Stochastic Analysis of Retroactivity in Transcriptional Networks through Singular Perturbation

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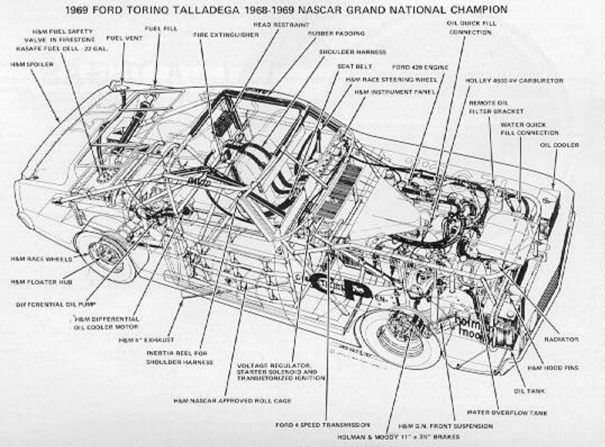
Network of elements

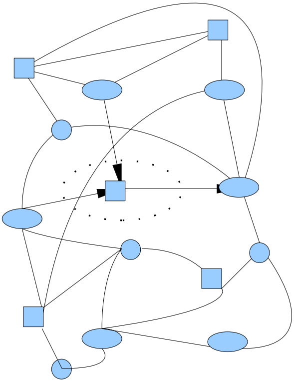
Computer motherboard.

Network of elements



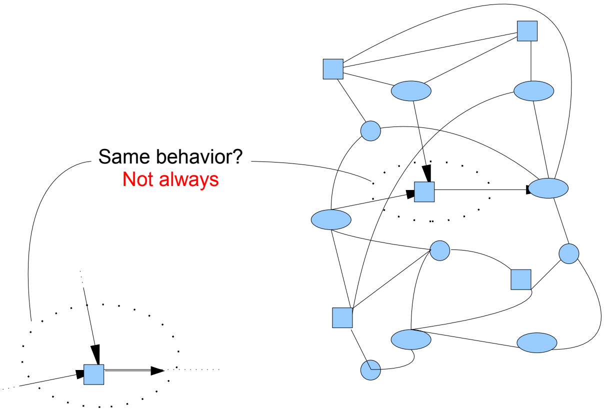
An old car.

In isolation vs in a network



Component behaves differently when isolated

In isolation vs in a network



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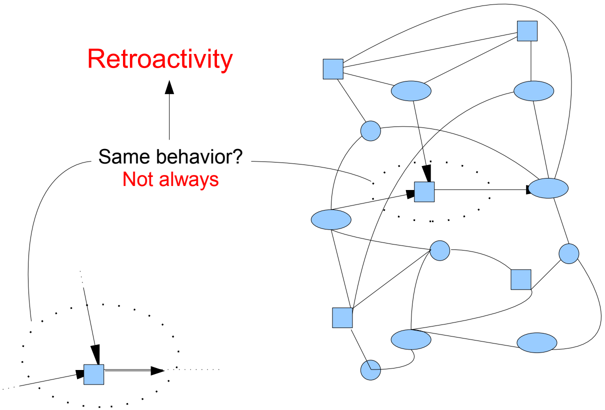

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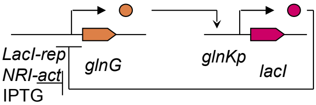
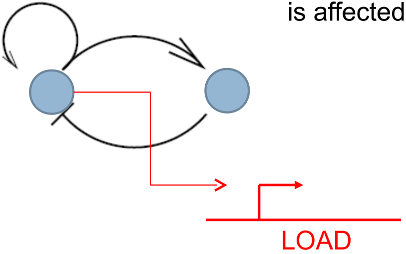


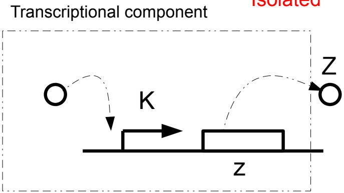
(Atkinson et al, *Cell* 2003)

The oscillating behavior is affected by load



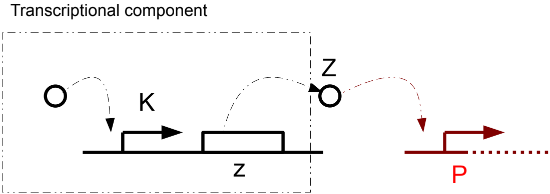
In isolation vs in a network

Isolated



The dynamic of the upstream system slows down according to ODE model.

