Outline

- Adaptation in signaling circuits
- Precise adaptation in bacterial chemotaxis
  - Introduction
  - A model of robust adaptation
- Defining circuit topologies for precise adaptation.

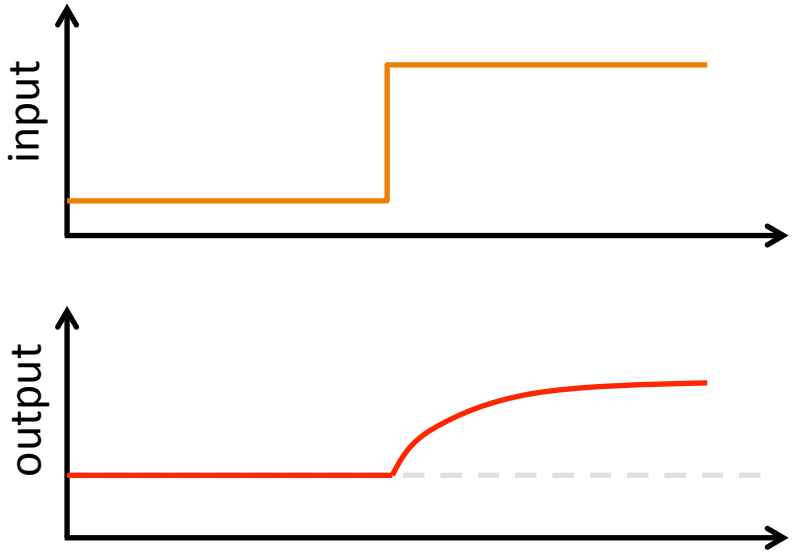
CONCEPT

- Biological circuits must operate robustly.
- A requirement for robustness imposes constraints on circuit design

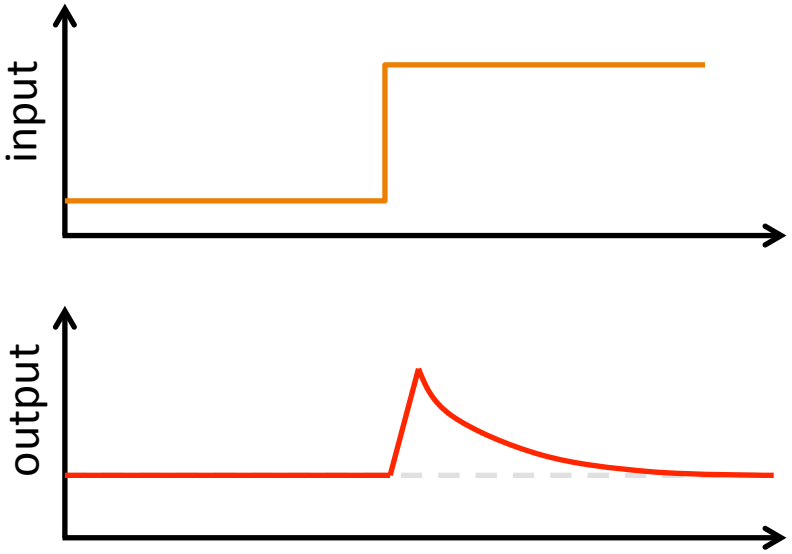
What is adaptation?

- The ability of a system to return to a set point after a change in input levels

