



北京国际数学研究中心  
BEIJING INTERNATIONAL CENTER FOR  
MATHEMATICAL RESEARCH



北京大学定量生物学中心  
CENTER FOR QUANTITATIVE BIOLOGY

# 计算系统生物学 Computational Systems Biology

## Lecture 1: Introduction of Systems Biology

张磊

# Course information

- **Lectures:**  
周二5–6节，周四3–4节（单周）
- **3 credits**
- **Textbooks:**  
**None - only lecture notes will be available**
- **Good references**
  - Uri Alon, [An Introduction to Systems Biology - Design Principles of Biological Circuits](#), 2007
  - J. Sneyd & J. Keener, [Mathematical Physiology](#), 2009
  - J. D. Murray, [Mathematical Biology](#), 2003

# Course information

- 授课教师：张磊
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- 助教：张潇逸
- Email: [xyzhang@stu.pku.edu.cn](mailto:xyzhang@stu.pku.edu.cn)

# Course information

- **Homework:** Bi-weekly homework will be assigned including coding.
- **Group presentation:** paper presentation
- **Final Exam:** take-home exam
- **Grade:** Homework 30% + Group presentation 30% + Final exam 40%

# Course information

- Challenge of this class:
  - ✓ read up on your biology or math if needed
  - ✓ Matlab will be used intensively during the course, make sure you have known (or learn) how to use it (necessary for problem sets)
- A key for this course: Pre-class reading, self-study
- We will create a "WeChat" group for course information, questions, and free discussion.

- The Dilemma of Modern Biology
  - The amount of data being collected is staggering. Knowing what to do with the data is in its infancy.
  - The parts list is nearly complete. How the parts work together to determine function is essentially unknown.
- How can mathematics help?
  - The search for general principles; organizing and describing the data in more comprehensible ways.
  - The search for emergent properties; identifying features of a collection of components that is not a feature of the individual components that make up the collection.

# Why do we need Mathematical Biology?

**“Most of science is biology”**

- quote from Michael Reed (Prof. of Math, Duke)



RESEARCH MATTERS

All biology is computational biology

Florian Markowetz\*

University of Cambridge, Cancer Research UK Cambridge Institute, Cambridge, United Kingdom

NOTICES OF THE AMS

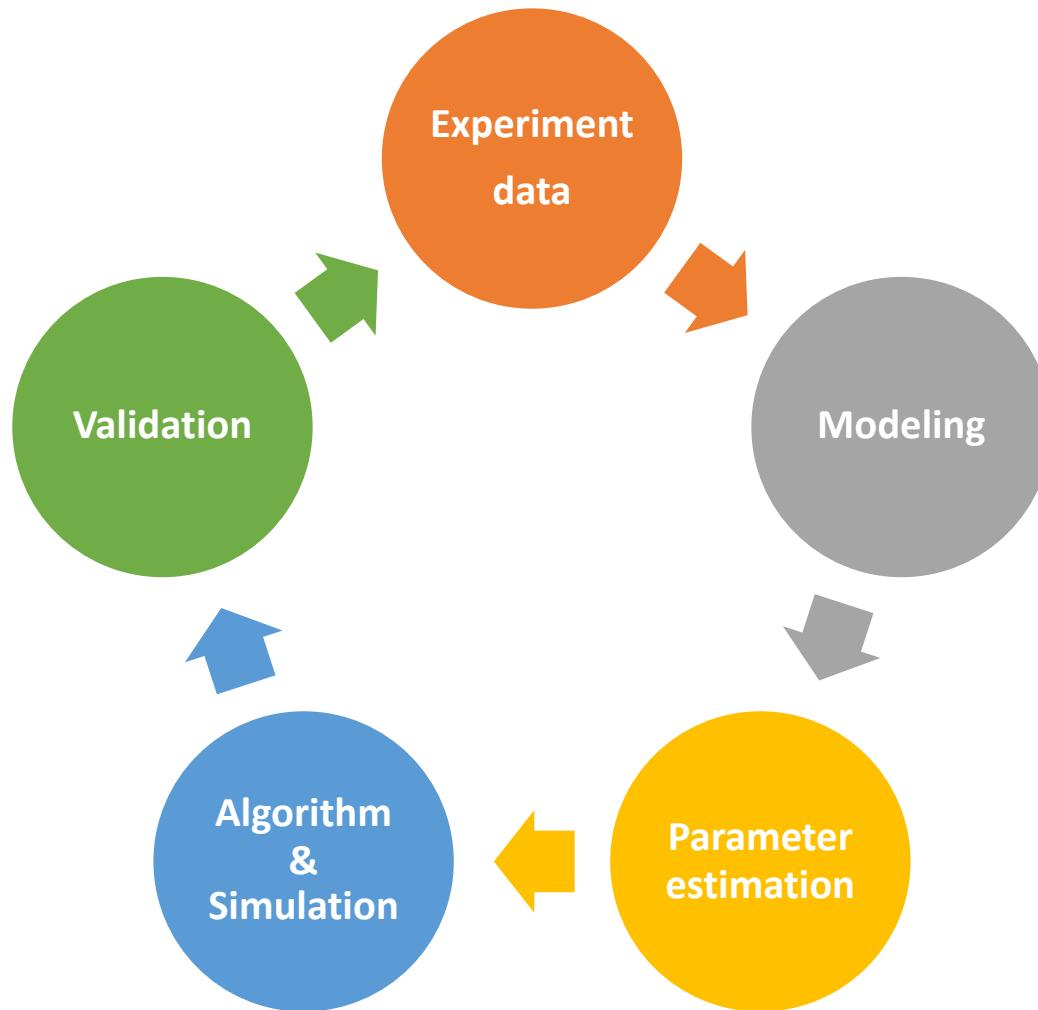
VOLUME 62, NUMBER 10

Mathematical Biology is  
Good for Mathematics

Michael C. Reed

# What is the mathematical biology?

- “Mathematical biology is an interdisciplinary scientific research field with a range of applications in biology, biotechnology, and medicine.” – from Wiki.



# Difference between Math and Biology

- A big difficulty in communication between Mathematicians and Biologists is because of different vocabulary.
- Examples:
  1. to **divide**
    - ✓ find the ratio of two numbers (Mathematician)
    - ✓ replicate the contents of a cell and split into two (Biologist)
  2. to **differentiate**
    - ✓ find the slope of a function (Mathematician)
    - ✓ change the function of a cell (Biologist)
  3. to **PDE**
    - ✓ Partial Differential Equation (Mathematician)
    - ✓ Phosphodiesterase 磷酸二酯酶 (Biologist)