Connected



Stochastic modeling

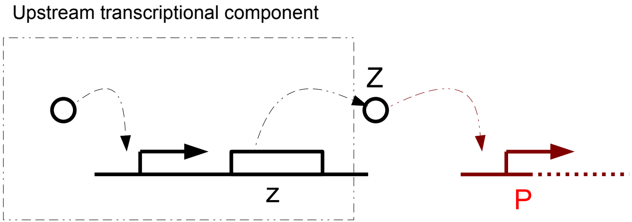
- Biological networks exhibit stochastic behavior and fluctuations $\rightarrow$ inherently stochastic systems.
- Stochastic models are valid even for very low molecule numbers.

$\rightarrow$ to have a complete and general characterization of retroactivity, we need to perform stochastic analysis.

Outline

- Introducing stochastic model of interconnected transcriptional component: Master equation
- Stationary analysis
- Singular perturbation analysis
- Analysis of Transient Behavior

Transcriptional System

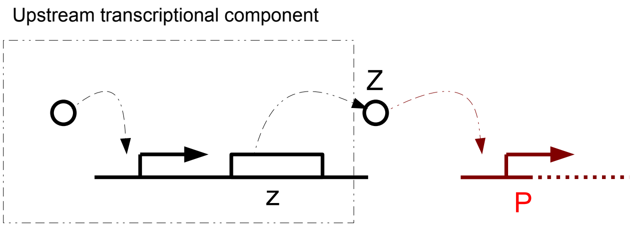


Interconnected transcriptional components.

$$\emptyset \underset{\delta}{\overset{k}{\rightleftharpoons}} Z, Z + \mathcal{P} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} C.$$

Total amount of DNA is conserved, i.e., $\mathcal{P} + C = p_T$

Transcriptional System



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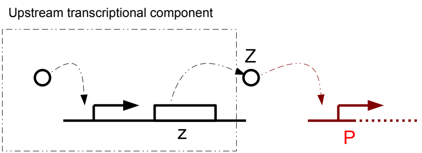
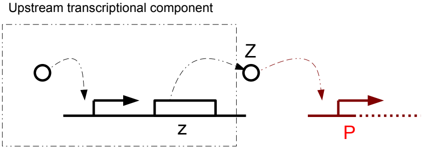
Deterministic retroactivity



- Analyzing the effect of downstream system on upstream: retroactivity.
- A deterministic approach is performed which analyzes the steady state as well as transient behavior of the concentration of Z[Del Vecchio et. al.]

Stochastic retroactivity

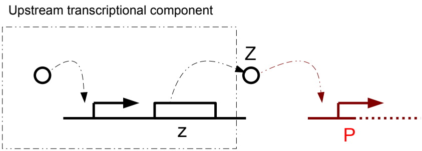


However

- The deterministic approach requires the number of molecules to be large.
- The deterministic approach does not provide an insight on how the load affects the intrinsic noise that is present in the system.

$\rightarrow$ Stochastic analysis.

