A_j) = (-1)^j \prod_{i=1}^{j} k_{n-i+1} \quad \text{for} \quad j = 2, \ldots, n \quad \text{where}$$

$$A_j = \begin{pmatrix} -(k_{n-j+1}+b_{n-j+1}) & b_{n-j+1} & & & \\ k_{n-j+2} & -(k_{n-j+2}+b_{n-j+2}) & & & \\ & & \ddots & & \\ & & & -(k_{n-1}+b_{n-1}) & b_{n-1} \\ & & & k_n & -k_n \end{pmatrix}$$

Iterative formula: $\text{Det } A_j = -k_{n-j+1} \text{Det } A_{j-1}$

Proof by induction. Compute $\text{Det } A_2 = k_{n-1} k_n$

Assume $\text{Det } A_{j-1} = -k_{n-j+2} \text{Det } A_{j-2}$

Proof of lemma cont...

Expansion by minors along the first column of A_j:

$$\begin{aligned}
\text{Det } A_j &= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) \\
&- \quad k_{n-j+2}\text{Det}\begin{pmatrix} b_{n-j+1} & 0 & 0 & \dots & 0 \\ k_{n-j+3} & -(k_{n-j+3} + b_{n-j+3}) & b_{n-j+3} & & \\ & & \ddots & & \\ & & & k_n & -k_n \end{pmatrix} \\
&= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) - k_{n-j+2}b_{n-j+1}\text{Det}(A_{j-2})
\end{aligned}$$

By inductive hypothesis,

$$\begin{aligned}
\text{Det } A_j &= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) + b_{n-j+1}\text{Det}(A_{j-1}) \\
&= -k_{n-j+1}\text{Det}(A_{j-1})
\end{aligned}$$

Geršgorin's Theorem

Let $A = [a_{i,j}]$ be an n by n matrix. Let

$$R_i(A) = \sum_{\substack{j=1 \\ j \neq i}}^{n} |a_{ij}|, \quad 1 \leq i \leq n$$

denote the *deleted absolute row sums* of A. Then all the eigenvalues of A are located in the union of n discs

$$\bigcup_{i=1}^{n} \{z \in \mathbb{C} : |z - a_{ii}| \leq R_i(A)\} \equiv G(A)$$

Theorem: For reversible chains,

$$\begin{aligned} \lim_{L\to\infty} \mathrm{Var}\ y_{t,L} &= \mathrm{Var}\ \xi \\ \lim_{L\to 0} \mathrm{Var}\ y_{t,L} &= 0 \end{aligned}$$

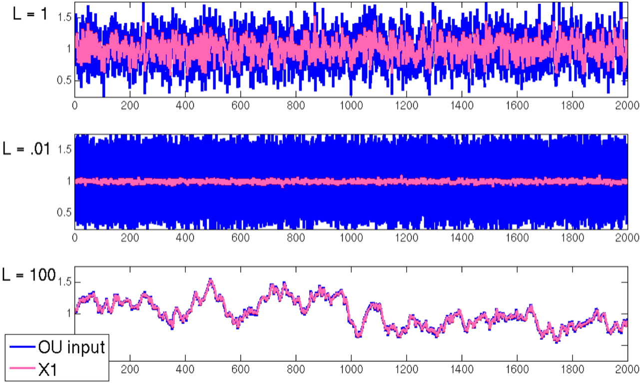
Sketch of Proof:

Consider matrix A of rate coefficients for y_i.
Show that all eigenvalues of A have negative real parts.
Then

$$y(t) = k_1 \mathtt{I} \int_{-\infty}^{t} e^{A(t-s)} e_1 ds + k_1 \int_{-\infty}^{t} e^{A(t-s)} \xi(s) ds$$

Apply similar argument as SSC case.

Conclusion



- Simple chains
- SSC networks
- Reversible chains

Magnitude of Rate Constants

Let $0 < \alpha_1 < \alpha_2$

$$\xrightarrow{\mathtt{I}+\xi_{t/L}} X_1 \xrightarrow{\alpha_1}$$

$$\xrightarrow{\mathtt{I}+\xi_{t/L}} X_2 \xrightarrow{\alpha_2}$$

Question: How does rate constant magnitude affect variance?

