Cell signaling and output robustness

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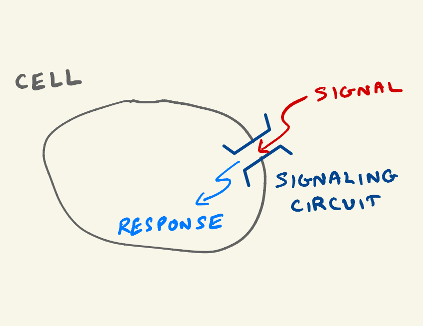
All living systems communicate.

- All living systems, at every spatial scale, communicate.
- Along with material and energy, living systems exchange information.
- Communication requires:
  - Sending a signal,
  - Receiving a signal,
  - Interpreting the signal/producing an appropriate response.

Signal Transduction



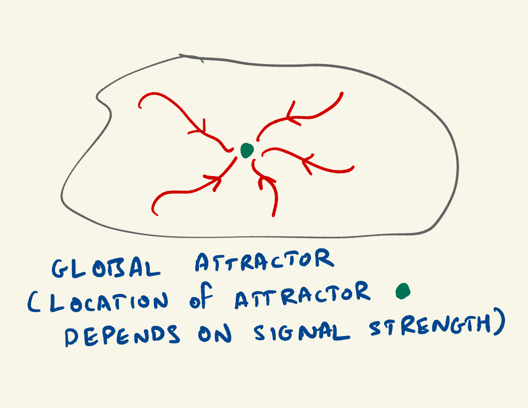
Required properties

- Response depends on signal strength
- NOT on internal state of cell/signaling circuit

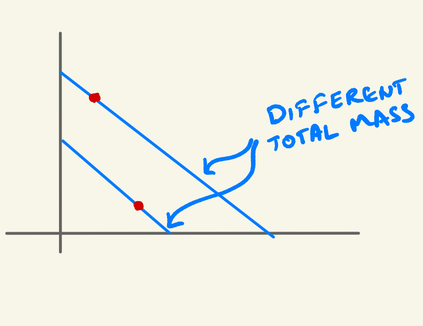
i.e. <u>Output robustness</u>

Encoding robustness in Mathematical Model

Biological System Property	:	Model Encoding
Signal Strength	:	Rate Constant/Parameter
Internal State of Signaling Circuit	:	Initial State
Signal Response	:	Final State



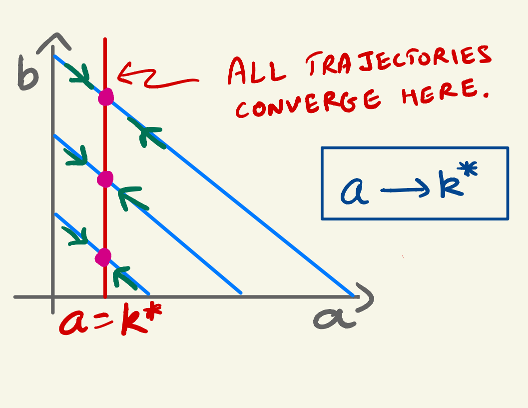
Conserved quantities in biological systems



Different initial states $\implies$ different final states

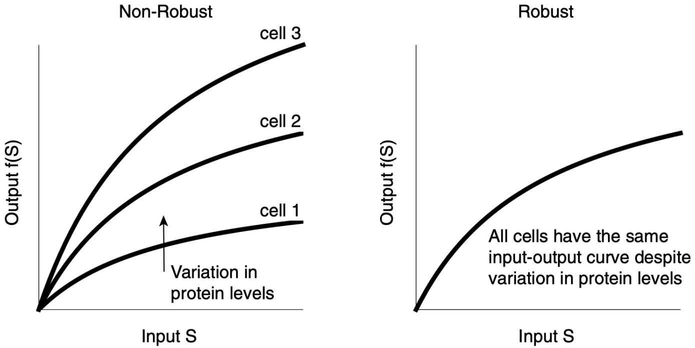
Robustness of output

- Output is concentration of single species.



