Mechanisms for Noise Attenuation in Molecular Biology Signaling Pathways

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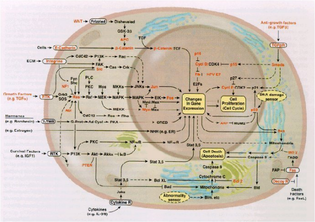
University of California, Irvine

May 25, 2011
On the occasion of Eduardo's 60th birthday

Feedback and noise in biological systems

- "Redundantly" many positive or negative feedback loops



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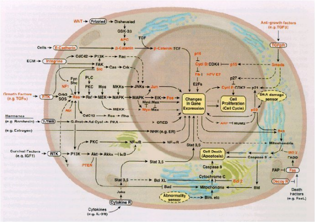
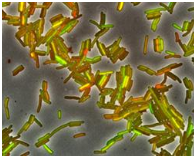
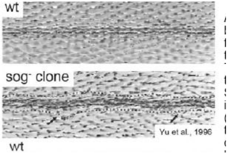


- noise (transcription, thermal fluctuation, volume changing, etc.)



noisy gene expressions



zig-zag vein

How does feedback affect a system's noise property?

- positive feedback amplifies noise and negative feedback attenuates noise (A. Becskei and L. Serrano, 2000; U. Alon, 2007)

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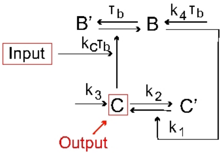
is there a quantity (rather than the sign of FD) to unify these results?

One-loop and two-loop systems

one-loop system



$$c' = k_1 b(1-c) - k_2 c + k_3$$
$$b' = (k_c s(t) c(1-b) - b + k_4)\tau_b$$

One-loop and two-loop systems

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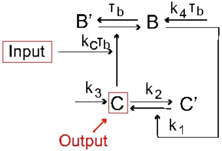

$$c' = k_1 b(1-c) - k_2 c + k_3$$
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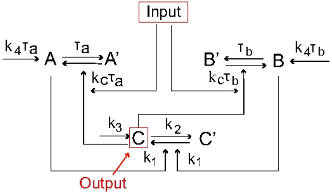
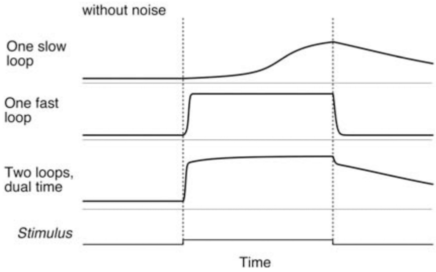
two-loop system

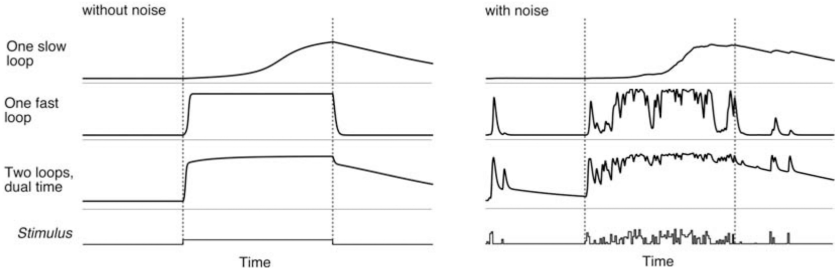


$$c' = k_1(b+a)(1-c) - k_2 c + k_3$$
$$b' = (k_c s(t) c(1-b) - b + k_4)\tau_b$$
$$a' = (k_c s(t) c(1-a) - a + k_4)\tau_a$$

Dynamical and noise properties



Dynamical and noise properties

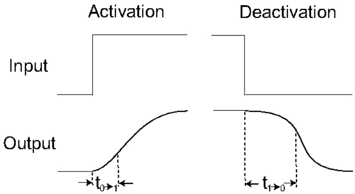


O. Brandman et al., *Science*, 2005

system's intrinsic time scales are crucial to noise attenuation

A conjecture

define activation and deactivation time scales.