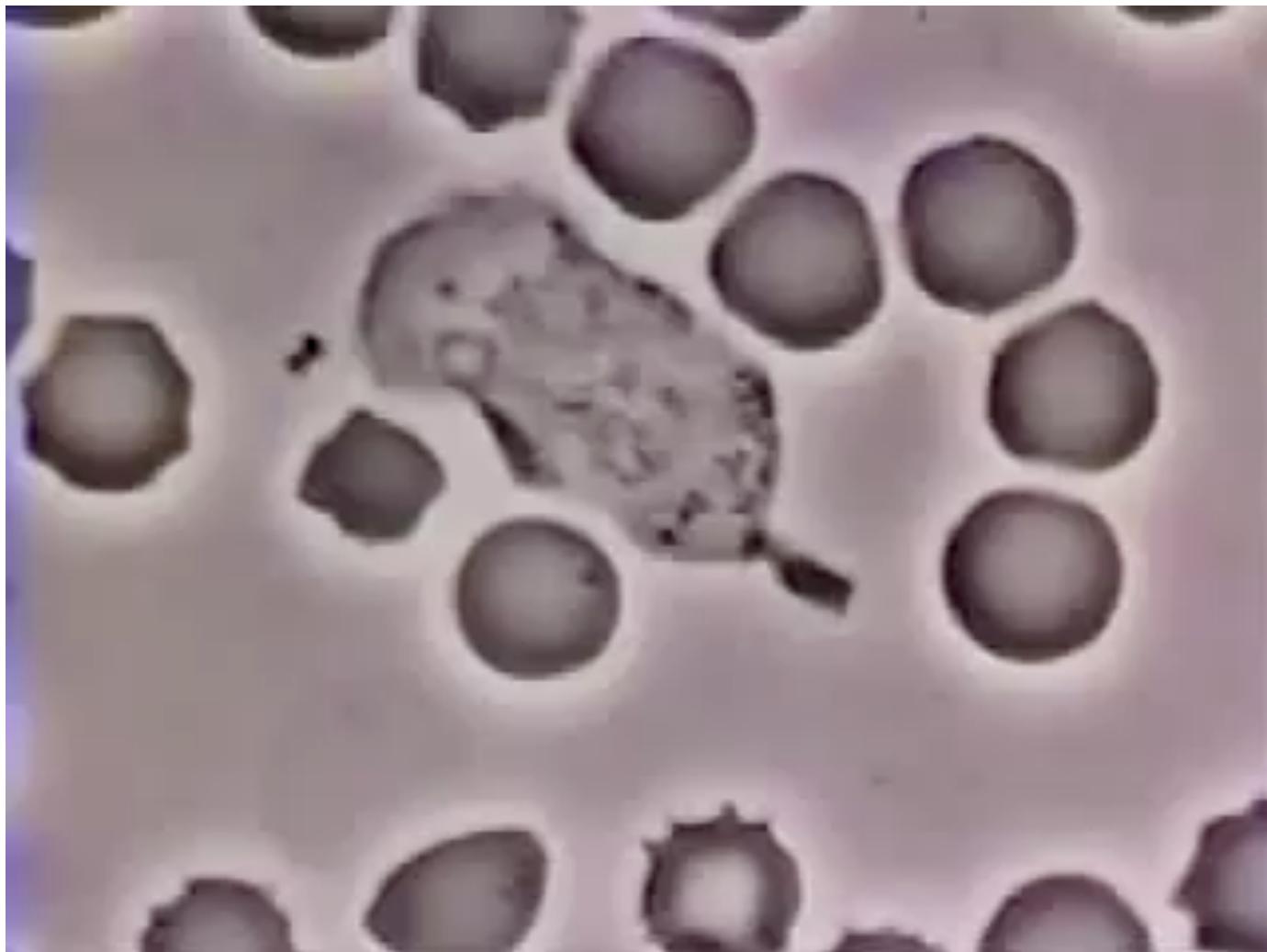
# A challenge

- The study of biological processes is over many space and time scales (roughly  $10^{16}$ ):
- **Space scales:** Genes → proteins → networks → cells → tissues and organs → organism → communities → ecosystems
- **Time scales:** protein conformational changes → protein folding → hormone secretion → protein translation → cell cycle → circadian rhythms → human disease processes → population changes → evolutionary scale adaptation

# What is systems biology?

- (From wiki) **Systems biology** is the computational and mathematical modeling of complex biological systems. An emerging engineering approach applied to biological scientific research, systems biology is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach to biological research.

# Crawling Neutrophil Chasing a Bacterium

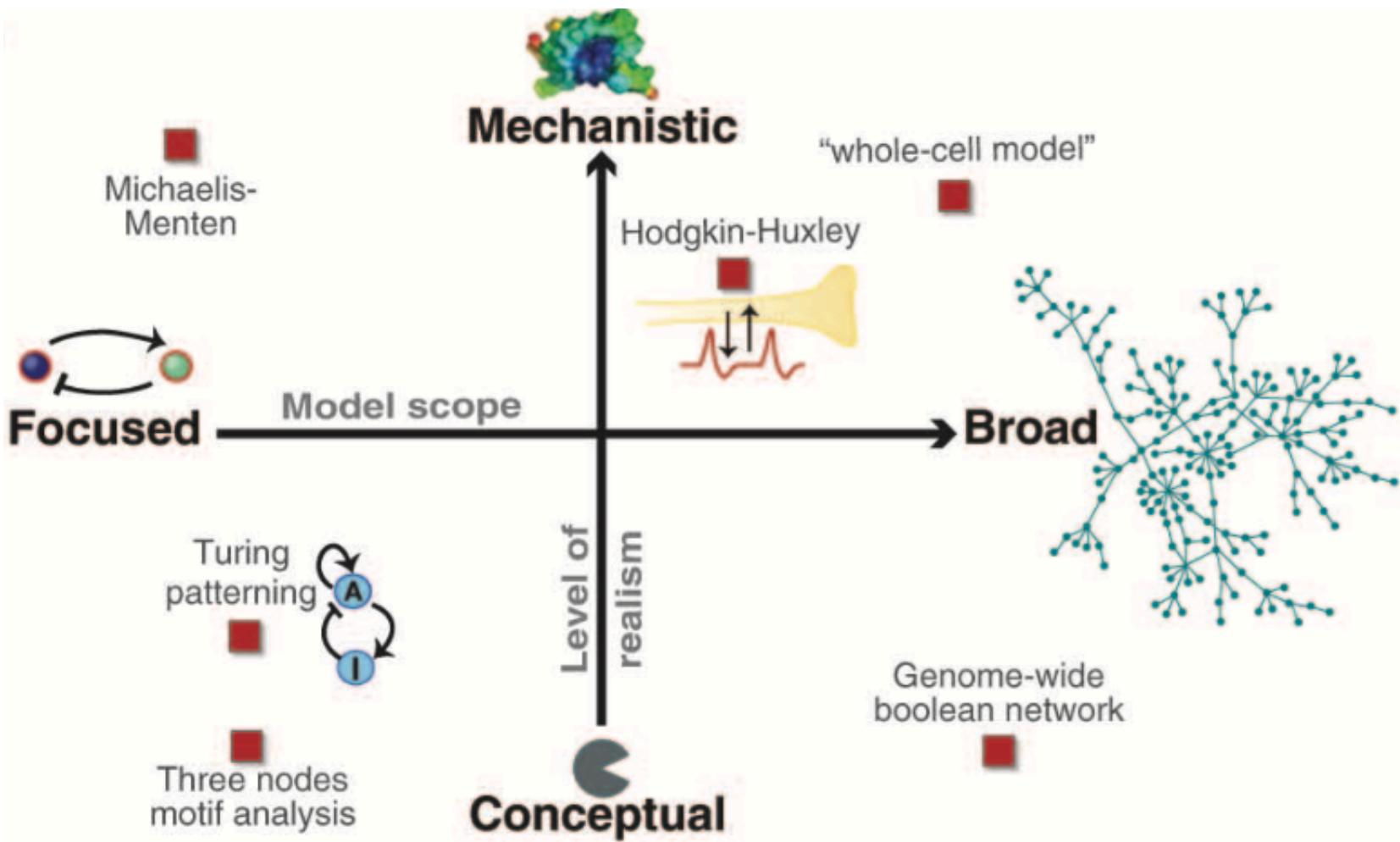


This video is taken from a 16-mm movie made in the 1950s by the late David Rogers at Vanderbilt University (YouTube).

# Two distinct communities in systems biology

1. Mathematicians & Physicists ✓  
simple models <-> experiments
  
2. Computer scientists and engineers  
Complex models & algorithms -> extract signal from large data sets.
  - Computational biology – Protein folding,
  - Bioinformatics - Genomes

# Mathematical Modeling



Mogilner, Allard, Wollman, Science 2012.

# Computational Approaches

- The first step is to formulate a mathematical model - theoretical description of the process of interest that captures the properties and interactions of the most relevant variables of the system at a level of detail that is both useful and tractable.
- Second step, we need to analyze the model – if it is simple and sufficiently tractable, we can use “pencil-and- paper” analysis and compare this analytical solution directly with experimental data.
- However, very often, the number of variables and the complexity of their interactions preclude the analytical approach, and the behavior of models must be solved or simulated by using computers in order to be understood and compared with data.
- This combined approach refers as computational biology.