Robust signal response

Figure source Uri Alon: An introduction to systems biology

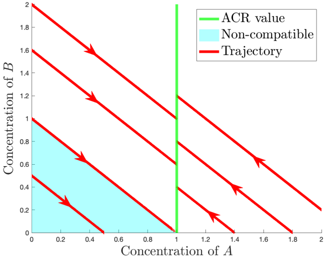


Simple two-dimensional system with output robustness

$$S + I \xrightarrow{k_1} 2I$$
$$I \xrightarrow{k_2} S$$

Mass-action ODE system:

$$ds/dt = -k_1 si + k_2 i$$
$$di/dt = k_1 si - k_2 i$$



Output robustness and applications

- **Biology question:** How to determine if a given system has output robustness?
  - Output robustness at network level (for any choice of rate constants)?
  - Output robustness at system level (only for some choices of rate constants)?
- **Engineering question:** Can we design a reaction network with desired robustness properties?
- **Control question:** Can we impose robustness on a biological system through an external control?

Need network conditions.

How to establish output robustness?

- Establishing system has output robustness requires understanding global dynamics.
- Global dynamics/global stability are challenging problems – even for moderate scales (> 3 dimensions).
- Divide the problem. Focus on location of steady states.
- **Absolute concentration robustness**: All positive steady states on hyperplane $\{x_i = a_i^*\}$ parallel to coordinate hyperplane. Network has absolute concentration robustness (ACR) in species X_i with value a_i^*.
- Shinar-Feinberg (2010) gave sufficient conditions for ACR in mass action systems.

Shinar-Feinberg network conditions

Setting: Mass action system.
Sufficient network conditions for ACR

- **Condition 1:** Network has deficiency one.
- **Condition 2:** Two non-terminal complexes differ in one species X.

Conclusion: Network has ACR in X.

Proof idea

- Low deficiency (0 or 1) gives steady state parameterization.
  - The entire set of steady states can be written using small number of coordinates compared to total number of species.
- Usually number of conservation conditions is same as number of coordinates/parameters used in steady state parameterization.
- When parameterization is combined with conservation conditions, we can get steady state values in a fixed compatibility class.
- Usually hard (also often unnecessary) to solve explicitly. Try to derive some relations/consequences.
- **Slightly more general conclusion** All ratios of non-terminal complexes are robust.

SIS model shows ACR in S

$$S + I \xrightarrow{k_1} 2I$$
$$I \xrightarrow{k_2} S$$

- Deficiency:
  $\delta = \#$ complexes - $\#$ linkage classes - dimension
  $= 4 - 2 - 1 = 1.$
- $S + I$ and I are nonterminal complexes.

Conclusion: ACR in $S \quad = (S + I) - (I)$.

Existence of positive steady states

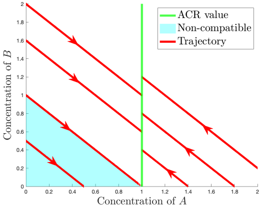
$$\dot{s} = i\,(k_2 - k_1 s)$$
$$\dot{i} = -i\,(k_2 - k_1 s)$$

- If there is a positive steady state it must satisfy $s = k_2/k_1$. Therefore a positive steady state can only exist if $s(0) + i(0) > k_2/k_1$.

Compare with dynamics

$$S + I \xrightarrow{k_1} 2I$$

$$I \xrightarrow{k_2} S$$



- SF conditions are network conditions. Location (value) of steady states depends on rate constants. But fact of whether or not system has ACR only depends on the reaction network (not rate constants).
- Need to separately check existence of positive steady states.
- Need to separately establish convergence to steady states.

