Random Input to Networks

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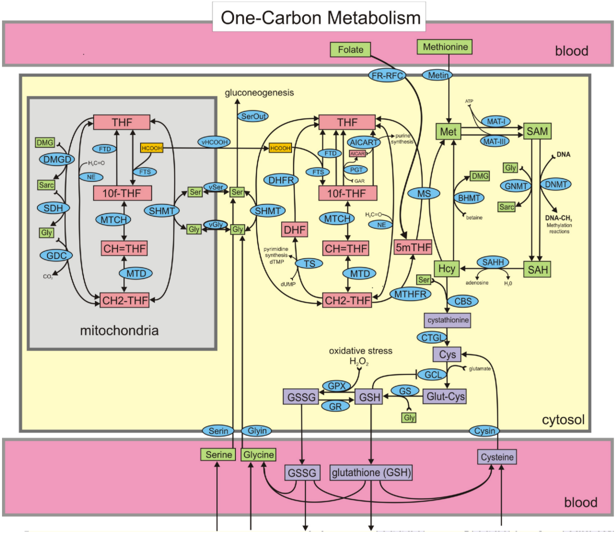
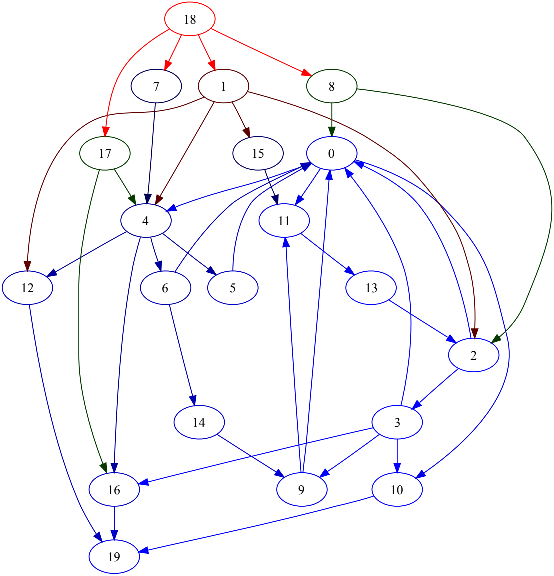
A Biology Problem



A Math Problem



A Simple Example

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

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

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

The Equations

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

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

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

Simple Chains

Variance decreases down a chain (Anderson)

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

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

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

Variance Lowers

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

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

Proof:

$$
\begin{aligned}
Var(x_i^*(t)) &= \mathbf{E}\left(\int_{-\infty}^{t} \xi(s) e^{A(t-s)} e_1 \cdot e_i ds\right)^2 \\
&= \mathbf{E}\left(\int_{-\infty}^{t} \xi(s) (e^{A(t-s)} e_1 \cdot e_i)^{1/2} (e^{A(t-s)} e_1 \cdot e_i)^{1/2} ds\right)^2 \\
&< \mathbf{E}\left(\int_{-\infty}^{t} \xi(s)^2 e^{A(t-s)} e_1 \cdot e_i ds\right)\left(\int_{-\infty}^{t} e^{A(t-s)} e_1 \cdot e_i ds\right) \\
&= Var(\xi)\left(\int_{-\infty}^{t} e^{A(t-s)} e_1 \cdot e_i ds\right)^2 \\
&= \left(\frac{m_i}{I}\right)^2 Var(\xi)
\end{aligned}
$$

Random Rate Constants

$$\xrightarrow{I+\xi(t)} X_1 \xrightarrow{k} \qquad \xrightarrow{I+\xi(t)} \hat{X}_1 \xrightarrow{\hat{k}}$$

If k a random variable with $\mathbf{E}k = \hat{k}$ and ξ white noise, then

$$\begin{aligned} Var(x_1^*) &> Var(\hat{x}_1{}^*) \\ Var(kx_1^*) &= Var(\hat{k}\hat{x}_1{}^*) \end{aligned}$$

Proof:

$$
\begin{aligned}
Var(x_1^*(t)) &= \mathbf{E}\left(\int_{-\infty}^{t} e^{-k(t-s)}\xi(s)ds\right)^2 \\
&= \mathbf{E}\int_{-\infty}^{t} e^{-2k(t-s)}ds \\
&= \mathbf{E}\frac{1}{2k} \\
&> \frac{1}{2\mathbf{E}k} \\
&= Var(\hat{x_1}^*(t))
\end{aligned}
$$