Stochastic retroactivity



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Stochastic modeling

$$\emptyset \underset{\delta}{\overset{k}{\rightleftharpoons}} Z, Z + \mathcal{P} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} C.$$

C, Z, and $\mathcal{P}$: stochastic processes

What we are looking for:

Starting in state $m_0 = (c_0, z_0, p_0)$ at time zero,

$$P_{C,Z,\mathcal{P}}(c, z, p; t, m_0)$$
$$= P(M(t) = m = (c, z, p) \mid M(0) = m_0)$$

Master equation

A linear differential equation characterizes the evolution of $P_{C,Z,\mathcal{P}}(c,z,p;t,m_0)$ over time:

$$\frac{d}{dt}P_{C,Z,\mathcal{P}}(c,z,p;t,m_0) = A(P_{C,Z,\mathcal{P}}(\cdot,\cdot,\cdot;t,m_0))$$

where A is a linear operator.

Probability distribution of a single molecule X with finite number of molecules is

$$\frac{d}{dt}P_X(x;t) = A(P_X(\cdot;t)) \quad (1)$$

or

$$\frac{d}{dt}P_X(\cdot;t) = AP_X(\cdot;t)$$

where $P_X(\cdot;t) = [P_X(0;t), P_X(1;t), \cdots, P_X(x_{max};t)]$ and A is matrix.

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Master equation

$$
\begin{aligned}
&\frac{d}{dt}P_{C,Z,\mathcal{P}}(c,z,p;t,m_0) \\
&= \Omega[k(t)P_{C,Z,\mathcal{P}}(c,z-1,p;t,m_0) \\
&+ \delta\frac{(z+1)}{\Omega}P_{C,Z,\mathcal{P}}(c,z+1,p;t,m_0) \\
&+ k_{on}\frac{(z+1)}{\Omega}\frac{(p+1)}{\Omega}P_{C,Z,\mathcal{P}}(c-1,z+1,p+1;t,m_0) \\
&+ k_{off}\frac{(c+1)}{\Omega}P_{C,Z,\mathcal{P}}(c+1,z-1,p-1;t,m_0) \\
&- (k+\delta\frac{z}{\Omega}+k_{on}\frac{zp}{\Omega^2}+k_{off}\frac{c}{\Omega})P_{C,Z,\mathcal{P}}(c,z,p;t,m_0)].
\end{aligned}
$$

Keep in mind:

$$C(t)+\mathcal{P}(t)=p_T=C(0)+\mathcal{P}(0)=c_0+p_0$$

Master equation

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&+k_{off}\frac{(c+1)}{\Omega}P_{C,Z,\mathcal{P}}(c+1,z-1,p-1;t,m_0)\\
&-(k+\delta\frac{z}{\Omega}+k_{on}\frac{zp}{\Omega^2}+k_{off}\frac{c}{\Omega})P_{C,Z,\mathcal{P}}(c,z,p;t,m_0)].
\end{aligned}
$$

Keep in mind:

$$C(t)+\mathcal{P}(t)=p_T=C(0)+\mathcal{P}(0)=c_0+p_0$$

Master equation: Modified

$$
\begin{aligned}
&\dot{P}_{C,Z}(c,z;t,m_0)\\
&= \Omega[kP_{C,Z}(c,z-1;t,m_0) + \delta\frac{(z+1)}{\Omega}P_{C,Z}(c,z+1;t,m_0)\\
&+ k_{on}\frac{(z+1)}{\Omega}\frac{(p_T-c+1)}{\Omega}P_{C,Z}(c-1,z+1;t,m_0)\\
&+ k_{off}\frac{(c+1)}{\Omega}P_{C,Z}(c+1,z-1;t,m_0)\\
&- \left(k+\delta\frac{z}{\Omega}+k_{on}\frac{z(p_T-c)}{\Omega^2}+k_{off}\frac{c}{\Omega}\right)P_{C,Z}(c,z;t,m_0)],
\end{aligned}
$$

where

$$
P_{C,Z}(c,z;t,m_0) = P(C(t)=c, Z(t)=z \mid C(0)=c_0, Z(0)=z_0).
$$

.