Theorem

Assume $0 < \alpha_1 < \alpha_2$. Let $\mathbb{E}\xi = \mathtt{I}$ and let

$$\begin{aligned} X_1'(t) &= \xi(t) - \alpha_1 X_1(t) \\ X_2'(t) &= \xi(t) - \alpha_2 X_2(t) \end{aligned}$$

If ξ is an Ornstein-Uhlenbeck process, then

- Var $\alpha_1 X_1 <$ Var $\alpha_2 X_2$
- Var $X_1 >$ Var X_2

Proof:

$$\frac{d}{dt}(\alpha_1 X_1 - \mathtt{I})^2 = 2(\alpha_1 X_1 - \mathtt{I}) \cdot \alpha_1 X_1'(t)$$
$$= 2\alpha_1(\alpha_1 X_1 - \mathtt{I})(-\alpha_1 X_1 + \xi)$$

Integrating, taking the expectation, and then differentiating,

$$\frac{d}{dt}\mathbb{E}(\alpha_1 X_1 - \mathtt{I})^2 = 2\alpha_1 \mathbb{E}[(\alpha_1 X_1 - \mathtt{I})(-\alpha_1 X_1 + \xi)]$$

If X_1^* is the stationary solution, then

$$2\alpha_1 \mathbb{E}[(\alpha_1 X_1^* - \mathtt{I})(-\alpha_1 X_1^* + \xi)] = 0$$

Proof cont...

$$\begin{aligned}
2\alpha_1\mathbb{E}[(\alpha_1 X_1^* - \mathtt{I})(-\alpha_1 X_1^* + \xi)] &= 0 \\
-\alpha_1^2\mathbb{E}(X_1^*)^2 + \alpha_1\mathbb{E}X_1^*\xi + \alpha_1\mathtt{I}\mathbb{E}X_1^* - \mathtt{I}\mathbb{E}\xi &= 0 \\
-\alpha_1^2\mathbb{E}(X_1^*)^2 + \alpha_1\mathbb{E}X_1^*\xi + \mathtt{I}^2 - \mathtt{I}^2 &= 0 \\
\mathbb{E}(\alpha_1 X_1^*)^2 &= \alpha_1\mathbb{E}X_1^*\xi
\end{aligned}$$

Similarly, $\mathbb{E}(\alpha_2 X_2^*)^2 = \alpha_2\mathbb{E}X_2^*\xi$.

Since $\mathbb{E}\alpha_1 X_1^* = \mathbb{E}\alpha_2 X_2^* = \mathtt{I}$,

it will suffice to show that $\alpha_1\mathbb{E}X_1^*\xi < \alpha_2\mathbb{E}X_2^*\xi$.

Proof cont...

$$\begin{aligned}
&\mathbb{E}[\alpha_1 X_1^* \xi - \alpha_2 X_2^* \xi] \\
&\quad = \mathbb{E}\left[\int_{-\infty}^{t} \left(\alpha_1 e^{-\alpha_1(t-s)} - \alpha_2 e^{-\alpha_2(t-s)}\right)\xi(s)\xi(t)ds\right] \\
&\quad = \int_{-\infty}^{t} \left(\alpha_1 e^{-\alpha_1(t-s)} - \alpha_2 e^{-\alpha_2(t-s)}\right)\frac{\sigma^2}{2\theta} e^{-\theta(t-s)} ds \\
&\quad = \frac{\sigma^2}{2\theta}\int_{-\infty}^{t} \left(\alpha_1 e^{-(\alpha_1+\theta)(t-s)} - \alpha_2 e^{-(\alpha_2+\theta)(t-s)}\right) ds \\
&\quad = \frac{\sigma^2}{2\theta}\left(\frac{\alpha_1}{\alpha_1+\theta} - \frac{\alpha_2}{\alpha_2+\theta}\right) \\
&\quad = \frac{\sigma^2}{2}\left(\frac{\alpha_1-\alpha_2}{(\alpha_1+\theta)(\alpha_2+\theta)}\right) < 0
\end{aligned}$$

Thus, Var $\alpha_1 X_1 <$ Var $\alpha_2 X_2$.