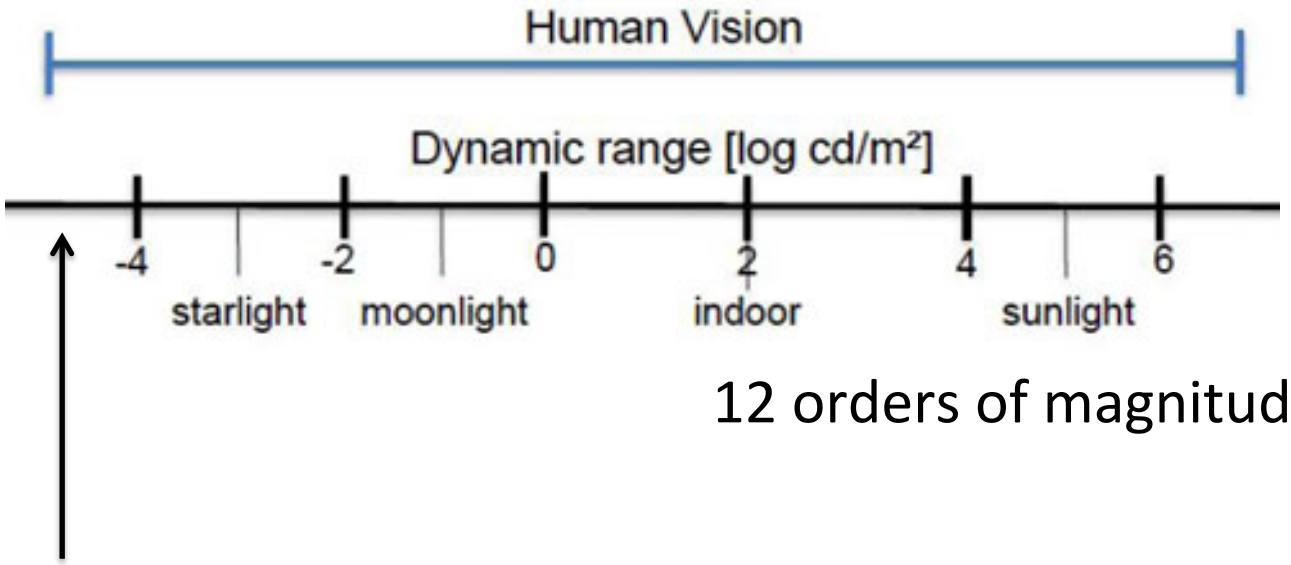
No adaptation



Precise adaptation

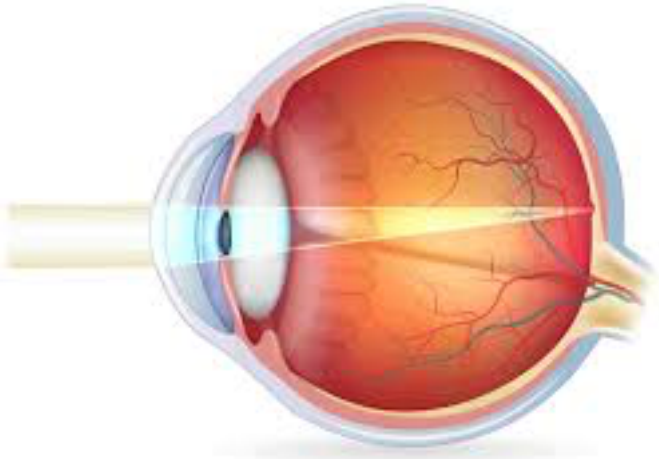


Adaptation expands the dynamic range of a sensory system



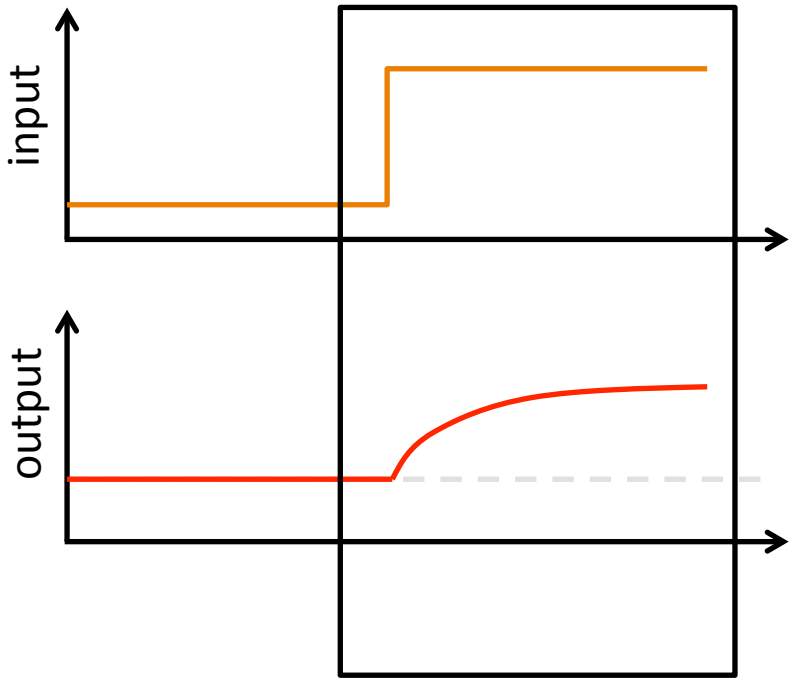
12 orders of magnitude!

Single photons



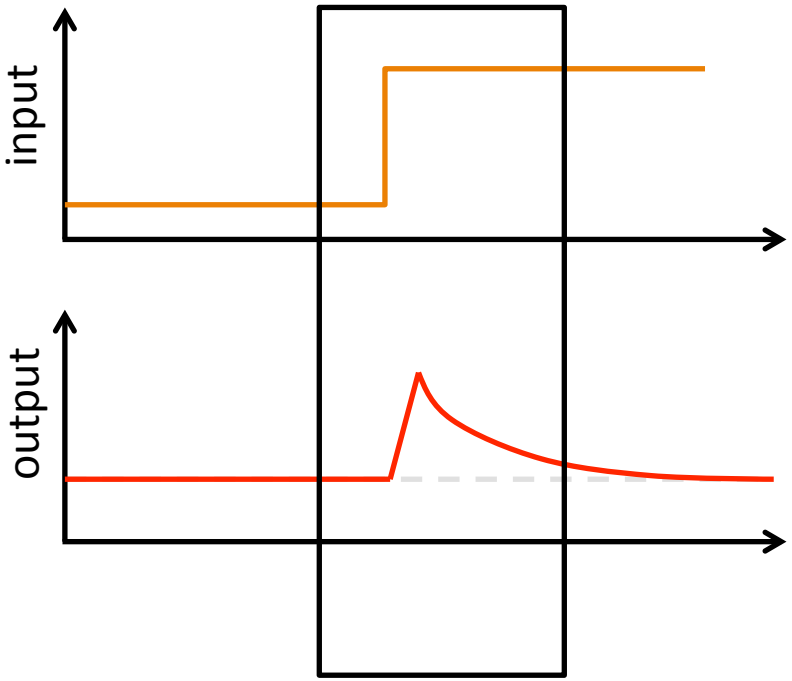
Adaptation allows for difference detection