# Computational Biology

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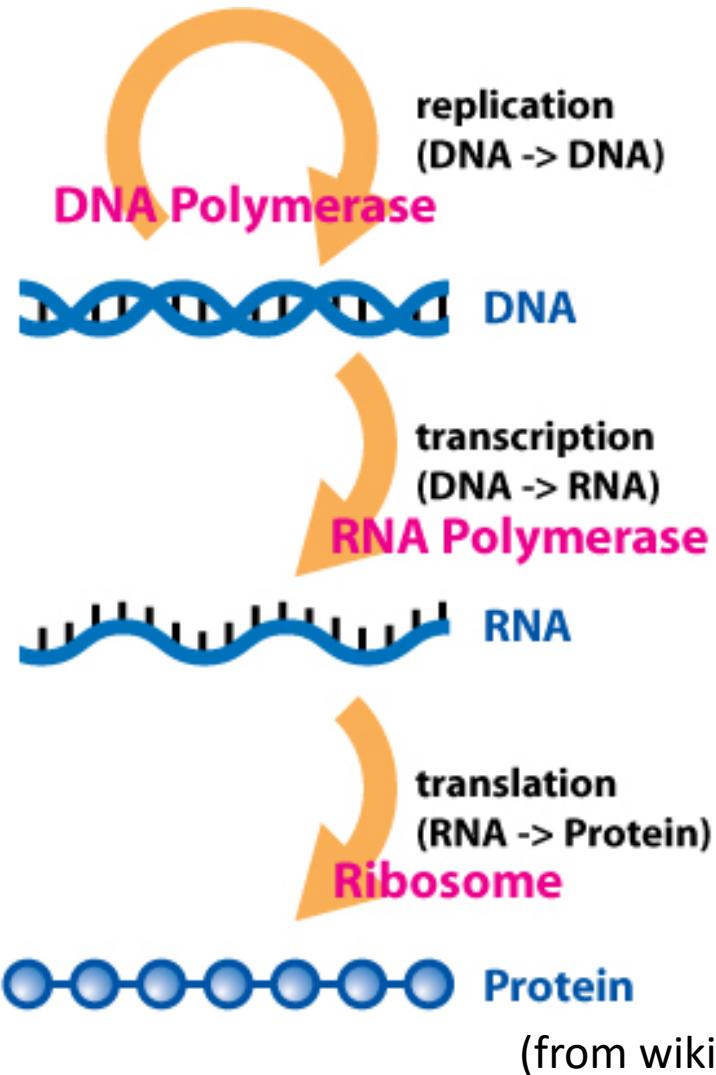
# Limitations of Computational Approaches

- **Drawback:** Although models are often useful in explaining and predicting developmental phenomena, the eventual fate of a given model is to be proven wrong and then modified or replaced.
  - Hypothesis of the model,
  - Lack of basic laws.
- So far the greatest impact of computational approaches is to force hypotheses to be precisely stated and to stimulate corresponding new quantitative experiments to test them.

# Overview of the lectures

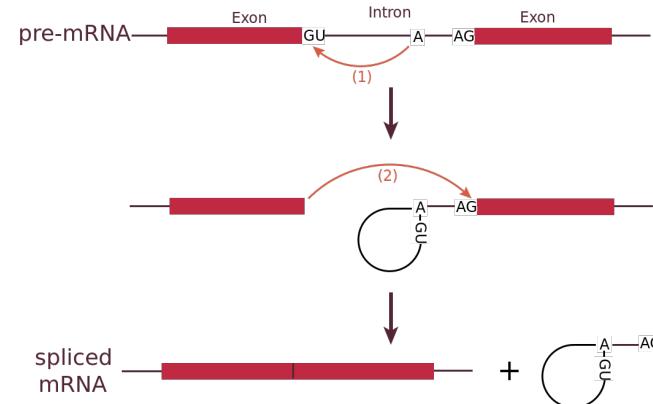
- Lecture 1: Introduction to the class and overview of topics
- Lecture 2: Michalis-Menten kinetics
- Lecture 3: Transcription Networks: Basic concepts and autoregulation
- Lecture 4 : Stability analysis and toggle switch
- Lecture 5 : Oscillatory genetic networks
- Lecture 6 : Feed-forward loop network motif
- Lecture 7 : Introduction to stochastic gene expression
- Lecture 8 : Stochastic modeling
- Lecture 9 : Robustness and bacterial chemotaxis
- Lecture 10 : Robustness in development and pattern formation
- Lecture 11 : Cell polarity models
- Lecture 12 : Reaction diffusion mechanism
- Group presentation

# Central dogma of molecular biology



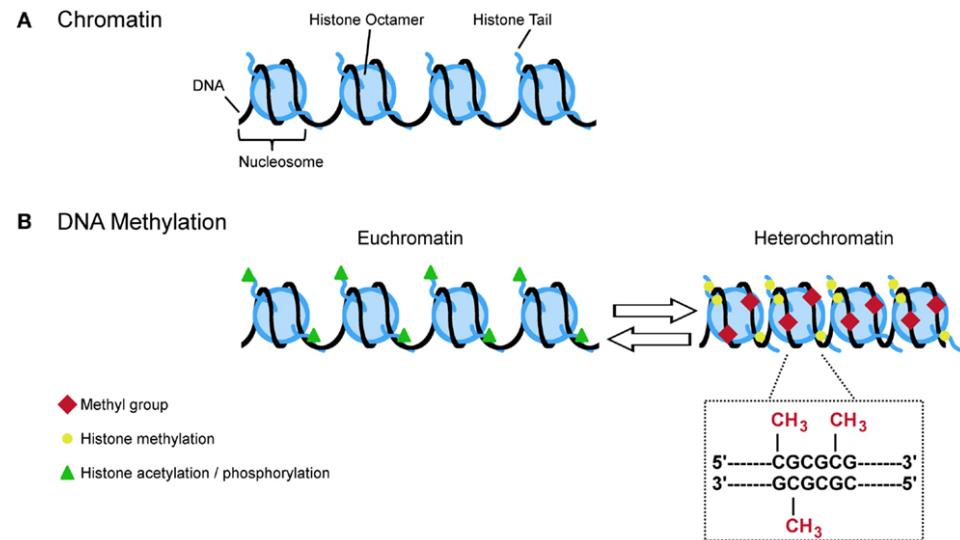
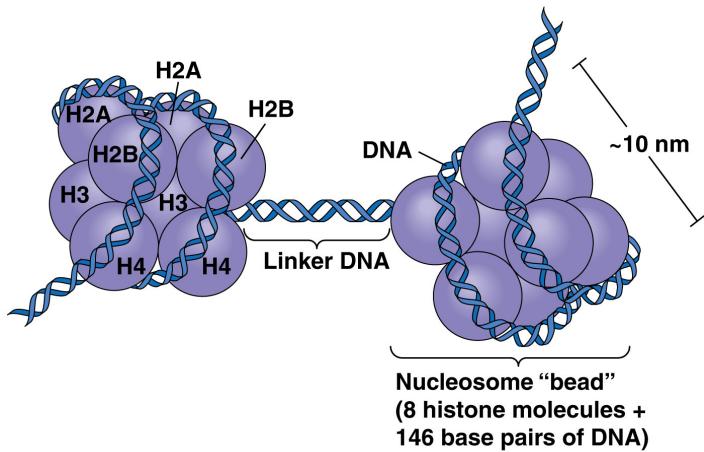
# Transfers of information not explicitly covered in the theory

- RNA editing & splicing



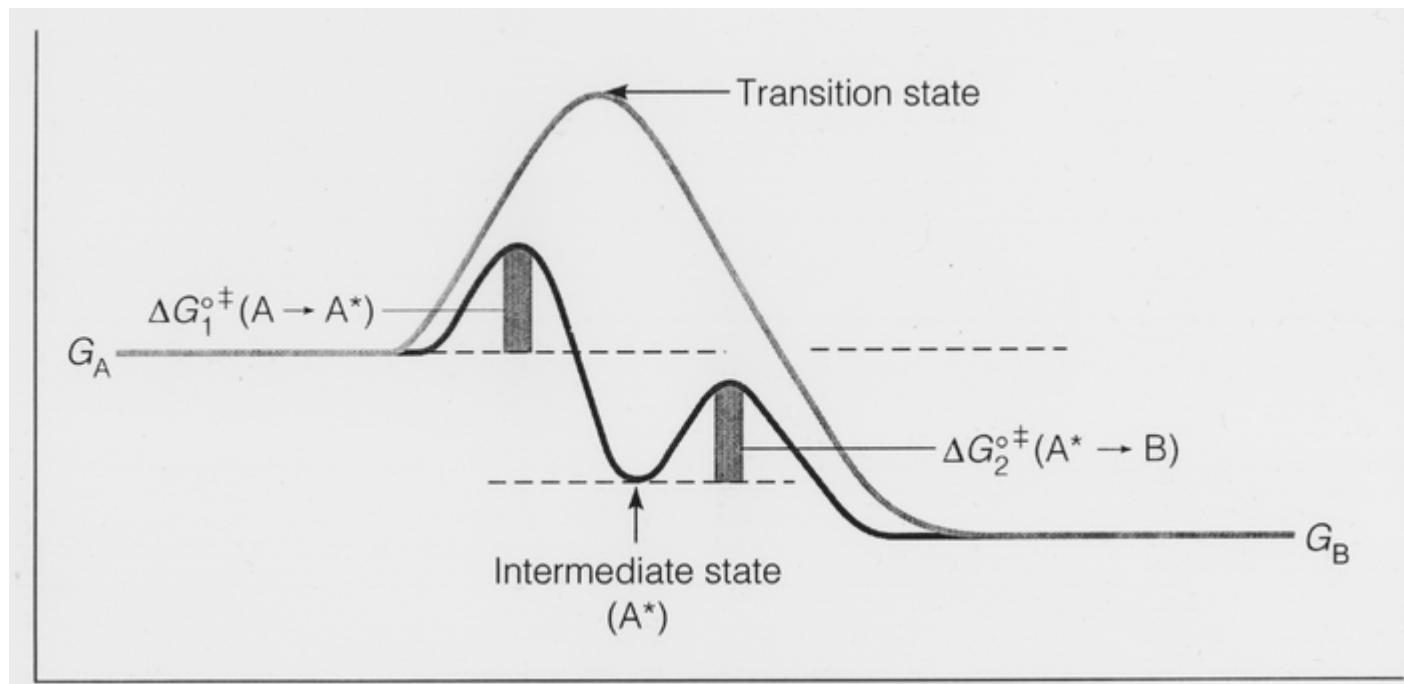
(from wiki)