Removing Nodes

$$\xrightarrow{I+\xi(t)} X_1 \xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \xrightarrow{k_3} \cdots$$

$$\xrightarrow{I+\xi(t)} Y_2 \xrightarrow{\qquad\qquad h_2 \qquad\qquad} Y_3 \xrightarrow{k_3} \cdots$$

In order for $Var(k_2 x_2) = Var(h_2 y_2)$, let $h_2 = \left(\frac{1}{k_1} + \frac{1}{k_2}\right)^{-1}$

In general, to remove $n-1$ nodes, let

$$h_n = \left(\frac{1}{k_1} + \ldots + \frac{1}{k_n}\right)^{-1}$$

Side Reactions

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

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

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)

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

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

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:

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

$$
\begin{tikzcd}
{} \arrow[r, "I+\xi(t)"] & Z_1 \arrow[r, "k_1"] & \cdots \arrow[r, "k_{n-1}"] & Z_n \arrow[r, "k_n"] \arrow[dll, "c"'] & {} \\
 & \boxed{\text{Subsystem}} \arrow[r, "f_1(t)"'] & Y_1 \arrow[r, "k_1"'] & \cdots & Y_{n-1} \arrow[ul, "k_{n-1}"']
\end{tikzcd}
$$

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

Feedforward Loops

$$
\begin{tikzcd}
{} \arrow[r, "I+\xi(t)"] & X_1 \arrow[r, "k_1"] \arrow[dr, "h"'] & \cdots \arrow[r, "k_{n-1}"] & X_n \arrow[r, "k_n"] & {} \\
& & \boxed{\text{Subsystem}} \arrow[ur, "f(t)"'] & &
\end{tikzcd}
$$

Feedforward Loops

$$\begin{tikzcd} {} \arrow[r, "I+\xi(t)"] & X_1 \arrow[r, "k_1"] \arrow[rr, bend right, "h"'] & \cdots \arrow[r, "k_{n-1}"] & X_n \arrow[r, "k_n"] & {} \end{tikzcd}$$

$$Var(k_n x_n^*) < \left(\frac{h+k_1}{k_1}\right)^2 Var(k_{n-1} x_{n-1}^*)$$

Splitting

$$
\begin{tikzcd}
 & & X_{1,2} \arrow[r, "k_2"] & \cdots \arrow[r, "k_{n-2}"] & X_{1,n-1} \arrow[dr, "k_{n-1}"] & & \\
{} \arrow[r, "I+\xi"] & X_1 \arrow[ur, "\frac{k_1}{m}"] \arrow[dr, "\frac{k_1}{m}"'] & \vdots & & & X_n \arrow[r, "k_n"] & {} \\
 & & X_{m,2} \arrow[r, "k_2"'] & \cdots \arrow[r, "k_{n-2}"'] & X_{m,n-1} \arrow[ur, "k_{n-1}"'] & &
\end{tikzcd}
$$

$$
\xrightarrow{I+\xi} \tilde{X}_1 \xrightarrow{k_1} \tilde{X}_2 \xrightarrow{k_2} \cdots \xrightarrow{k_{n-2}} \tilde{X}_{n-1} \xrightarrow{k_{n-1}} \tilde{X}_n \xrightarrow{k_n}
$$

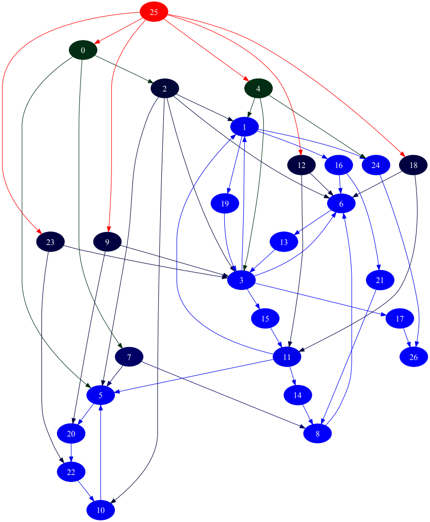
Question:

How can any network with one input and one output be reduced to a chain with:

- Side reaction systems
- Feedback loops
- Feed-forward loops

Computer Simulation

1. Generate random network
2. Assign edge directions
3. Add input node
4. Add output node
5. Provide noisy input and simulate
6. Analyze time series of node concentrations



High dimensional data set

Ex: Record the concentrations at 50 nodes over 20,000 time steps

$$\begin{bmatrix} \quad \text{species x time} \quad \end{bmatrix}$$

Can think of this as 20,000 points in 50-dimensional space.
The set may have a lower intrinsic dimensionality.

