Stochasticity and robustness

Lecture 5 of Introduction to Biological Modeling
Oct. 20, 2010

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Last week
- gene regulatory networks
- graphs
- Boolean networks
- transcription dynamics
- motifs

Reading

Rao, Wolf, and Arkin, "Control, exploitation and tolerance of intracellular noise" *Nature* 420:231-237, 2002.

(Arkin, Ross, and McAdams, "Stochastic kinetic analysis of developmental pathway bifurcation in phage λ-infected *Eshcherichia coli* cells" *Genetics* 149:1633-1648.)

Sources and amount of stochasticity

Amplifying stochasticity

Reducing stochasticity

Modeling stochasticity

Summary

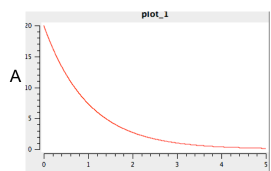
Deterministic vs. stochastic

$$A \xrightarrow{k} B$$

Deterministic

$$\frac{d[A]}{dt} = -k[A]$$

$$[A] = [A]_0 \, e^{-kt}$$



Deterministic vs. stochastic

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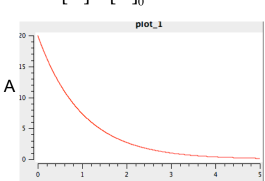
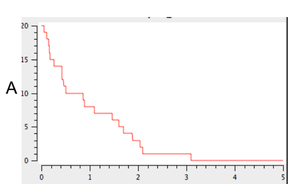


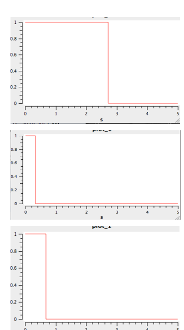
Stochastic

many possible trajectories



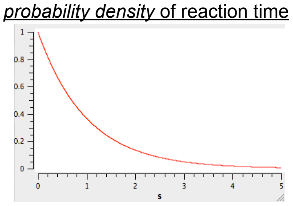
Stochasticity origins

$$A \rightarrow B$$



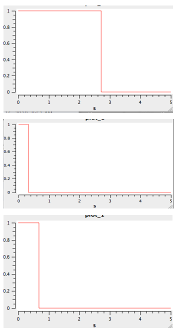
Reaction ***timing*** is random

probability density of reaction time



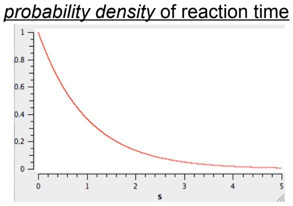
Stochasticity origins

A + B → C



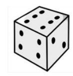
Reaction ***timing*** is random
now, determined by diffusion
and reaction rate upon collision

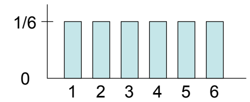
probability density of reaction time



Probability vs. probability density

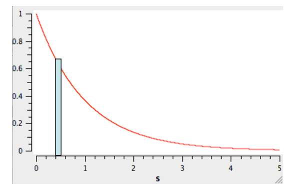
probability for discrete events





each bar is probability of a specific event
partial sum is cumulative probability
total sum of bars = 1

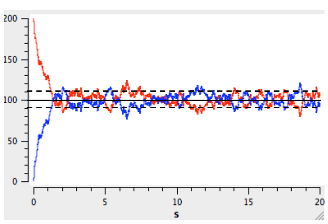
probability density for continuous events



rectangle area is probability of event being in that range
integral is cumulative probability
total area under curve = 1

How much variation?

A ↔ B



At equilibrium,

average = $\bar{n}$

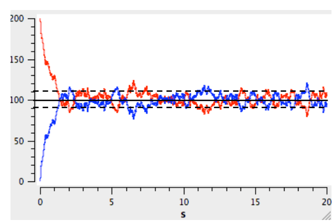
std. dev. ~ $\sqrt{\bar{n}}$

Absolute noise increases with more molecules: $\sqrt{\bar{n}}$

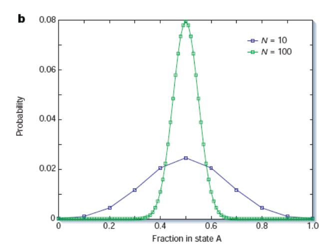
Relative noise decreases with more molecules: $\frac{\sqrt{\bar{n}}}{\bar{n}} = \frac{1}{\sqrt{\bar{n}}}$

How much variation?

A ↔ B



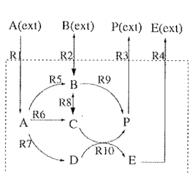
probability density for fraction in state A



the *relative* noise decreases with more molecules ~ $1/\sqrt{\bar{n}}$

Credit: Rao *et al. Nature* 420:231, 2002.