- Histone modification;

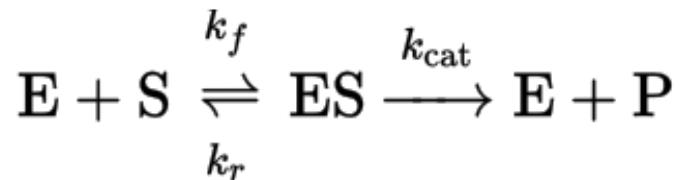


# Michaelis-Menten kinetics

- Biochemical reactions in living cells are often catalyzed by enzymes.
- These enzymes are proteins that bind and subsequently react specifically with other molecules defined as substrates.



# Michaelis-Menten kinetics

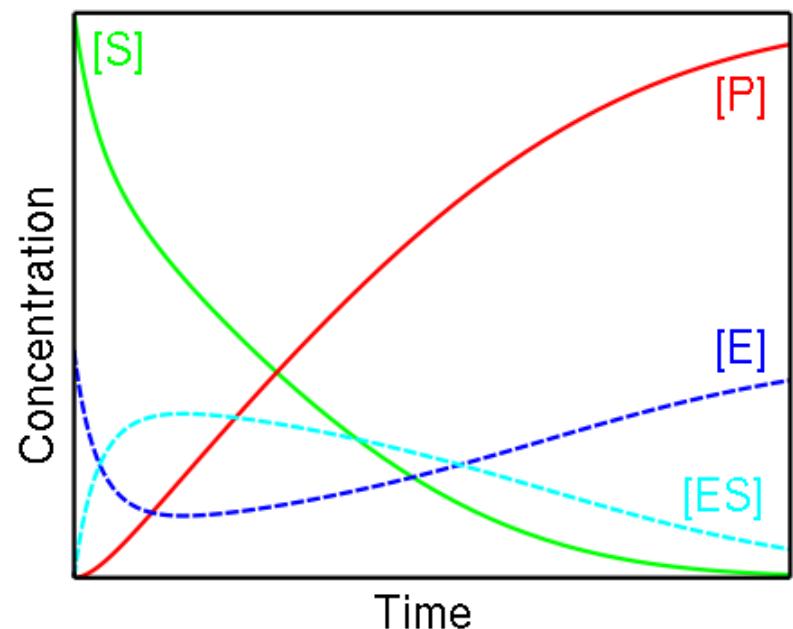


$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[ES]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + (k_{-1} + k_2)[ES]$$

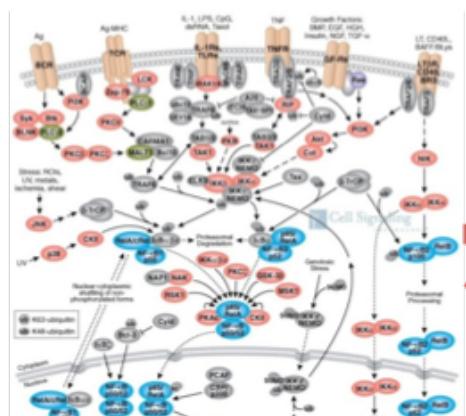
$$\frac{d[ES]}{dt} = k_1[E][S] - (k_{-1} + k_2)[ES]$$

$$\frac{d[P]}{dt} = k_2[ES] \equiv v$$



# Function of Biological network

- Network design principle

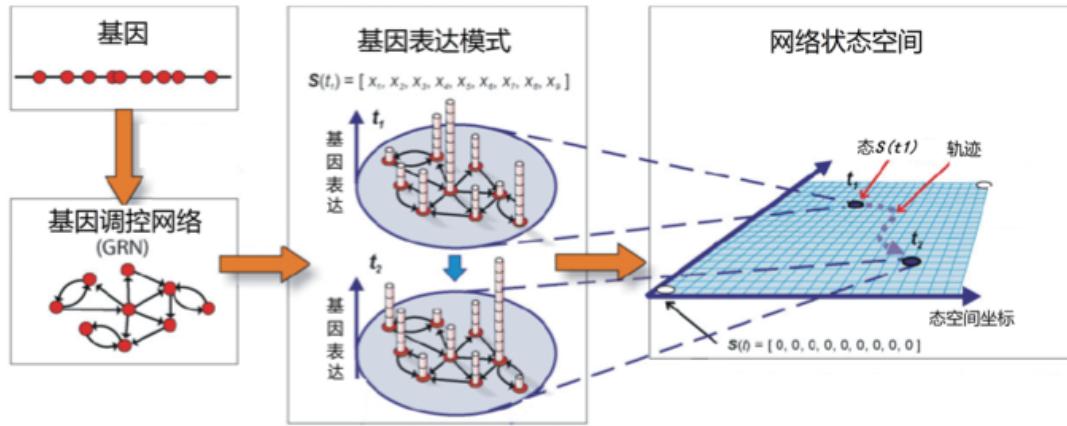


复杂网络  
粗粒化、模块化

模块组装  
多功能、复杂功能

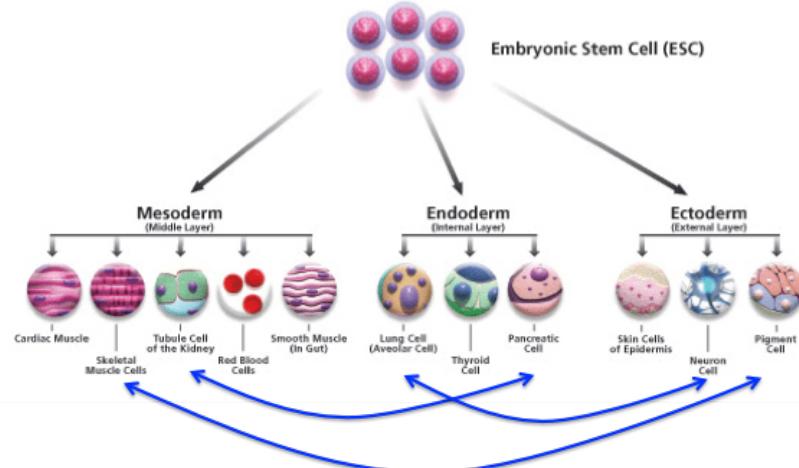


## ❖ 生物系统可以看作一个动力学系统



细胞状态=动力学系统相空间的一个点  
稳定细胞类型=相空间中的吸引子

## ❖ 细胞命运(类型)之间的转化

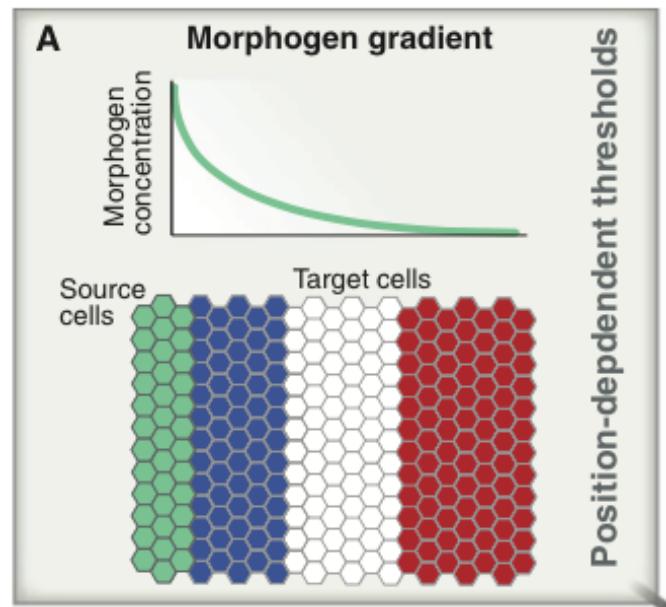


不同吸引子之间的转化

# Patterning with Signaling Gradients/Morphogens

- Morphogens are diffusible signaling molecules that can activate target genes in a concentration-dependent manner.
- Cells sense morphogen levels to determine their position within the tissue and differentiate accordingly.