Singular Value Decomposition

Any $m \times n$ matrix A can be factored

$$A = U\Sigma V^* \qquad \begin{array}{ll} U & m \times m \text{ orthonormal} \\ V & n \times n \text{ orthonormal} \\ \Sigma & m \times n \text{ diagonal} \end{array}$$

The σ_i are the singular values of A. They are in descending order:

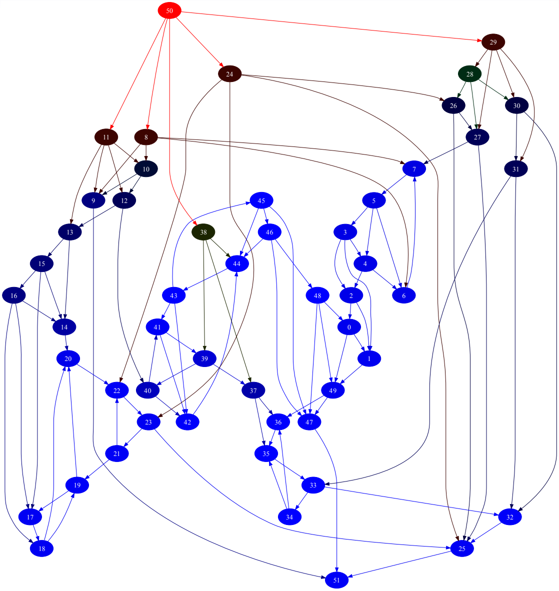
$$\sigma_1 \geq \sigma_2 \geq \ldots \geq \sigma_{m \wedge n}$$

U is an orthonormal basis for the range of A.
Vectors in V corresponding to $\sigma_i = 0$ are a basis for $Null(A)$

$$\begin{aligned} AV &= U\Sigma \\ Av &= \sigma u \end{aligned}$$

We can pick off the most significant singular values to reduce a higher dimensional data set to lower dimensional set.

$$\left[\text{species x time}\right]\left[\quad \mathrm{V} \quad\right] = \left[\ \mathrm{U}\ \right]\left[\begin{matrix}\sigma_1 & \ldots & \\ & & \end{matrix}\right]$$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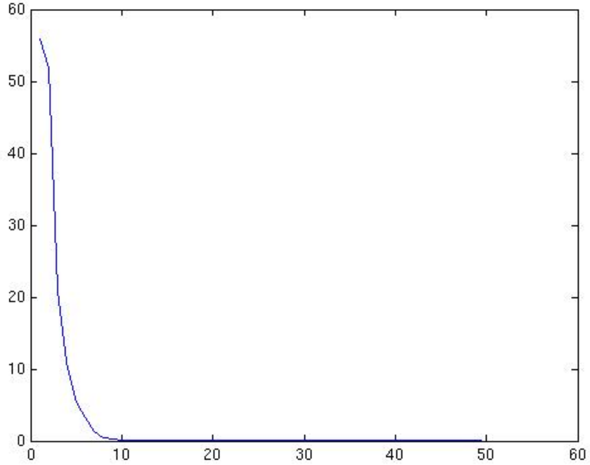
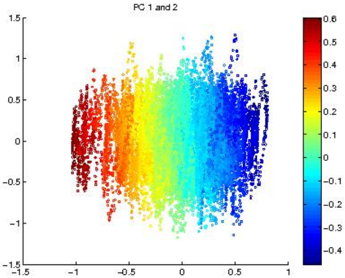
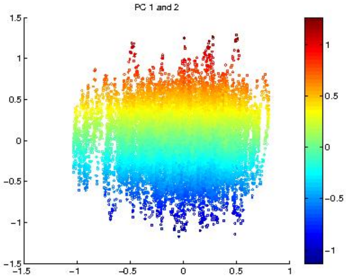
Singular Values



Principal Components 1,2



colored by concentration of output node



colored by concentration of input node

Conclusion

Ways to explore networks:

- Analytic estimates on particular structures
- Simulations on large networks
- Decomposing large networks and putting them back together

Acknowledgements

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