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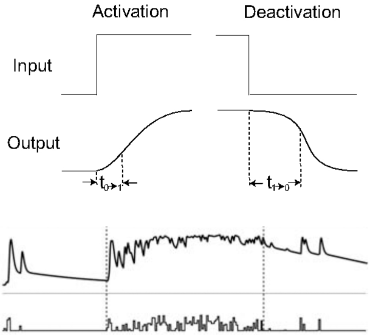


...... guess: at the "on" state,

$$t_{1\to 0} \gg 1/\omega,\ t_{0\to 1} \ll 1/\omega \quad \Rightarrow \text{ better noise attenuation}$$

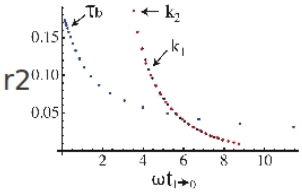
ω: the frequency of the input noise.

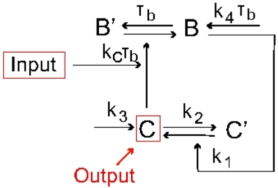
Testing the conjecture

define noise amplification rate: $r_2 = \dfrac{\mathrm{std(output)}/\langle \mathrm{output} \rangle}{\mathrm{std(input)}/\langle \mathrm{input} \rangle}$

G. Hornung and N. Barkai, *PLoS Comp. Bio.*, 2008

testing in the one-loop system:

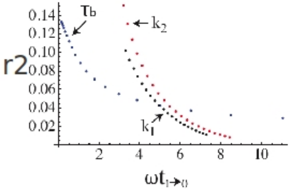


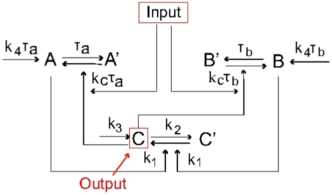


$t_{1\to0} \gg 1/\omega \Rightarrow$ better noise attenuation

Testing the conjecture

in the two-loop system:





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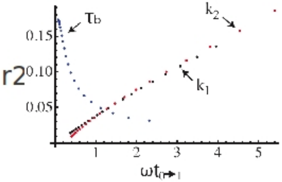
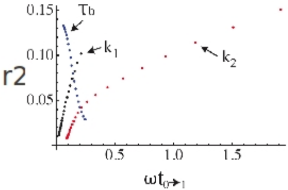
Testing the conjecture

one-loop system



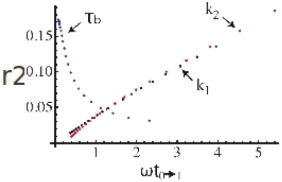
two-loop system



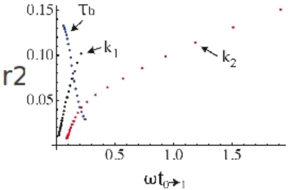
why is τ_b inconsistent?

Testing the conjecture

one-loop system

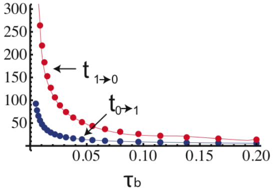


two-loop system



why is τ_b inconsistent?

... a closer look



is there a simple way to take into account both changes?

A critical quantity: signed activation time

- signed activation time (SAT) $= t_{1\to 0} - t_{0\to 1}$
- SAT has a negative relation with the noise amplification rate

Analytical studies using the Fluctuation Dissipation Thm

$$r_2^2 \approx \frac{\tau_b/\omega}{\langle s\rangle(k_1 k_c/k_2 - 1)(k_1/k_2 + 1)\frac{k_c}{k_c+1}}$$

key observation:

- r_2 negatively depends on k_c and k_1/k_2.

linear analysis of the noise-free ODE:

- SAT positively depends on k_c and k_1/k_2

$\Rightarrow$ r_2 negatively depends on SAT$= t_{1\to 0} - t_{0\to 1}$

Analytical studies - two-time-scale analysis

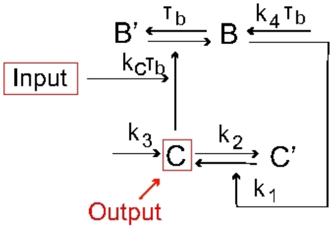
$$c' = k_1 b(1-c) - k_2 c + k_3$$
$$b' = (k_c s(t) c(1-b) - b + k_4)\tau_b$$

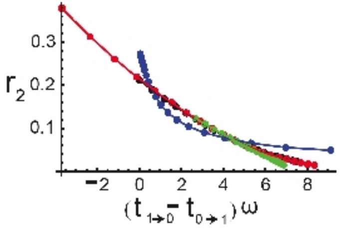
When $\varepsilon := \tau_b \ll k_2$, $\exists$ two time scales: $t_f = t$ and $t_s = \varepsilon t$,

$$c = c_0(t_s, t_f) + \varepsilon c_1(t_s, t_f) + \varepsilon^2 c_2(t_s, t_f) + \cdots$$
$$b = b_0(t_s, t_f) + \varepsilon b_1(t_s, t_f) + \varepsilon^2 b_2(t_s, t_f) + \cdots$$

- $s(t)$ varies on the time scale of $t_f \Rightarrow$ noise is filtered out in c_0.
- $s(t)$ varies on the time scale of $t_s \Rightarrow$ noise persists in c_0.