◆ **Question:** How these gradients are formed, and whether they are sufficient to control differentiation in very precise domains, are open questions that have benefited from computational approaches.



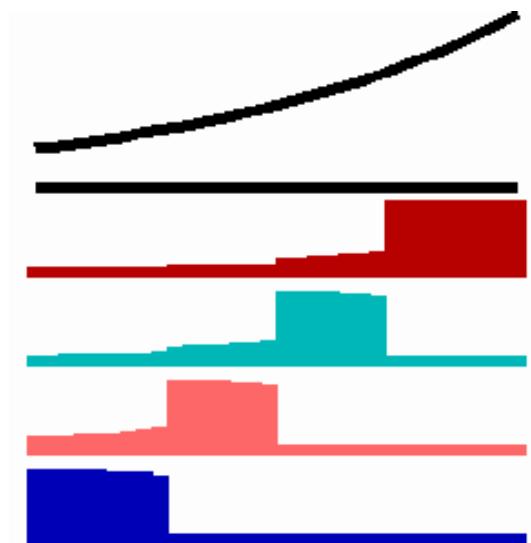
# Activation of genes by a morphogen gradient

## □ Unidirectional promotion:

activation of several genes by a single gradient

$$\frac{dg_i}{dt} = \frac{c_i g_i^2 + b_i g_{i-1} m}{\sum_{i=1}^n c_i g_i^2} - r_i g_i,$$

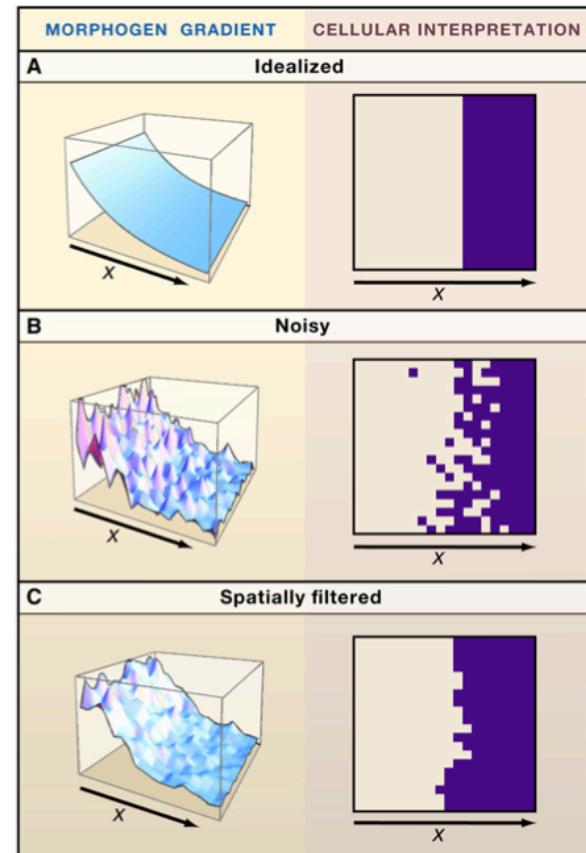
- Each gene  $g_i$  has an autocatalytic feedback on its own gene activation and an inhibitory action on the activation of alternative genes.
- The morphogen  $m$  has an additional activating influence on the genes.
- In this example it is assumed that the activation of the gene  $g_{i+1}$  requires the presence of the gene product of the gene  $g_i$ .



H Meinhardt, 1978

# Reducing Noise in Pattern Formation

- A major contribution of systems biology has been to increase awareness of the roles played by noise in biological systems.
- In boundary-organized pattern formation, the ability of cells to form organized patterns depends upon the accuracy with which they can measure their positions within a morphogen gradient.



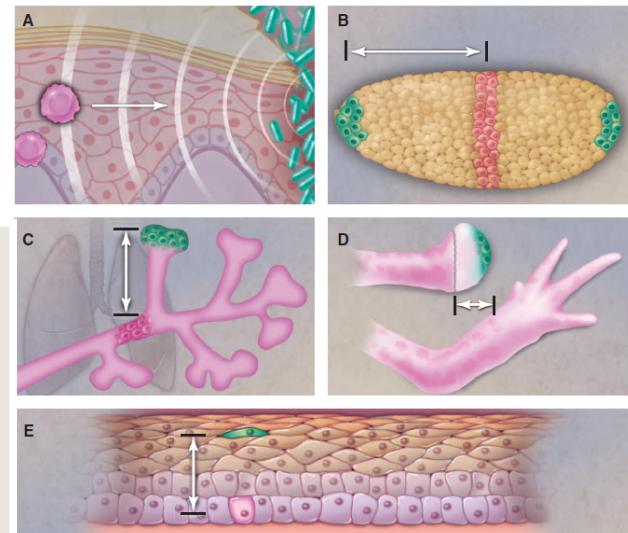
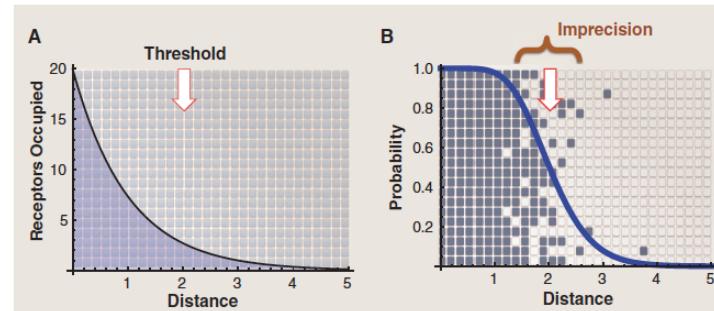
(Lander, Cell 2011)