No adaptation



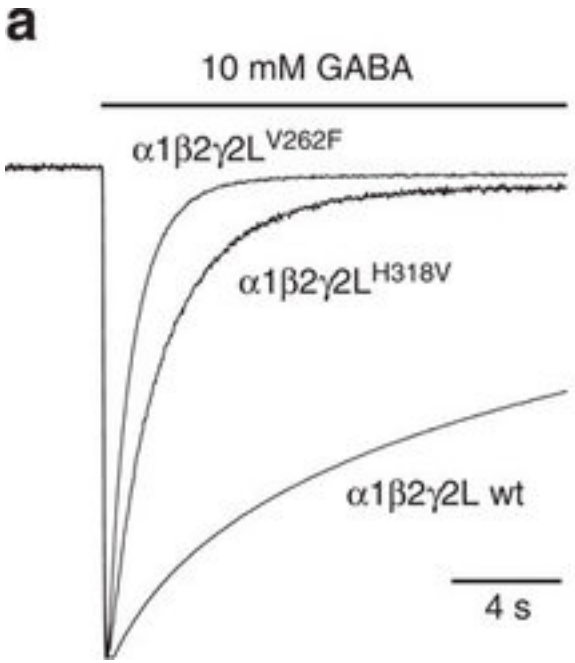
Sustained output change

Perfect adaptation

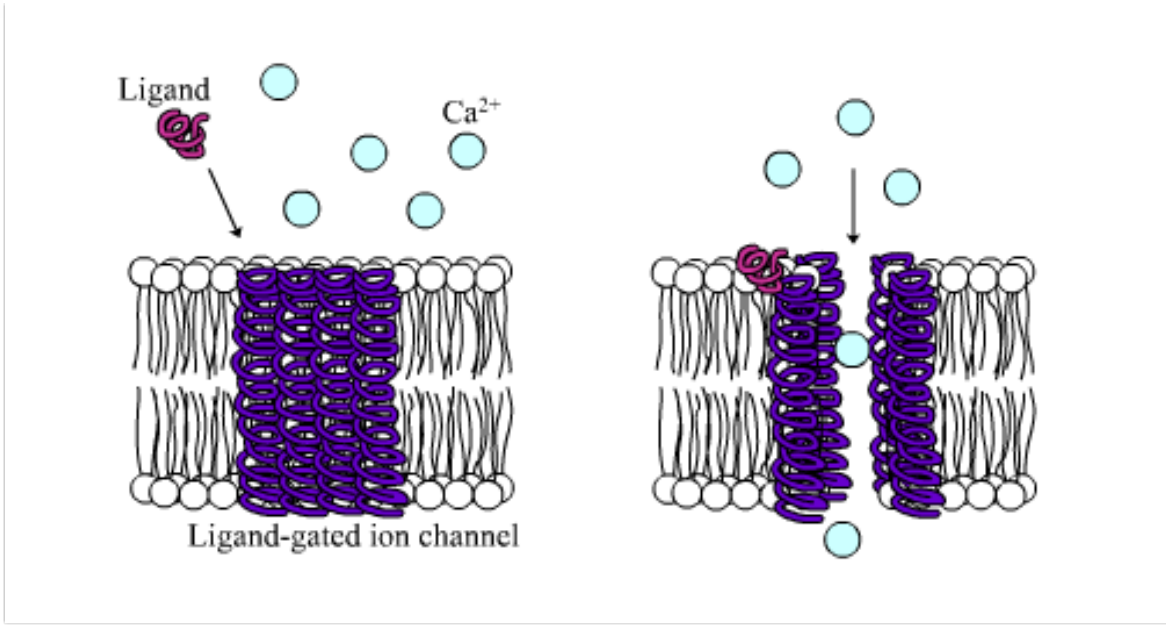


Output only when Change occurs

Adaptation allows for response attenuation



Ligand-gated ion channel



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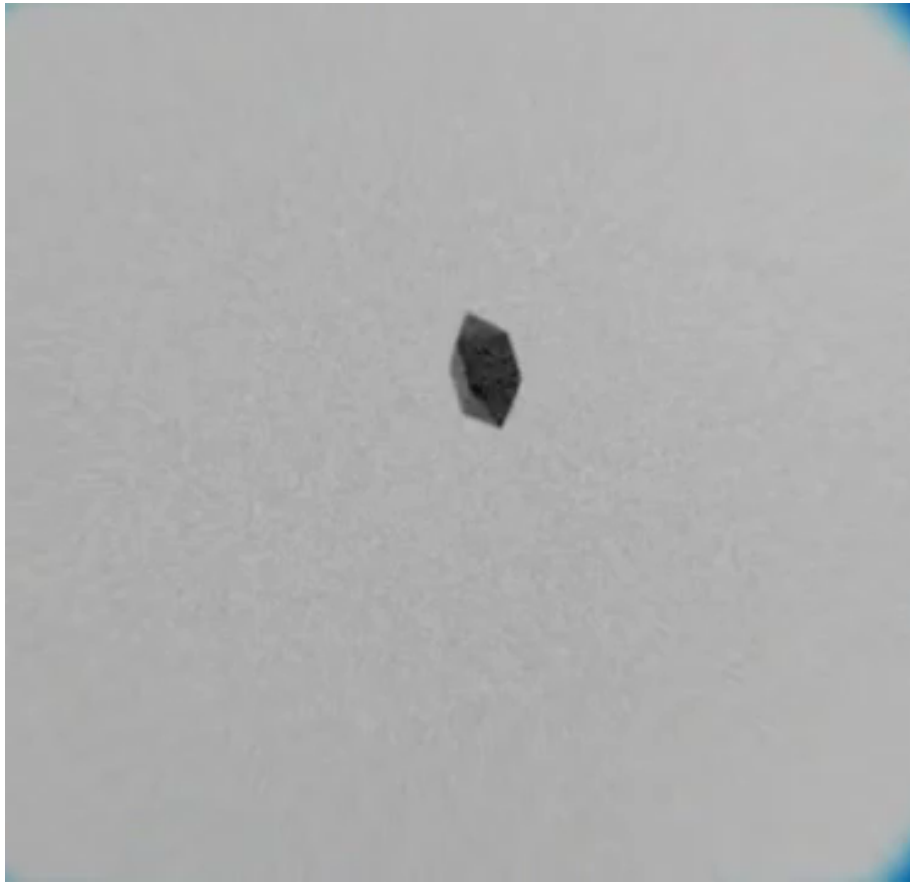
How do bacteria find food?



Chemotaxis – the ability to move along or against a gradient of increasing chemical concentration

Attractants: Nutrients, e.g. aspartate, serine

Repellents: Metal ions, leucine

https://www.youtube.com/watch?v=F6QMU3KD7zw

The bacterial chemotaxis machinery sensitive over a wide dynamic range

1 μm

- Sensitivity: up to 1 molecule / cell length
- Dynamic range: up to 5 orders of magnitude

This exquisite sensitivity holds amid destabilizing effects of Brownian motion. **How?**

1 μm

- Sensitivity: up to 1 molecule / cell length
- Dynamic range: up to 5 orders of magnitude

Due to Brownian motion, bacterial swimming direction changes by 90^{o} after 10 seconds of motion

This exquisite sensitivity holds amid destabilizing effects of Brownian motion. **How?**

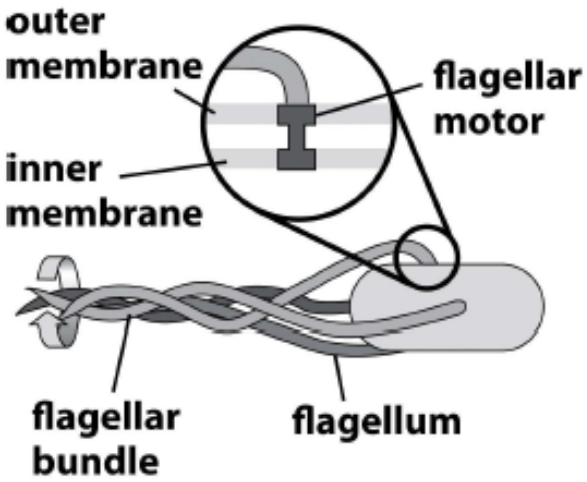
1 μm

- Sensitivity: up to 1 molecule / cell length
- Dynamic range: up to 5 orders of magnitude

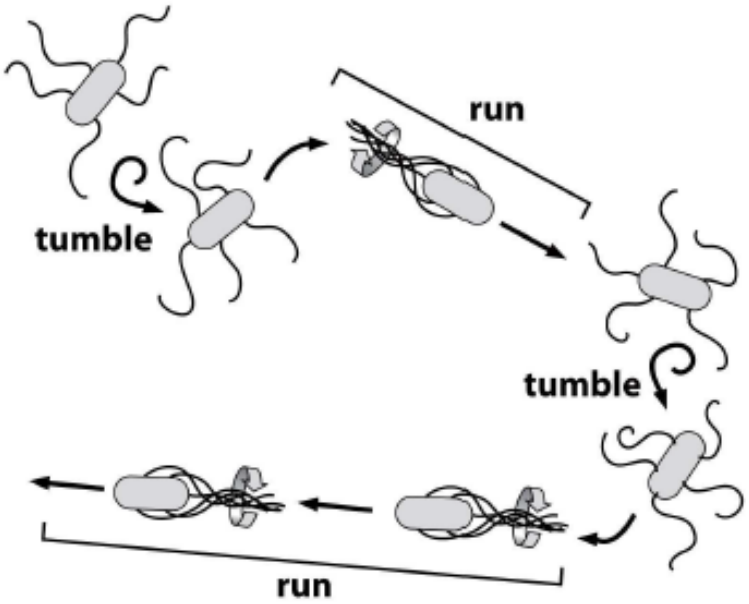
Due to Brownian motion, bacterial swimming direction changes by 90^{o} after 10 seconds of motion