How much variation?



At, or near, steady state

variation is still ~ $\frac{1}{\sqrt{\bar{n}}}$

<u>molecules</u>	<u>variation</u>	<u>stochasticity</u>
10,000	1%	not important
1000	3%	probably not important
100	10%	probably important
10	30%	very important
1	100%	essential

Credit: Klamt and Stelling in *System Modeling in Cellular Biology* ed. Szallasi *et al.* p. 73, 2006.

where does stochasticity matter?

<u>species</u>	<u>copies</u>	<u>stochastic?</u>
DNA	1 or 2 (or 4)	no, tightly controlled
mRNA	0 to 100s	yes
proteins	1 nM = 1 molec. in *E. coli* (2 fl)	yes
	= 300 molec. in yeast (500 fl)	probably
	1 µM = 1000 molec. in E. coli	maybe
	= 300,000 molec. in yeast	no
metabolites	µM to mM	usually no

Sources and amount of stochasticity

Amplifying stochasticity

Reducing stochasticity

Modeling stochasticity

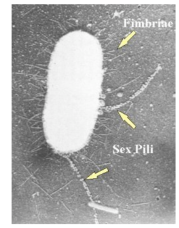
Summary

Benefits of stochasticity

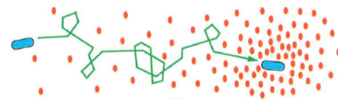
Population heterogeneity
(phase variation)
- *E. coli* pili variation
- *Salmonella* flagella
- phage λ lysis-lysogeny

Waiting mechanism
- phage λ lysis-lysogeny

Exploration strategies
- *E. coli* chemotaxis

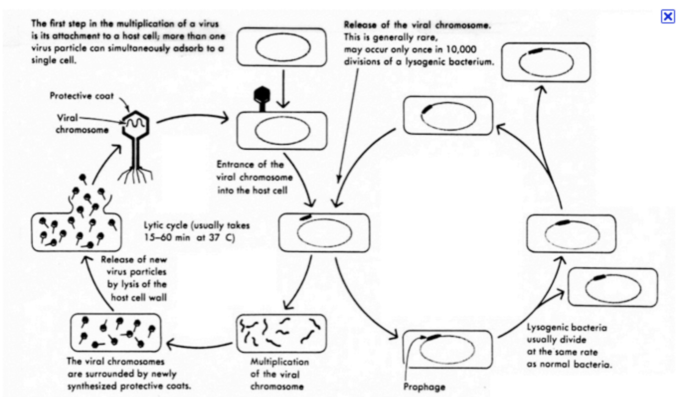


Similar benefits in ecology and in evolution



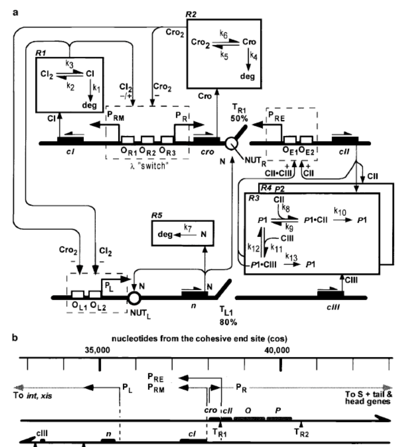
Credits: http://www.biologyjunction.com/fimbriae_article.htm; Alberts, *et al.*, *Molecular Biology of the Cell, 3rd ed.* Garland Publishing, 1993.

Phage λ lysis-lysogeny



Credit: http://textbookofbacteriology.net/themicrobialworld/Phage.html

Phage λ lysis-lysogeny



Lysis-lysogeny model of Arkin, Ross, and McAdams, 1998.

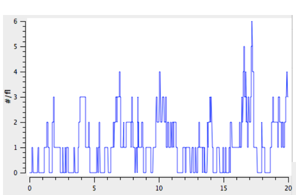
Stochastic decision upon initial infection.

Stochastic departure from lysogeny to lysis.

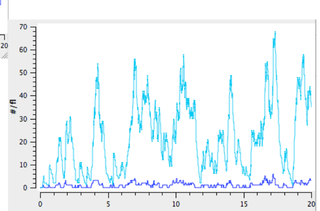
Credit: Arkin et al. *Genetics* 149:1633, 1998

Amplification with transcription/translation

DNA ⟶ RNA ⟶ protein

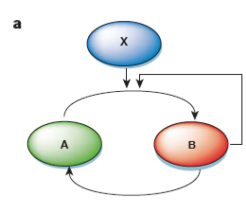


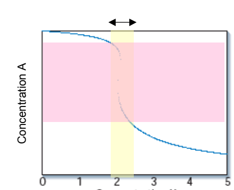
DNA is fixed at 1 (or 2 or 4)
RNA follows $\sqrt{n}$ rule