# Noise in developmental patterning

SCIENCE VOL 339 22 FEBRUARY 2013

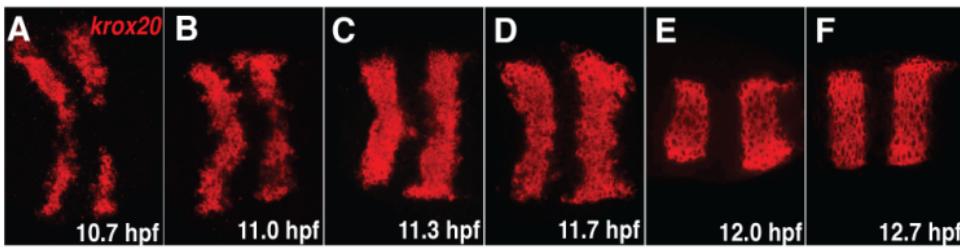
## How Cells Know Where They Are

Arthur D. Lander

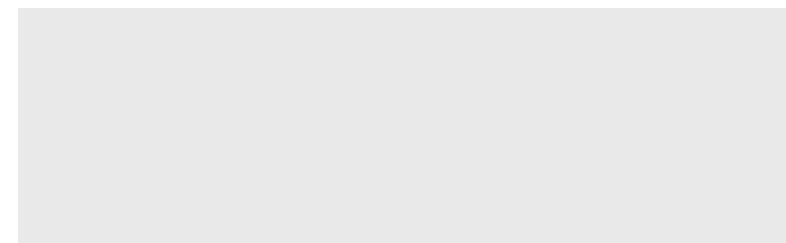


### ☐ Boundary sharpening in zebrafish hindbrain

Experiment



Model simulation

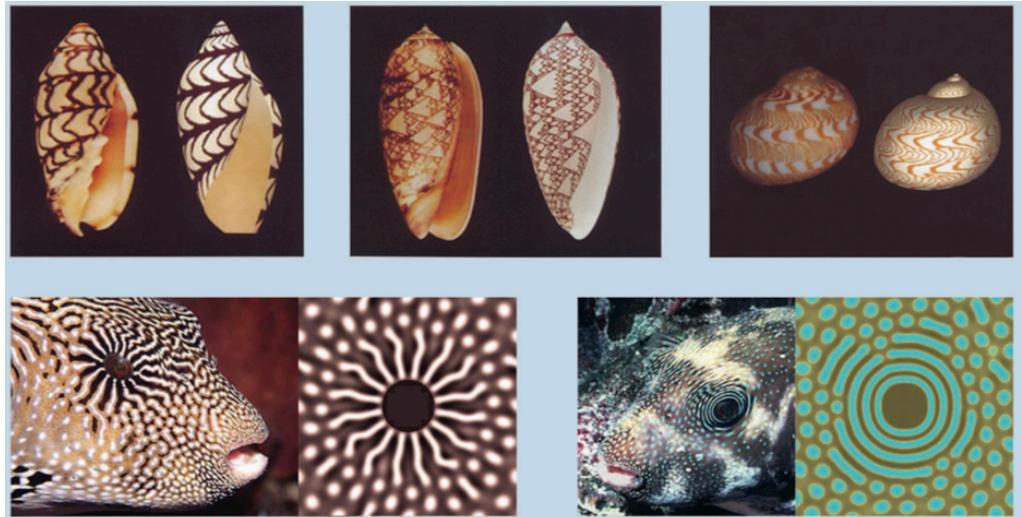
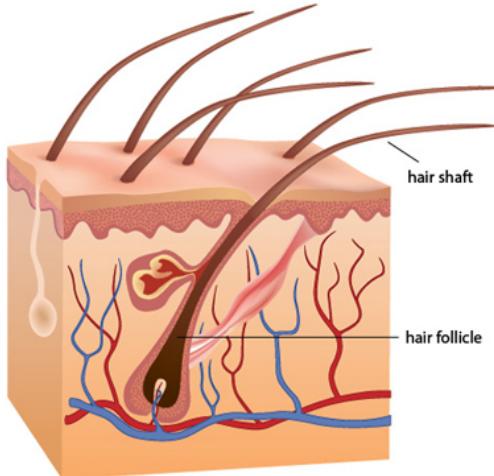


### ☐ We found that Intracellular noise induces gene switching to lead the boundary sharp.

Zhang et al, Molecular Systems Biology, 2012

# Turing pattern

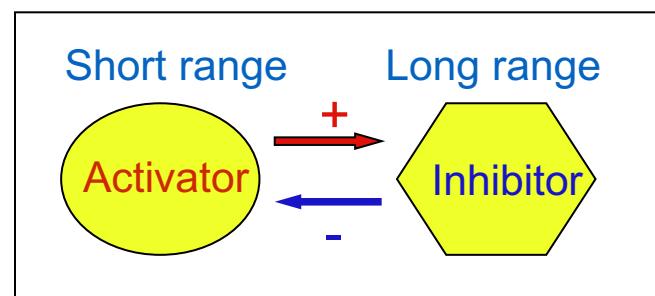
- Turing pattern has been widely found in biological systems.  
(Hair follicle: *Sick et al, Science 2006*; Skin pattern: *Kondo, Nature 1995*)



(H. Meinhardt [sea shell pattern] and A. R. Sanderson [fish pattern])

- The system is of the form

$$\begin{cases} u_t = \Delta u + \gamma f(u, v), \\ v_t = D\Delta v + \gamma g(u, v), \end{cases}$$



# Diffusion-driven instability

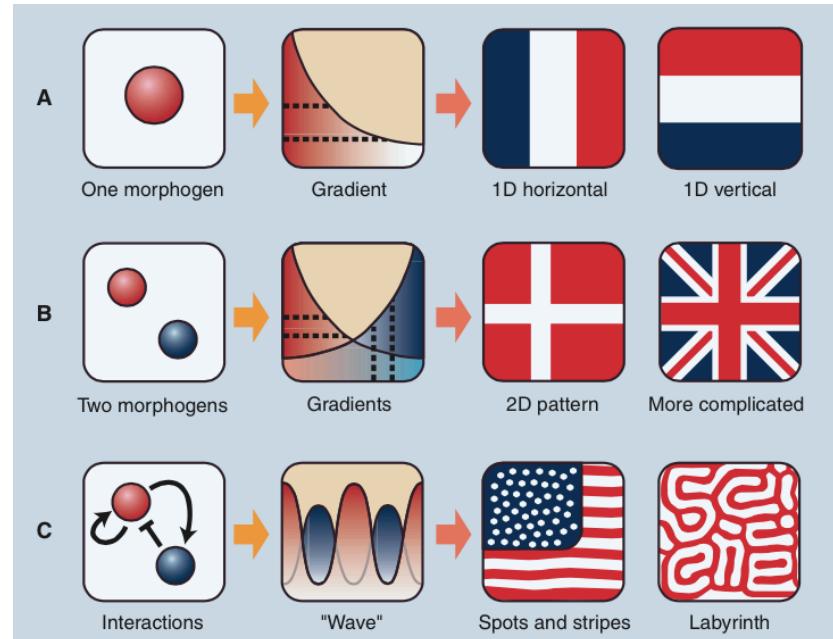
- We consider the system is of the form

$$\begin{cases} \frac{\partial u}{\partial t} = D_u \Delta u + F(u, v), \\ \frac{\partial v}{\partial t} = D_v \Delta v + G(u, v), \end{cases}$$

- Turing's (1952) idea is a simple but profound one: if in the absence of diffusion (effectively  $D_u = D_v = 0$ ),  $u$  and  $v$  tend to a linearly stable uniform steady state then, under certain conditions, which we shall derive, spatially inhomogeneous patterns can evolve by *diffusion driven instability* if  $D_u$  is not equal to  $D_v$ .
- Diffusion is usually considered a *stabilising* process which is why this was such a novel concept.
- Then we describe the process in terms of reacting and diffusing morphogens and derive the necessary conditions on the reaction kinetics and diffusion coefficients.

# Questions and Properties

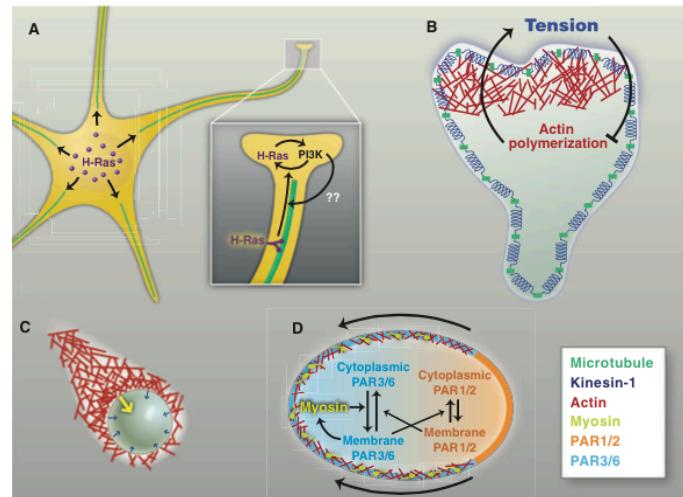
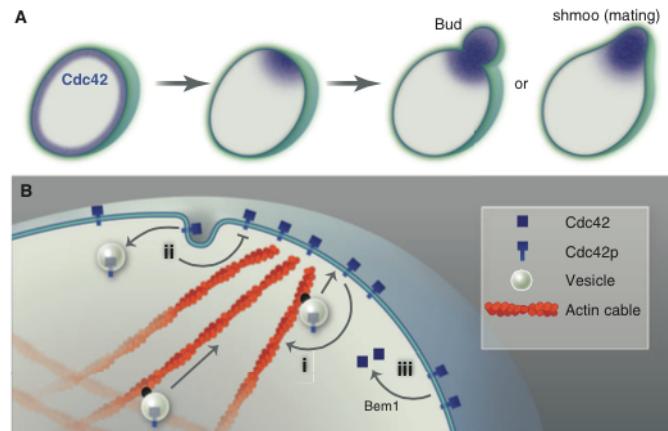
- Turing structures exist in Chemistry
- Morphogen exists
- Basic requirement:  
short-range positive feedback with  
a long-range negative feedback.
- Do Turing structures exist in Biology?
- Is there Self-Organisation?
- Properties/Predictions
  - Minimum domain size for pattern
  - Pattern complexity increases with domain size
  - Effects of geometry – spots and stripes
  - Developmental constraints



Kondo-Miura, Science 2010

# Single cell level - Cell Polarity

- Cell polarity can be defined as a state which has an asymmetric distribution of specific molecules and organelles along a geometric axis ('front to back') in morphology.
- Polarity in various cell types
  - Budding yeast
  - Fish keratocyte
  - Neuron
  - *C. elegans*
  - More...
- It is essential for various kinds of cell functions including migration, asymmetric division, etc.