Bacteria measure temporal differences in attractant concentrations as they move

Bacteria alternate between two distinct modes of movement



Tumbling (CW flagellar movement):
Randomizing direction

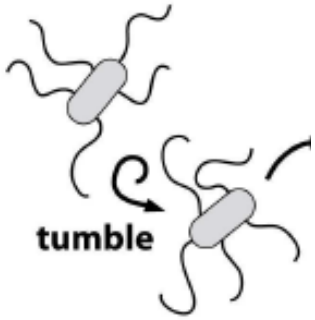


Run (CCW flagellar motor):
Swimming straight

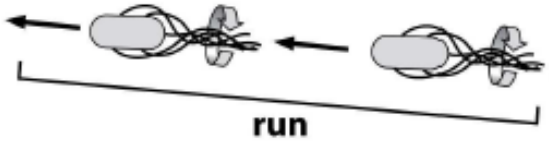
(Phillips, Kondev and Theriot, 2009)

Temporal changes in attractant concentration modulates tumbling frequency

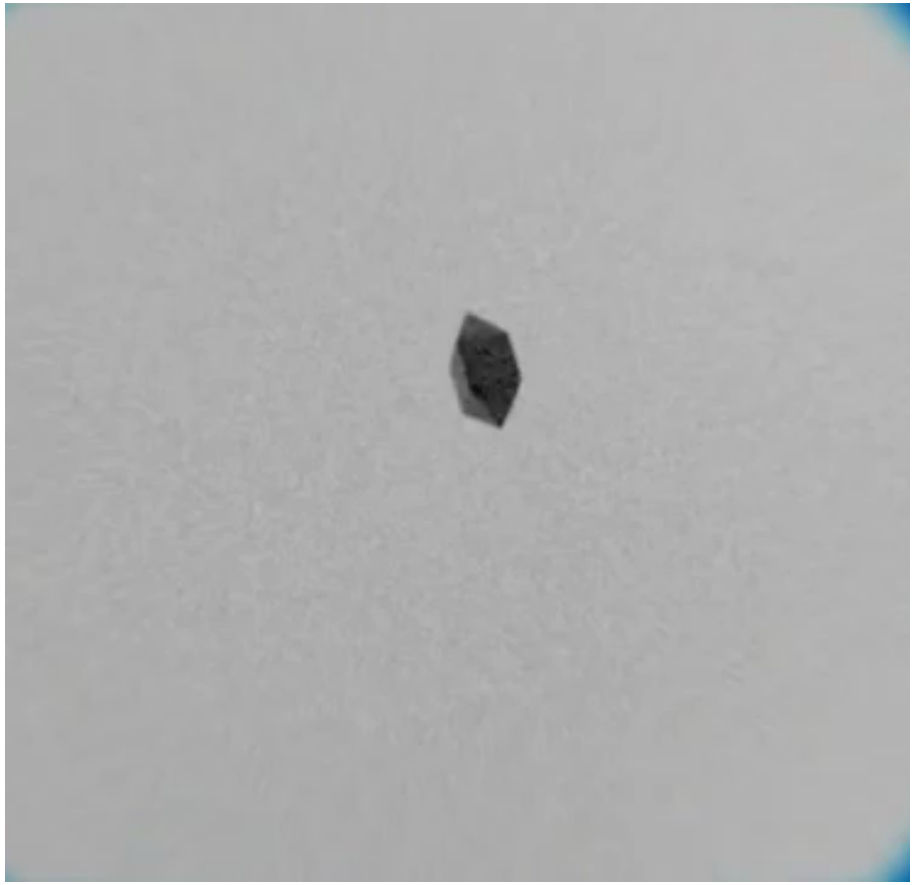
Conditions worsen:
Increase tumbling frequency



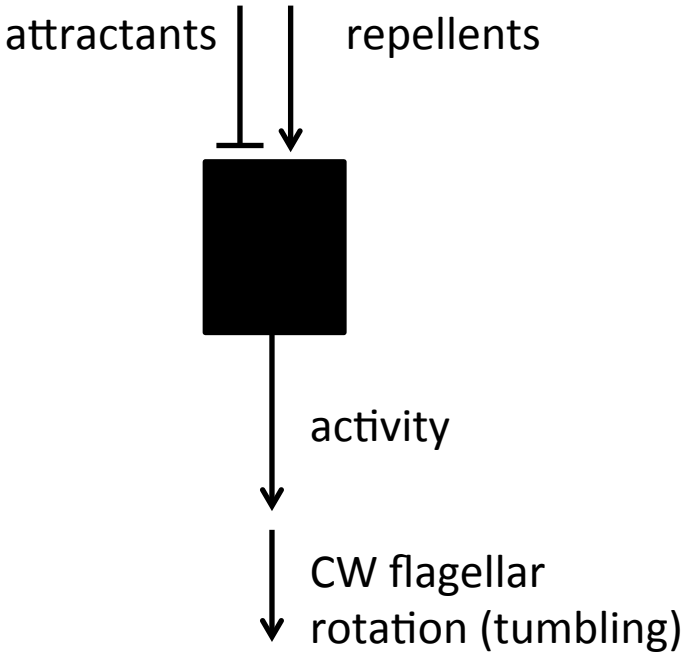
Conditions improve:
decrease tumbling frequency



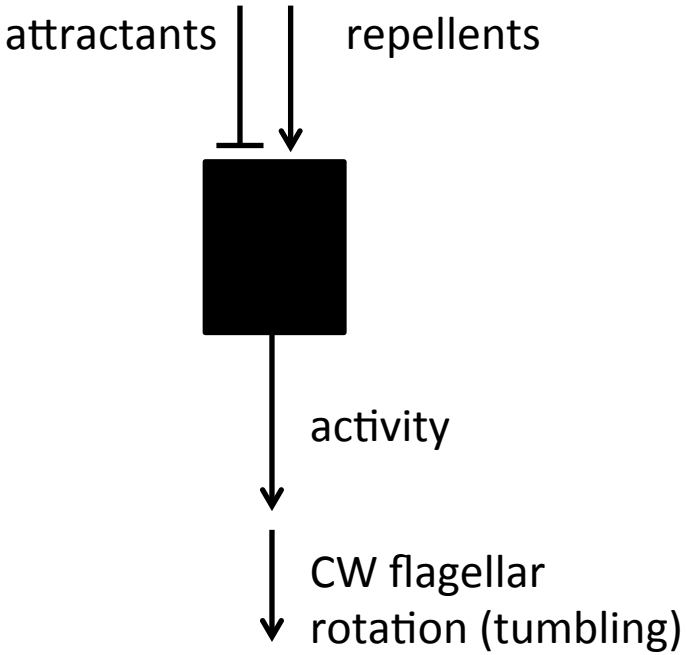
Temporal differences in attractant concentration modulates tumbling frequency