Stationary analysis

What would happen if we wait for a long time?

$$P((C(t), Z(t)) = (c, z)) \to \pi_{C,Z}(c, z) \text{ as } t \to \infty$$

$\pi_{C,Z}(c, z)$ is the unique *stationary distribution* of (C, Z), which is the product of *stationary distribution* of the random process Z, $\pi_Z(z)$, and *stationary distribution* of the random process C, $\pi_C(c)$, i.e.,

$$\pi_{C,Z}(c, z) = \pi_C(c)\pi_Z(z).$$

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Stationary analysis

$$\pi_{C,Z}(c,z) = \pi_C(c)\pi_Z(z).$$

- C has binomial *stationary distribution* as follows

$$\pi_C(c) = \frac{p_T!}{c!(p_T-c)!(k_d k_z)^c}\left(1+\frac{1}{k_d k_z}\right)^{-p_T}, \qquad k_d := \frac{k_{off}}{k_{on}},\ k_z := \frac{\delta}{k}, \tag{2}$$

- Z has Poisson *stationary distribution* given by

$$\pi_Z(z) = \frac{\Omega_z^z}{z!}e^{-\Omega_z},\ \Omega_z := \frac{\Omega}{k_z}. \tag{3}$$

Implication of the stationary analysis

At steady state, the downstream and upstream systems are statistically independent.

Namely, $Z(\infty)$ and $C(\infty)$ are independent random variables.

$$E(Z) = \Omega_z = \frac{k}{\delta}\Omega$$

$$Var(Z) = \Omega_z$$

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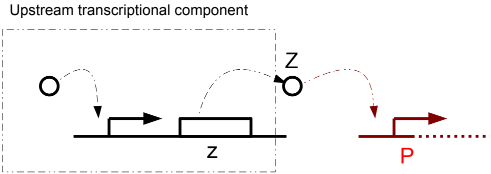


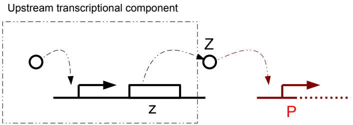
Singular perturbation analysis

We want to characterize the transient behavior of mean and variance of Z.

Define $Y := C + Z$.

$$P_{C,Y}(c, y; t, m_0) := P(C(t) = c, Y(t) = y \mid C(0) = c_0, Y(0) = y_0)$$

.



$$\emptyset \underset{\delta}{\overset{k}{\rightleftharpoons}} Z, Z + \mathcal{P} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} C.$$

Singular perturbation analysis

Defining $\epsilon := \frac{\delta}{k_{off}}$, $k_d := \frac{k_{off}}{k_{on}}$, $\bar{k}_{on} := \frac{\delta}{k_d}$, and $\bar{k}_{off} := \delta$, the Master equation can be written in the following form:

$$\begin{aligned}
&\dot{P}_{C,Y}(c, y; t, m_0) = \Omega[kP_{C,Y}(c, y-1; t, m_0) \\
&+ \delta\frac{(y-c+1)}{\Omega}P_{C,Y}(c, y+1; t, m_0) \\
&+ \frac{1}{\epsilon}\bar{k}_{on}\frac{(y-c+1)}{\Omega}\frac{(p_T-c+1)}{\Omega}P_{C,Y}(c-1, y; t, m_0) \\
&+ \frac{1}{\epsilon}\bar{k}_{off}\frac{(c+1)}{\Omega}P_{C,Y}(c+1, y; t, m_0) \\
&\qquad - \left(k + \delta\frac{y-c}{\Omega} + \frac{1}{\epsilon}\bar{k}_{on}\frac{(y-c)(p_T-c)}{\Omega^2}\right. \\
&\qquad \left. + \frac{1}{\epsilon}\bar{k}_{off}\frac{c}{\Omega}\right)P_{C,Y}(c, y; t, m_0)].
\end{aligned} \tag{4}$$

Singular perturbation analysis

Equivalently:

$$\frac{d}{dt}P_{C,Y}(c,y;t,m_0) = (A + \frac{1}{\epsilon}B)(P_{C,Y}(\cdot,\cdot;t,m_0)) \qquad (5)$$