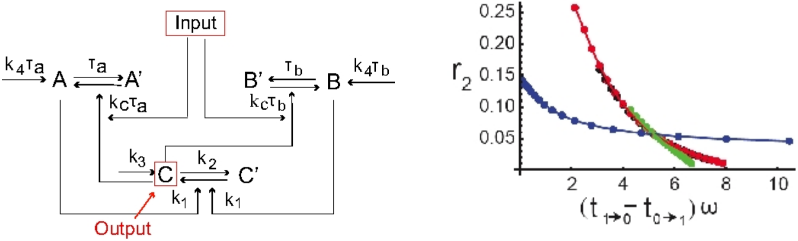
SAT in one-loop systems





r_2 decreases in SAT

SAT in two-loop systems



r_2 decreases in SAT

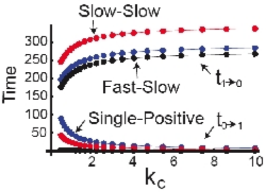
How to achieve large SAT?

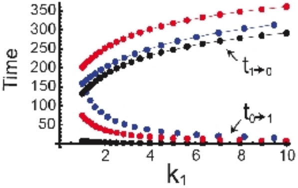
- linear stability analysis

	single	slow-slow	fast-slow
activation	$\frac{k_c+1}{(K_a+1)k_c}$	$\frac{k_c+1}{(2K_a+1)^2 k_c}$	$\frac{k_c+1}{2(2K_a+1)^2 k_c}$
deactivation	$\frac{(K_a+1)k_c}{1+k_c}$	$\frac{(2K_a+1)k_c}{1+k_c}$	$\frac{(K_a+1/2)k_c}{1+k_c}$

$\Rightarrow$ large k_c and $K_a := k_1/k_2$

- simulations





Why multiple loops?

- faster activation

	single	slow-slow	fast-slow
activation	$\frac{k_c+1}{(K_a+1)k_c}$	$\frac{k_c+1}{(2K_a+1)^2 k_c}$	$\frac{k_c+1}{2(2K_a+1)^2 k_c}$

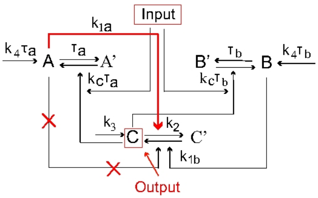
- more robust (w.r.t. parameter changes)

$k_c \in (0.5, 10)$	single	slow-slow	fast-slow
activation	$(8.2, 89.9)$	$(0.8, 3.9)$	$(4.5, 43.7)$

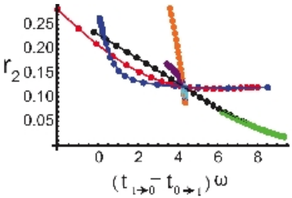
$k_1 \in (1, 10)$	single	slow-slow	fast-slow
activation	$(15.6, 158.2)$	$(0.9, 8.4)$	$(8.9, 75)$

Does SAT apply to negative feedback systems?

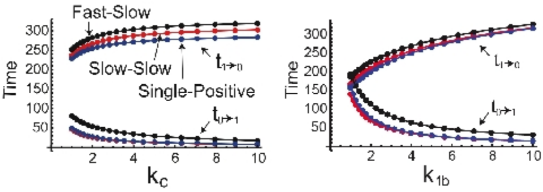
a system with negative feedback



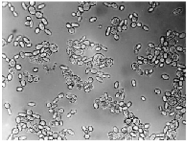
r_2 decreases in SAT

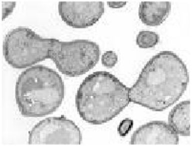


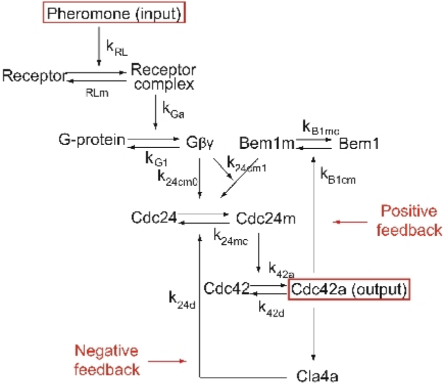
to achieve large SAT:



The yeast polarization system

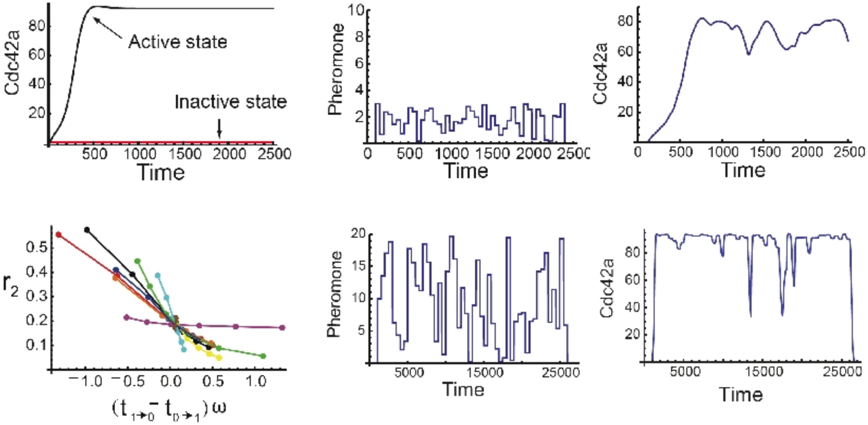




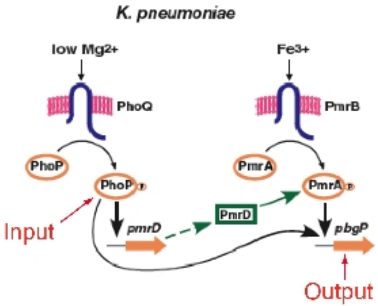


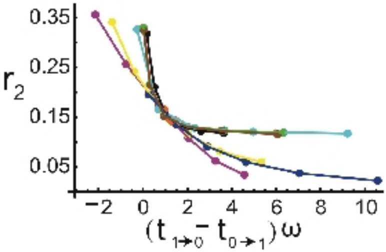
A non-spatial model,
simplied from C.S. Chou et al., 2008

SAT in the yeast cell polarization system

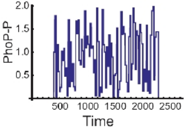


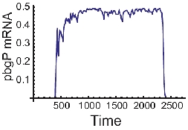
SAT in a Polymyxin B resistence model



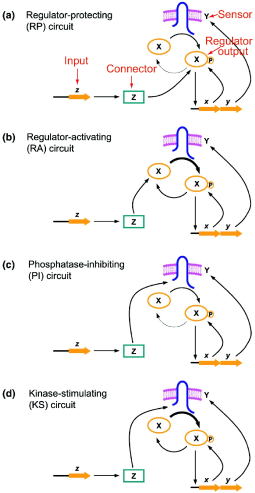


13 parameters are varied in ±3 range.

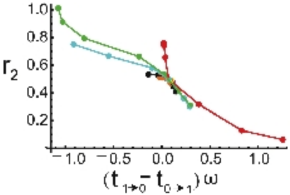




SAT in connector-mediated models



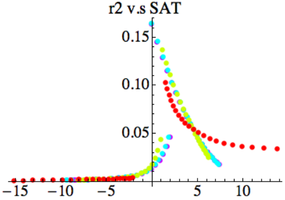
	RP	RA	KS	PI
activation	30.1	30.4	4.5	62.4
deactivation	45.2	37.2	5.9	6.4
SAT	0.76	0.34	0.07	−2.8
r_2	0.14	0.34	0.5	0.85



A.Y.Mitrophanov and E.A. Groisman, 2010

Summary and future work

- proposed a new quantity $\text{SAT} = t_{1\to0} - t_{0\to1}$
- at ON state, r_2 (noise amplification rate) decreases in SAT.
- SAT is the intrinsic time scale determined by network structure and parameters
- additional positive feedback drastically reduces the activation time and makes the system more robust to parameter variations
- what is the prediction for OFF state? bistable system? PDE?



Acknowledgements

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Tau-Mu Yi
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Congratulations on your achievements!

Happy Birthday!