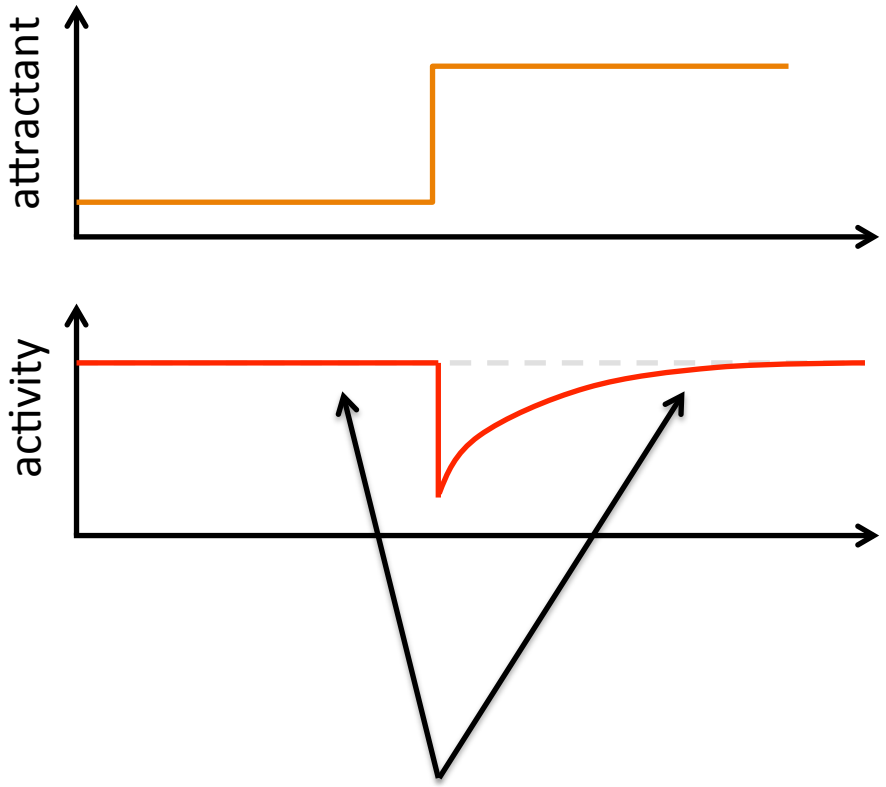


A signaling circuit controlling the flagellar motor rotation underlies chemotaxis



To detect temporal differences, this circuit must adapt precisely





Must be
exactly the same!

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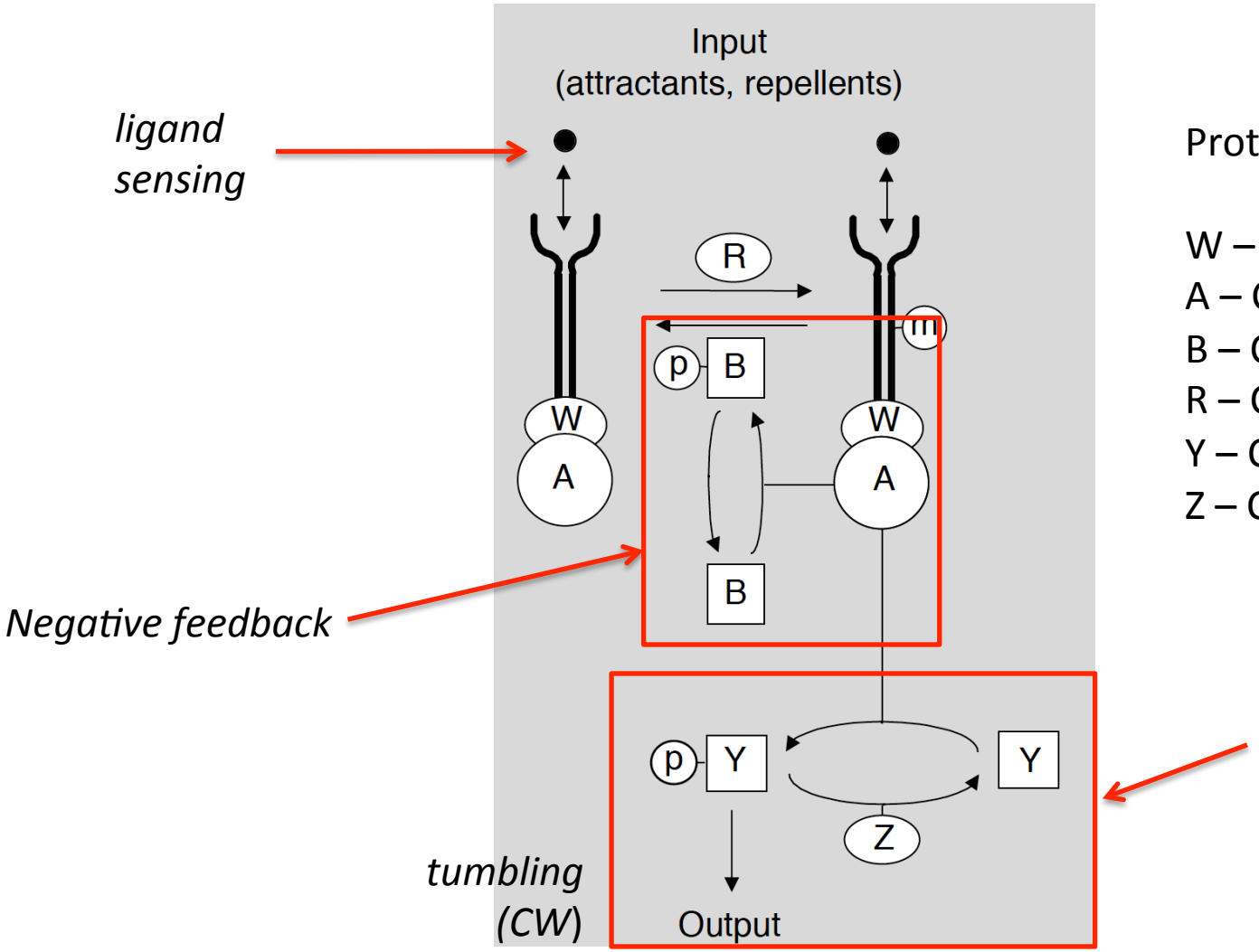
The control circuitry for bacterial chemotaxis