Mogilner-Allard-Wollman, Science (336) 2012

# Existing mathematical models based on chemical-reactions mechanism

- “Turing-Type” pattern formation

Gierer-Meinhardt 1972, 1974; Subramanian-Narang 2004; Narang 2006; Otsuji 2007; Ferrell 2002; Maly et al 2004; Lo-Park-Chou, 2014

- Gradient-sensing models

Levchenko-Iglesias 2002; Ma et al 2004; Krishman-Iglesias 2007; Levine-Kessler-Rappel 2006; Chou-Nie-Yi 2007, 2008, 2011

- Excitable Network and Wave-Based Models

Maree et al 2006; Jilkine-Maree-Edelstein-Keshet 2007; Mori-Jilkine-Edelstein-Keshet 2008; Hecht-Kessler-Levine 2010; Xiong et al 2010

- Stochastic models

Altschuler et al. 2008; Gamba 2005, 2007; Van Haastert 2010; Chau et al. 2012

- Detailed Biochemistry-Based Models

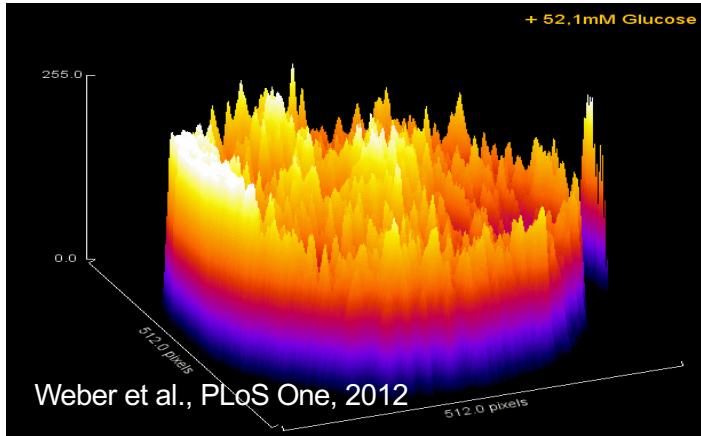
Goryachev-Pokhilko 2008; Causin et al. 2009; Marée et al. 2006; Dawes-Edelstein-Keshet 2007; Onsum-Rao 2007

# Network design principle for dual function of adaptation and noise attenuation

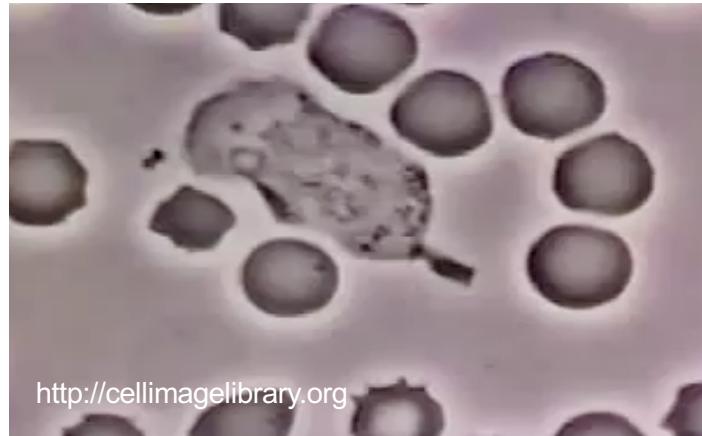
Lingxia Qiao, Wei Zhao, Chao Tang, Qing Nie, Lei Zhang,  
*Cell Systems* 2019.

# Network topology, dynamics, function

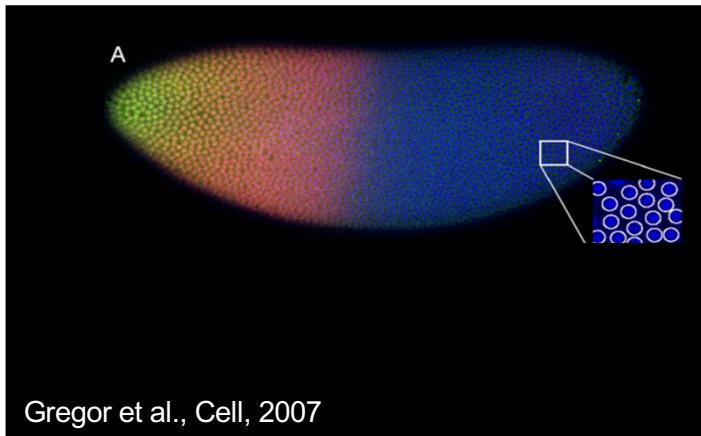
## Oscillation in yeast glycolysis



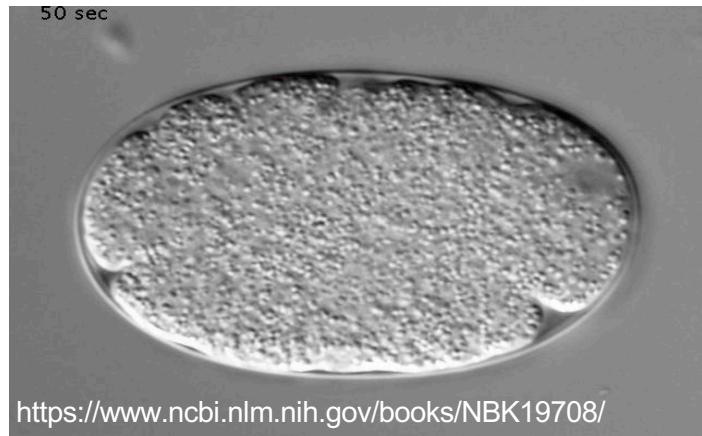
## Chemotaxis of neutrophil



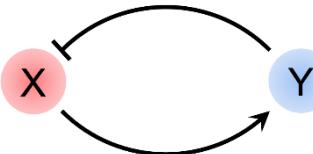
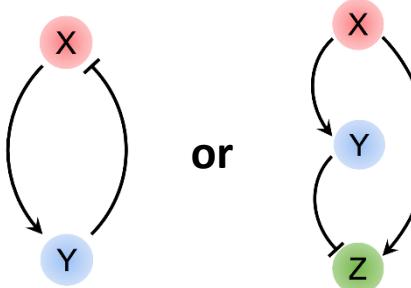
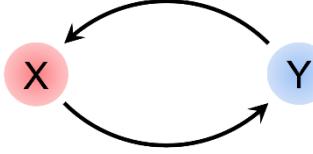
## Noise attenuation in gene expression boundary



## Cell polarization in fertilized egg



# Cellular circuits show general network design principles

| Complex cellular circuits  | Network design principle   | Biological function   |
|--|--|---|
| NF-κB signaling pathway;<br>circadian rhythm pathway;<br>calcium signaling pathway |    | Oscillation<br>    |
| Chemotaxis signaling pathway in bacteria and amoebae                               |    | Adaptation<br>     |
| Yeast budding pathway;<br>neutrophil chemotaxis pathway                            |  | Polarization<br> |

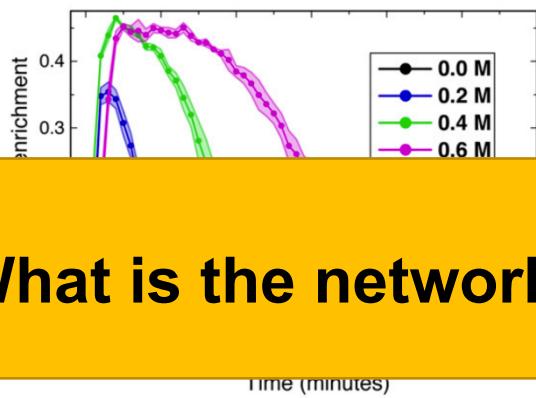
# **Why important to study the network design principle?**

- **Understand how cell works**
- **Predict cell behaviors**
- **Be utilized for biological engineering**
- **Provide guidance for drug intervention**

# Cell can execute multi-functions simultaneously

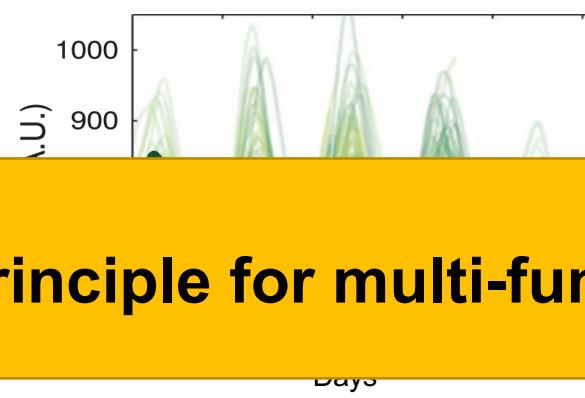
## Adaptation & Noise attenuation: osmoregulation in yeast

Muzey et al., Cell, 2009



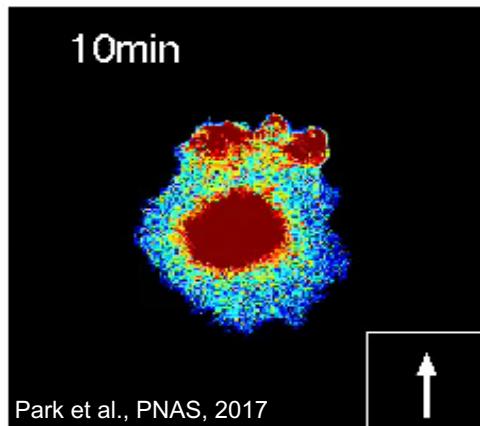
## Oscillation & Noise attenuation: circadian clock in *S. elongatus*

Shu-Wen Teng et al., Science, 2013



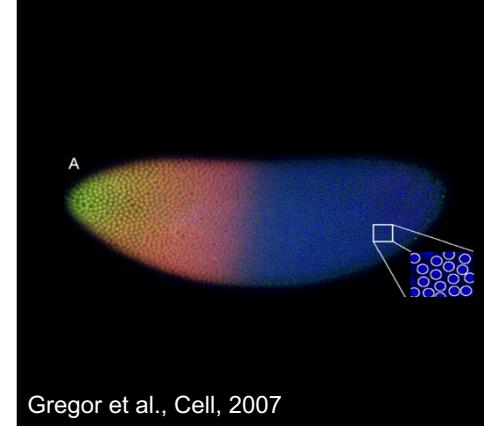
What is the network design principle for multi-functions ?