Singular perturbation analysis

Slowly varying Prob. Dist $P_Y(y;t)$

$$\sum_y \left(\frac{d}{dt} P_{C,Y}(c,y;t,m_0) = (A)(P_{C,Y}(\cdot,\cdot;t,m_0)) \right).$$

Define $P_Y^s(y;t)$ as the solution of the following forward equation:

$$\dot{P}_Y^s(y;t) = \Omega[kP_Y^s(y-1;t) + \delta\frac{(y+1-E^s(C|Y=y+1))}{\Omega}P_Y^s(y+1;t) - (k+\delta\frac{y-E^s(C|Y=y)}{\Omega})P_Y^s(y;t)],$$

with initial distribution $P_Y^s(y;0) = P_Y(y;0)$.
$E^s(C|Y=y)$: conditional expectation at stationary distribution.

Singular perturbation analysis

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Singular perturbation analysis

Fast varying Prob. Dist

$$\sum_y \left(\frac{d}{dt} P_{C,Y}(c, y; t, m_0) = (\frac{1}{\epsilon} B)(P_{C,Y}(\cdot, \cdot; t, m_0)) \right).$$

Let $P^f_{C,Y}(c, y; \tau)$ denote the solution to the following forward equation

$$\frac{d}{dt} P^f_{C,Y}(c, y; t)$$
$$= \Omega[\bar{k}_{on} \frac{(y-c+1)}{\Omega} \frac{(p_T-c+1)}{\Omega} P^f_{C,Y}(c-1, y; t)$$
$$+ \bar{k}_{off} \frac{(c+1)}{\Omega} P^f_{C,Y}(c+1, y; t)$$
$$- (\bar{k}_{on} \frac{(y-c)(p_T-c)}{\Omega^2} + \bar{k}_{off} \frac{c}{\Omega}) P^f_{C,Y}(c, y; t)].$$

with initial distribution $P^f_{C,Y}(c, y; 0) = P_{C,Y}(c, y; 0) - P^s_Y(y; 0)\pi_{C|Y}(c|y).$

Singular perturbation analysis

Fast varying Prob. Dist

$$\sum_y \left(\frac{d}{dt} P_{C,Y}(c,y;t,m_0) = (\frac{1}{\epsilon} B)(P_{C,Y}(\cdot,\cdot;t,m_0)) \right).$$

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\end{aligned}$$

with initial distribution
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Singular perturbation analysis

$$P^e_{C,Y}(c,y;t,\epsilon) := P^s_Y(y;t)\pi_{C|Y}(c|y) + P^f_{C,Y}(c,y;\frac{t}{\epsilon})$$

approximates

$$P_{C,Y}(c,y;t)$$

of order of $O(\epsilon)$ over $[0,T]$ for any T.

Moreover, there exists $\kappa > 0$ and $\alpha > 0$ such that $\|P^f_{C,Y}(\cdot,\cdot;\tau)\|_1 < \kappa e^{-\alpha\tau}$.

Analyzing the reduced Master equation

Now we have reduced Master equation to analyze the transient behavior of system:

$$\dot{P}_Y^s(y;t) = \Omega[kP_Y^s(y-1;t)$$
$$+\delta\frac{(y+1-E^s(C|Y=y+1))}{\Omega}P_Y^s(y+1;t)$$
$$-(k+\delta\frac{y-E^s(C|Y=y)}{\Omega})P_Y^s(y;t)],$$

We need to characterize $E^s(C|Y=y)$

Analyzing the reduced Master equation

$E^s(C|Y=y)$ can be written as follows

$$E^s(C|Y=y) = \sum_{c=0}^{\min y, p_T} c\pi_{C|Y}(c|y)$$
$$= \frac{\sum_{c=0}^{\min(p_T,\Omega)} \frac{c}{c!(p_T-c)!(\Omega k_d)^c(y-c)!}}{\sum_{c=0}^{\min(p_T,\Omega)} \frac{1}{c!(p_T-c)!(\Omega k_d)^c(y-c)!}}. \quad (6)$$

Hard to characterize in this form

Analyzing the reduced Master equation

$$E^s(C|Y=y) = \frac{[p_T - E^s(C|Y=y-1)]y}{p_T + k_d\Omega - E^s(C|Y=y-1)}$$
$$=: \Upsilon(E^s(C|Y=y-1), y),$$

with $E^s(C|Y=0) = 0$.