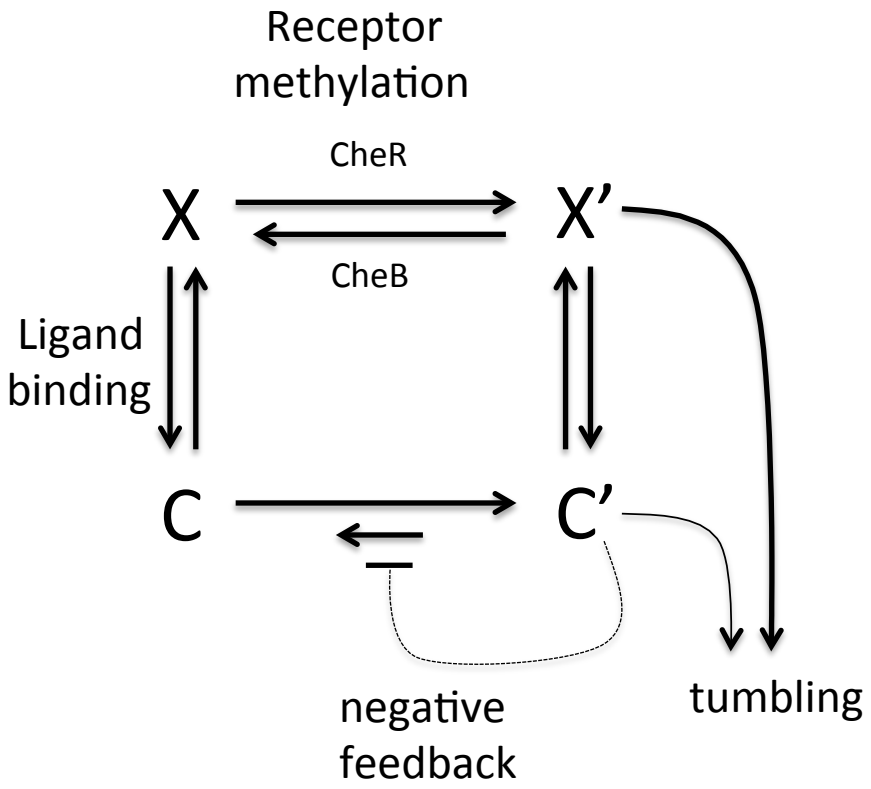


Proteins

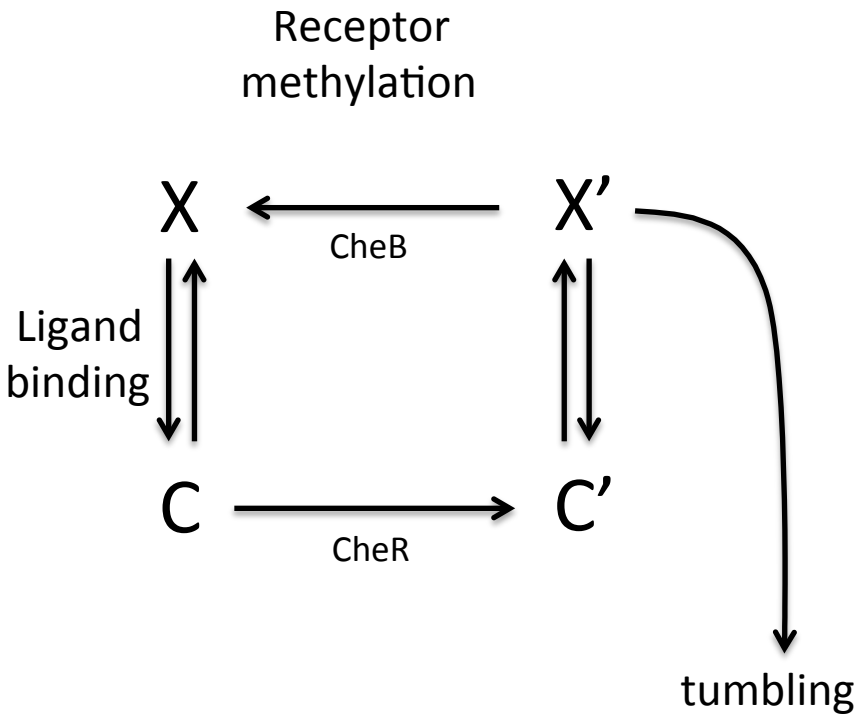
W – CheW
A – CheA
B – CheB
R – CheR
Y – CheY
Z – CheZ

Two models can explain adaptation in bacterial chemotaxis

Model I



Model II



Download these scripts from the course website:

`chemotaxis-model1.py`

`chemotaxis-model2.py`

1) Familiarize yourself with the two models. What are the main differences between the two reaction schemes?
2) Simulate each system under the provided parameters. Describe its response to addition of ligand (`t = 400`).
3) Now, apply small perturbations to each system. How are adaptation dynamics affected?

   Under what conditions do these models break down?

Robustness describes the effects of a given change on a given behavior

Parameter conditions	Dynamic behavior
Protein levels	Precision of adaptation
Rate constants	Time of adaptation
Noise	Steady-state activity

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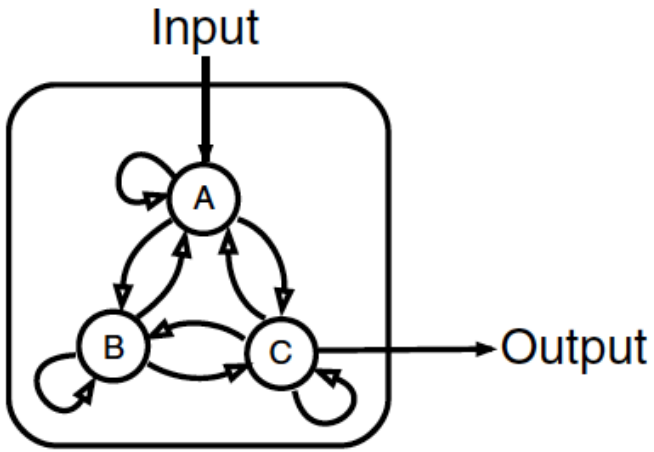
What types of signaling circuits undergo precise adaptation?

Defining Network Topologies that Can Achieve Biochemical Adaptation

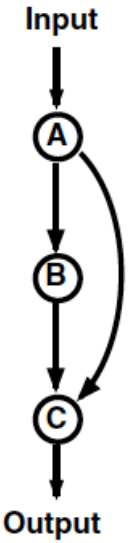
Wenzhe Ma,[1,2,3] Ala Trusina,[2,3] Hana El-Samad,[2,4] Wendell A. Lim,[2,5,*] and Chao Tang[1,2,3,4,*]

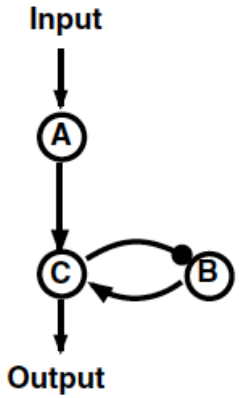
(Cell, 2009)

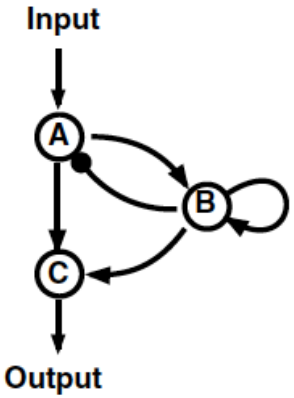
Enumeration and testing all possible architectures enables identification of functional designs