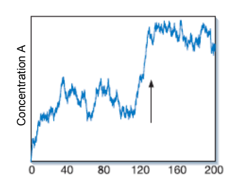
noise is amplified in translation, so protein noise >> $\sqrt{n}$

Amplification with positive feedback



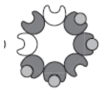


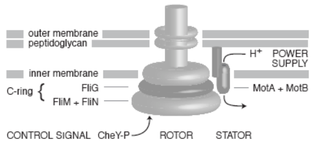
small variation of x causes switching between A and B



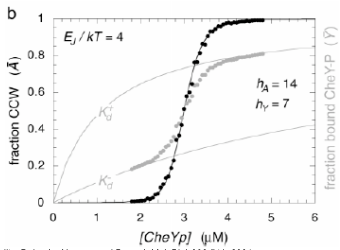
Credit: Rao *et al.* *Nature* 420:231, 2002.

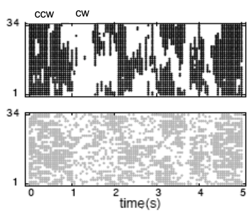
More amplification with positive feedback





Positive feedback in *E. coli* motor randomly switches it between cw and ccw.





Credits: Duke, Le Novere, and Bray, *J. Mol. Biol.* 308:541, 2001.

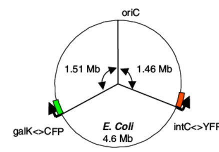
intrinsic vs. extrinsic noise

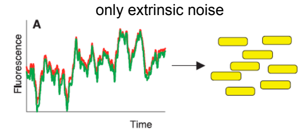
Question: is noise arising from factors *intrinsic* to gene expression, or upstream *extrinsic* factors?

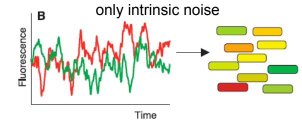
IPTG ⊣ LacI ⊣ DNA → RNA → protein

extrinsic noise   intrinsic noise

Solution: 2 GFP genes, same chromosome, same promotors, *same extrinsic* noise. *Different intrinsic* noise.





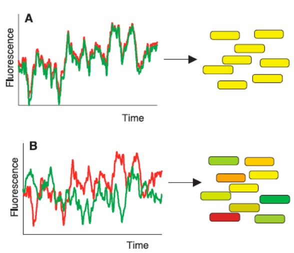


Credits: Elowitz *et al. Science* 297:1183, 2002.

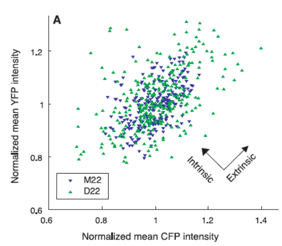
intrinsic vs. extrinsic noise

IPTG ⊣ LacI ⊣ DNA → RNA → protein

extrinsic noise   intrinsic noise



quantify using a scatter plot



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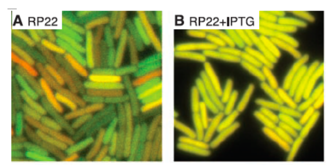
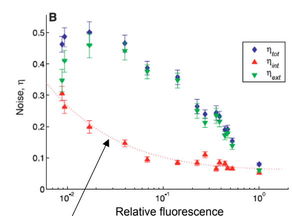


low expression level
few mRNA
high intrinsic noise

high expression level
many mRNA
low intrinsic noise



intrinsic noise decreases with higher expression levels

Credits: Elowitz *et al. Science* 297:1183, 2002.

Problems of stochasticity

- development
- signaling

Noisy inputs, and want to make best decision possible.

Noise reduction with negative feedback

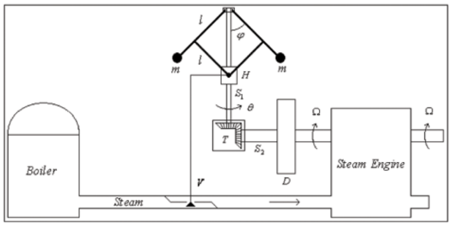
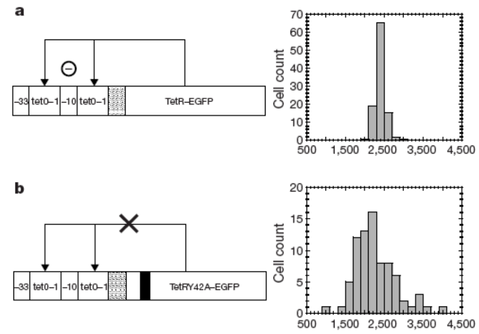


Figure 1 – Watt-centrifugal-governor-steam-engine system.