Signal transduction with bifunctional enzyme

Source: Uri Alon: An Introduction to Systems Biology

- T: ATP, D: ADP, P_i: inorganic phosphate,
- Y_0: unphosphorylated substrate, Y_p: phosphorylated substrate,
- X_0, X_p, A enzyme (unbound, phosphorylated, bound with ATP) that transfers phosphate,
- $A = [XT], B = [X_p Y_0], C = [AY_p]$,
- $\nu_a(S), \nu_p(S)$ signal strength dependent rate constants.

$$X_0 + T \underset{k_1'}{\overset{k_1}{\rightleftarrows}} A \xrightarrow{\nu_a(S)} X_p + D$$

$$X_p + Y_0 \underset{k_2'}{\overset{k_2}{\rightleftarrows}} B \xrightarrow{\nu_t} Y_p + X_0$$

$$A + Y_p \underset{k_3'}{\overset{k_3}{\rightleftarrows}} C \xrightarrow{\nu_p(S)} Y_0 + A + P_i$$

Signal transduction with bifunctional enzyme

- Assume abundant ATP (T).
- D and P_i are only produced.

$$X_0 \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} A \xrightarrow{\nu_a(S)} X_p$$

$$X_p + Y_0 \underset{k_2'}{\overset{k_2}{\rightleftharpoons}} B \xrightarrow{\nu_t} Y_p + X_0$$

$$A + Y_p \underset{k_3'}{\overset{k_3}{\rightleftharpoons}} C \xrightarrow{\nu_p(S)} Y_0 + A$$

Signal transduction with bifunctional enzyme

$$X_0 \underset{k_1'}{\overset{k_1}{\rightleftarrows}} A \xrightarrow{\nu_a(S)} X_p$$

$$X_p + Y_0 \underset{k_2'}{\overset{k_2}{\rightleftarrows}} B \xrightarrow{\nu_t} Y_p + X_0$$

$$A + Y_p \underset{k_3'}{\overset{k_3}{\rightleftarrows}} C \xrightarrow{\nu_p(S)} Y_0 + A$$

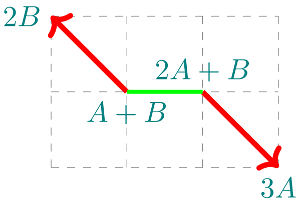
Exercise 1

a. Calculate deficiency of the network.
b. Show Shinar-Feinberg conditions are satisfied.
c. Find all robust ratios.
d. Which species have ACR? Find their ACR value.

Exercise 2

$$A + B \xrightarrow{k_1} 2B$$

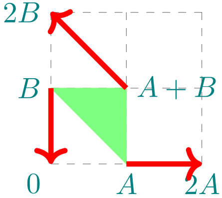
$$2A + B \xrightarrow{k_2} 3A$$



- (a) Show Shinar-Feinberg conditions are satisfied and find ACR species.
- (b) Explicitly write the ODEs and show that all positive steady states are unstable.
- (c) Will the system show output robustness?

Lotka-Volterra model

Exercise 3 $A \xrightarrow{k_1} 2A, \quad B \xrightarrow{k_2} 0, \quad A + B \xrightarrow{k_3} 2B$



1. (a) Show Shinar-Feinberg conditions are satisfied and show both species have ACR
2. (b) Explicitly write the ODEs and show that there is a unique positive steady state but it is unstable.
3. (c) Will the system show output robustness?

Two-step covalent modification with bifunctional enzyme

$$S_1 + E \rightleftarrows C_1 \to S_2 + E \rightleftarrows C_2 \to S_3 + E$$
$$S_3 + C_\alpha \rightleftarrows D_1 \to S_2 + C_\alpha \rightleftarrows D_2 \to S_1 + C_\alpha$$

Exercise 4

a. Show Shinar-Feinberg conditions fail.
b. Write the differential equations explicitly for $\alpha = 1$ and $\alpha = 2$.
c. Identify the ACR species and its ACR value in each case.

Summary

- Students give a short summary presentation.
- What do the four exercises say collectively about the strengths and weaknesses of Shinar-Feinberg conditions for determining ACR?

Thank you!