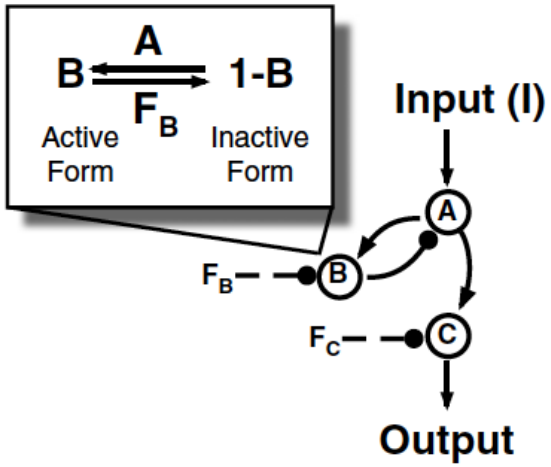
16038 networks



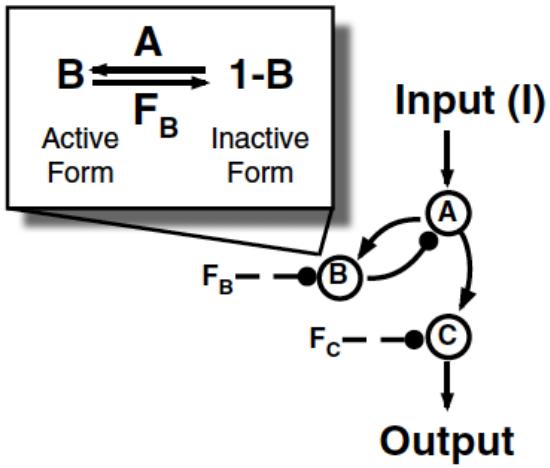




Nodes represent Proteins with modification states



Signaling circuits are modeled using ordinary differential equations

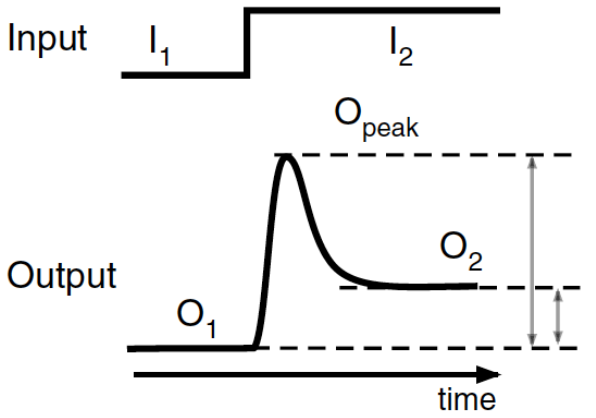


$$\frac{dA}{dt} = k_{IA} I \frac{(1-A)}{(1-A)+K_{IA}} - k'_{BA} B \frac{A}{A+K'_{BA}}$$

$$\frac{dB}{dt} = k_{AB} A \frac{(1-B)}{(1-B)+K_{AB}} - k'_{F_B B} F_B \frac{B}{B+K'_{F_B B}}$$

$$\frac{dC}{dt} = k_{AC} A \frac{(1-C)}{(1-C)+K_{AC}} - k'_{F_C C} F_C \frac{C}{C+K'_{F_C C}}$$

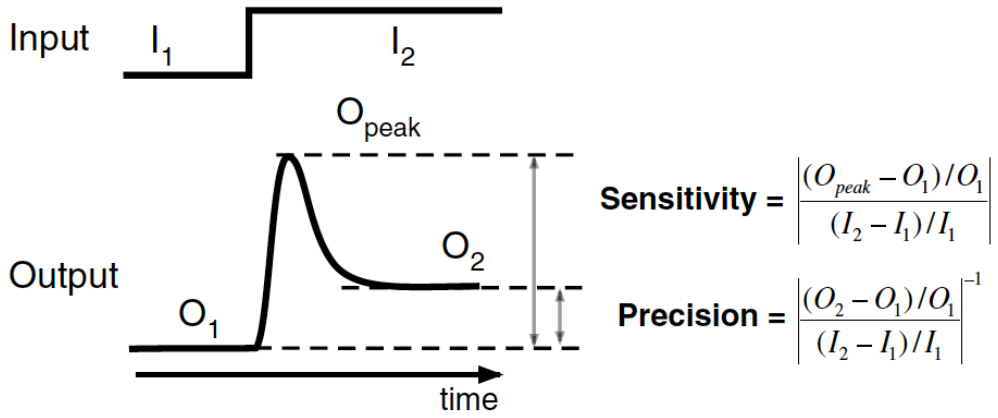
Defining the sensitivity and precision of an adaptive response

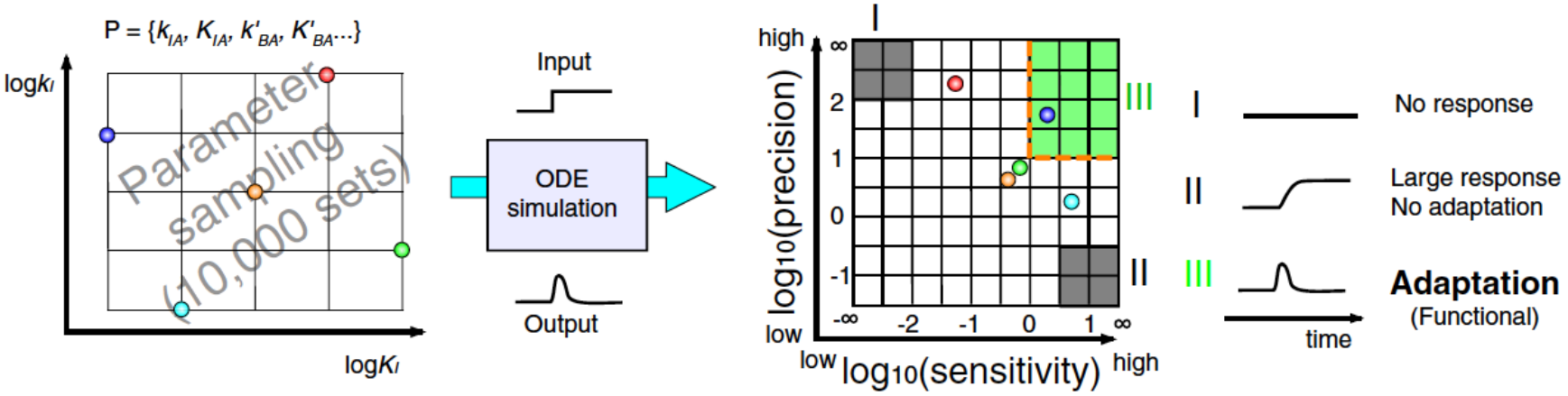


$$\textbf{Sensitivity} = \left| \frac{(O_{peak} - O_1)/O_1}{(I_2 - I_1)/I_1} \right|$$