Analyzing the reduced Master equation

$\hat{f}$ that is the fixed point of the map Υ at y, i.e., $\hat{f}(y) = \Upsilon(\hat{f}(y), y)$, is a good approximation of $E^s(C|Y = y)$. with some algebraic manipulation:

$$\hat{f}(y) = \frac{y + p_T + k_d\Omega - \sqrt{(y + p_T + k_d\Omega)^2 - 4yp_T}}{2} \approx E^s(C|Y = y).$$

Analyzing the reduced Master equation

Assuming that k_d is sufficiently large compared to $\frac{p_T}{\Omega}$ and $\frac{y}{\Omega}$, which is often a reasonable assumption, we have

$$\hat{f}(y) = \frac{2yp_T}{y + p_T + k_d\Omega + \sqrt{(y + p_T + k_d\Omega)^2 - 4yp_T}} \approx \frac{p_T}{p_T + k_d\Omega} y. \tag{7}$$

Analyzing the reduced Master equation: $E(Y)$

Defining $\beta := \frac{k_d\Omega}{k_d\Omega + p_T}$,

$$E^s(C|Y = y) \approx (1 - \beta)y. \tag{8}$$

with

$$\dot{P}^s_Y(y;t) = \Omega[kP^s_Y(y-1;t) + \delta\frac{(y+1-E^s(C|Y=y+1))}{\Omega}P^s_Y(y+1;t) - (k + \delta\frac{y - E^s(C|Y=y)}{\Omega})P^s_Y(y;t)],$$

we have

$$\frac{d}{dt}E^s(Y;t) = -\delta\beta E^s(Y;t) + k\Omega. \tag{9}$$

with $\beta < 1$. For isolated system we have $\beta = 1$.

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with $\beta < 1$. For isolated system we have $\beta = 1$.

Analyzing the reduced Master equation: $Var(Y)$

$$\frac{d}{dt}E^s(Y^2;t) = E^s(2Y(k\Omega - \delta\beta Y);t) + E^s(\delta\beta Y + k\Omega;t)$$
$$- 2\delta\beta E^s(Y^2;t) + (2k\Omega + \delta\beta)E^s(Y;t) + k\Omega. \quad (10)$$

$E^s(Y^2;t)$ with time constant $\frac{1}{2\delta\beta}$, $\rightarrow$ time constant of the variance.

Analyzing the reduced Master equation: $E(Z)$, $Var(Z)$

$$E^s(Z^2;t) \approx \beta^2 E^s(Y^2;t) + \beta(1-\beta)E^s(Y;t). \tag{11}$$

and

$$E^s(Z;t) \approx \beta E^s(Y;t) \tag{12}$$

$\rightarrow$ the dynamics of $E(Z)$ and $Var(Z)$ slows down when interconnected with downstream component.

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$\rightarrow$ the dynamics of $E(Z)$ and $Var(Z)$ slows down when interconnected with downstream component.

Conclusion

we studied the stochastic effects of retroactivity in a transcriptional module connected to downstream systems:

- We developed singular perturbation analysis for the Master equation.
- We provided a reduced Master equation describing the slow processes and demonstrated that the solution of the original Master equation fast approaches a neighbor of the solution of the reduced Master equation.
- We mathematically analyzed how retroactivity impacts both transient and stationary behavior of the system
- We observed that the upstream system and the downstream one are statistically independent at the steady state.
- The interconnection slows down the dynamics of both the expectation and the variance of the output of the upstream transcriptional module.

Conclusion

we studied the stochastic effects of retroactivity in a transcriptional module connected to downstream systems:

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