Noise reduction with negative feedback



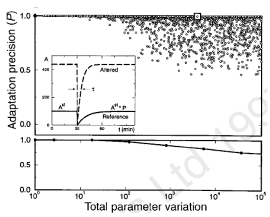
Noise reduction with integral negative feedback

Barkai and Leibler, 1997 showed bacterial chemotaxis adaptation is robust to protein number variation.

Postulated: CheB only demethylates active receptors

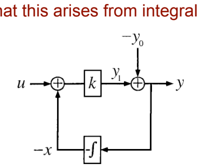
Result

adaptation robust to variable protein concentrations



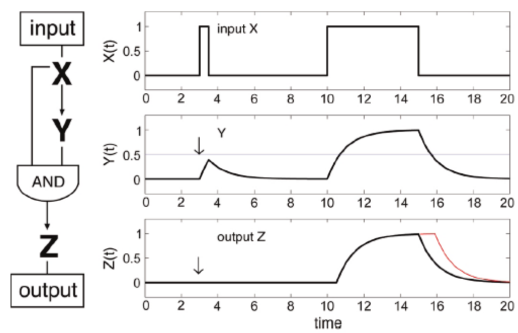
Yi, Huang, Simon, and Doyle, 2000 showed that this arises from integral negative feedback.

- adaptation is from integral
- robustness is from negative feedback



Noise reduction with feed-forward motif

filters out brief inputs – noise reduction



Sources and amount of stochasticity

Amplifying stochasticity

Reducing stochasticity

Modeling stochasticity

Summary

Stochastic modeling

2 approaches

- compute every possible outcome at once, with probabilities
- simulate individual trajectories, and then analyze results

Chemical master equation approach

Calculate the probability of every possible system state, as a function of time

$A \xrightarrow{k} B$

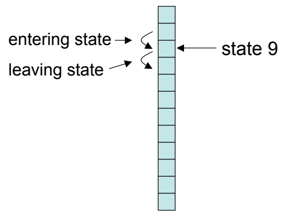
State is number of A molecules
P_a is probability system is in state a.

$$\frac{dP_a}{dt} = kP_{a+1} - kP_a$$

rate of entering state

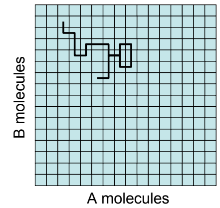
rate of leaving state

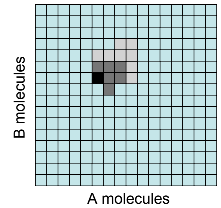
states



Chemical master equation approach

More generally, a trajectory is a random walk in state space. The master equation computes the probability of being in each state as a function of time.





Exact solution for all trajectories, but
• doesn't give sense of trajectories
• is hopelessly complicated for realistic system

Langevin approach

$A \xrightarrow{k} B$

deterministic

$$\frac{d[A]}{dt} = -k[A]$$

$$\Delta[A] = -k[A]\Delta t$$

stochastic

$$\frac{d[A]}{dt} = -k[A] + x(t)$$

noise term

$$\Delta[A] = -k[A]\Delta t + \overbrace{X\sqrt{k[A]\Delta t}}$$

Gaussian distributed random variable with mean 0, std. dev. 1

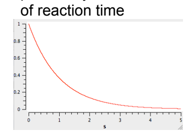
Result has correct level of noise, but
• number of molecules is not discrete
• A can increase as well as decrease

Gillespie algorithm

$A \xrightarrow{k} B$

1. For each reaction path
   • decide *when* the next reaction will be:
     τ is drawn from an exponential distribution
   • decide what the product will be:
     Here, B is the only option

probability distribution of reaction time



2. Step the system forward to the next reaction

3. Perform the reaction

4. Repeat

Method is exact, but simulates slowly.

Gillespie algorithm

$A \xrightarrow{k} B$

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   • decide *when* the next reaction will be:
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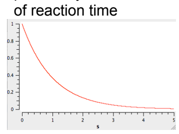

2. Step the system forward to the next reaction

3. Perform the reaction

4. Repeat

variants: Gibson-Bruck, direct method, first-reaction method, optimized direct method.

Summary

Source of stochasticity
- reaction timing

Amount of stochasticity
- $\sqrt{n}$ is rule-of-thumb

Amplification
- good for population heterogeneity, etc.
- transcription/translation
- positive feedback
- intrinsic/extrinsic noise

Reduction
- negative feedback
- feed-forward motif

Modeling
- chemical master equation
- Langevin equation
- Gillespie algorithm

Homework

No class next week. Instead, a talk by Herbert Sauro.

In two weeks, development and pattern formation.

<u>Read</u>
?