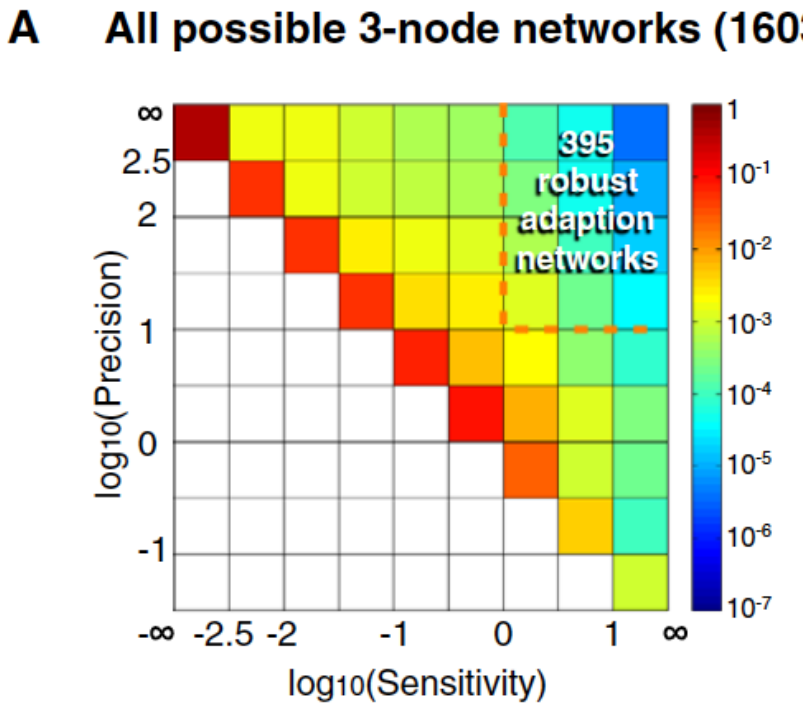
$$\textbf{Precision} = \left| \frac{(O_2 - O_1)/O_1}{(I_2 - I_1)/I_1} \right|^{-1}$$

Adaptation sensitivity and precision are measured for different circuit parameters and topologies





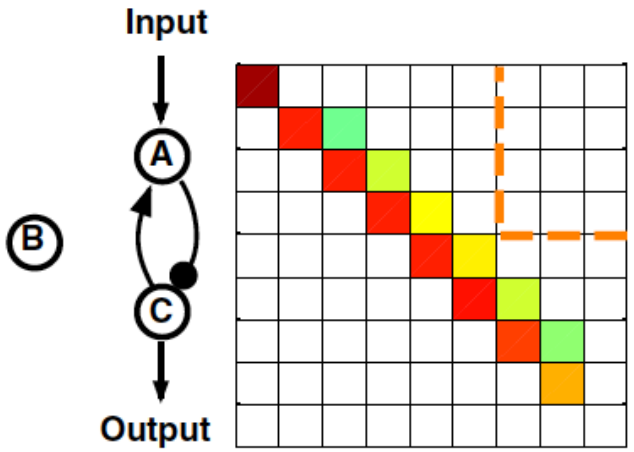
How many types of circuits can give rise to perfect adaptation?

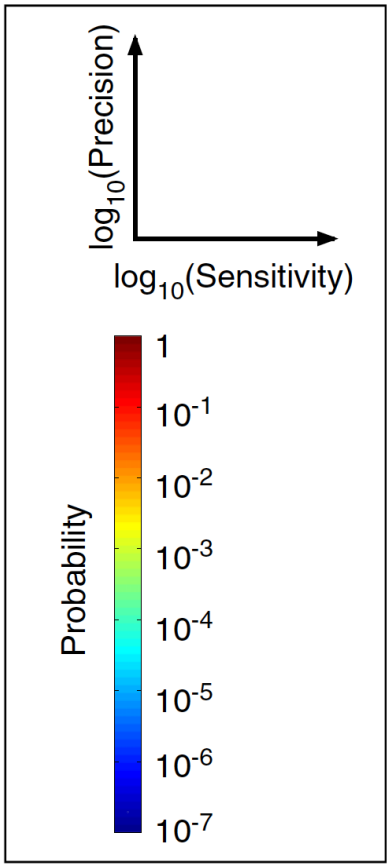


- 395/16038 adaptive circuits

Here is a *non*-adaptive circuit…

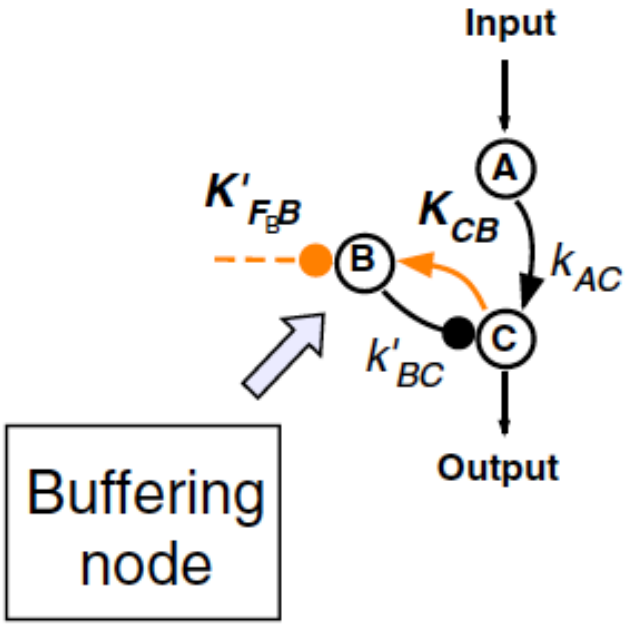
Direct negative feeedback





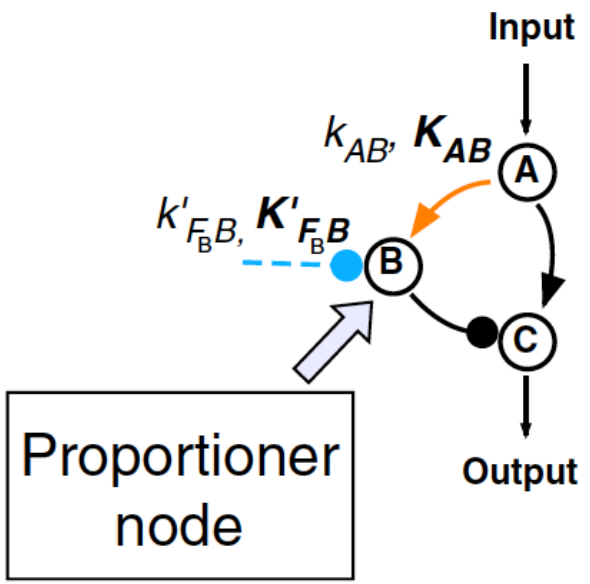
Only two classes of core topologies can show precise adaptation

Negative feedback loop
With buffering node



(Bacterial Chemotaxis)

Incoherent feedforward loop
With proportioner node



(Bacterial

Key points

- Adaptation enables cells to sense differences, keep a wide dynamic range, and limit responses.
- The bacterial chemotaxis circuit undergoes precise adaptation in a robust manner.
- **A requirement for robustness imposes constraints on circuit architecture.**

Further reading

Barkai, N. & Leibler, S. Robustness in simple biochemical networks. *Nature* **387,** 913–917 (1997).

Ma, W., Trusina, A., El-Samad, H., Lim, W. A. & Tang, C. Defining network topologies that can achieve biochemical adaptation. *Cell* **138,** 760–773 (2009).

Alon, U. An introduction to systems biology : design principles of biological circuits. (2007). Chapter 7