## Polarization & Oscillation: polarity pattern in melanoma cell



Park et al., PNAS, 2017

## Polarization & noise attenuation: sharp boundary in drosophila embryo

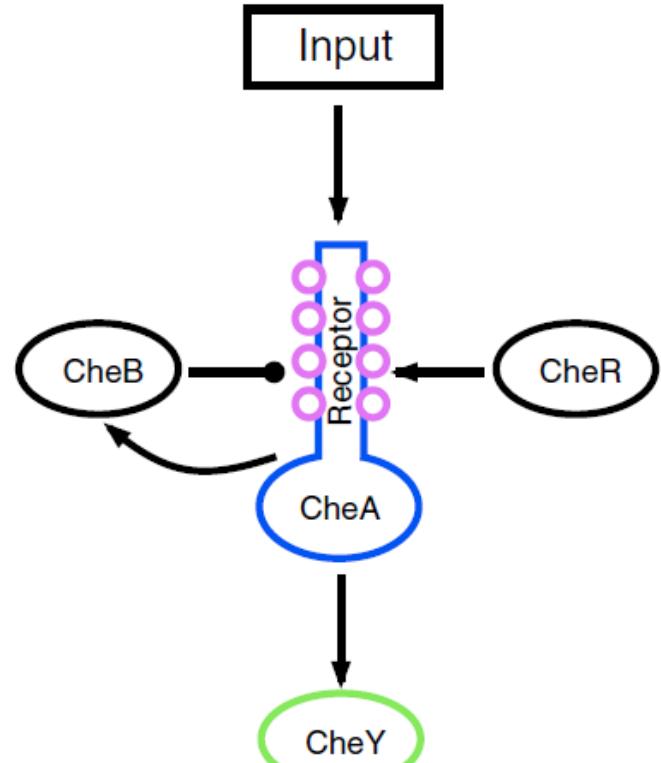
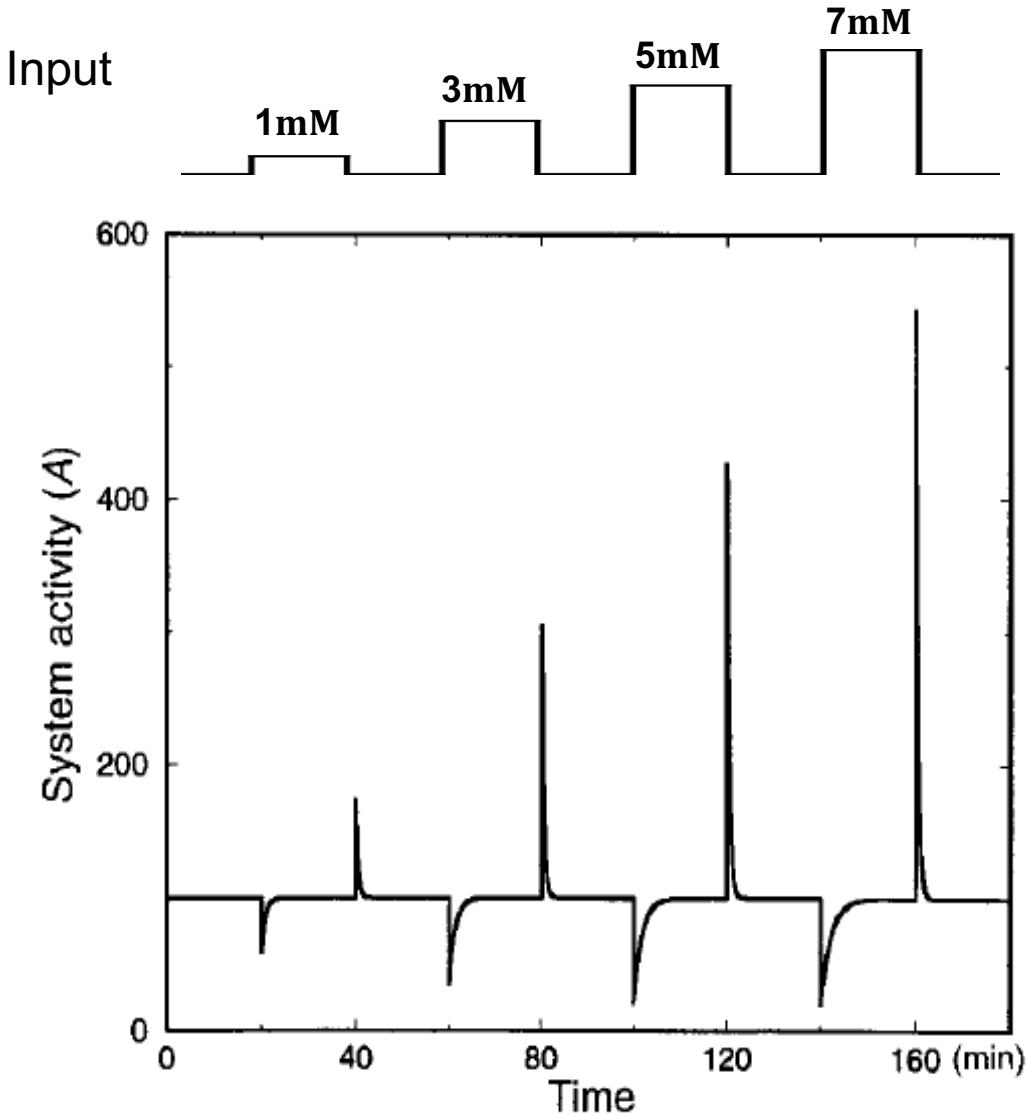


Gregor et al., Cell, 2007

# Adaptation

- 1. Adaptation widely exists in biological systems:**
  - bacterial chemotaxis (N. Barkai and S. Leibler, Nature, 1997)
  - olfactory sensory neurons in Drosophila ( L.H. Cao et al., PNAS, 2016)
- 2. Adaptive system can**
  - Sense a wide range of change
  - Terminate signal response after an appropriate time
  - Resist the changed environment to maintain their stability.

# Adaptation in bacterial chemotaxis

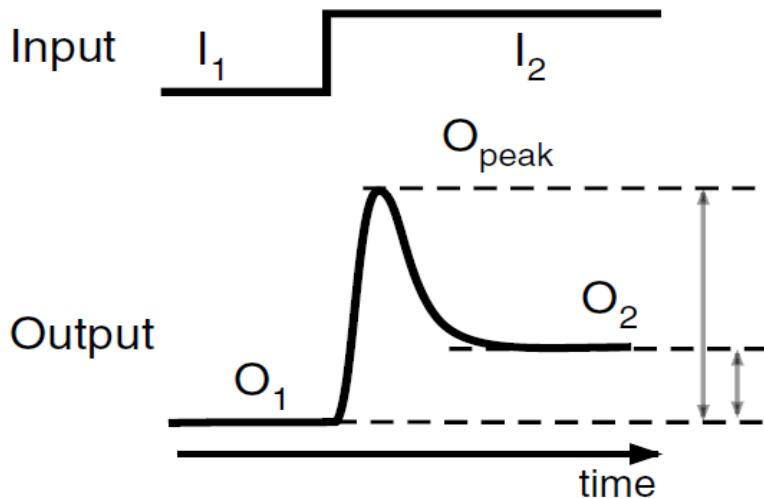


N. Barkai & S. Leibler, Nature, 1997

Ma et al., Cell, 2009

# Quantify adaptation

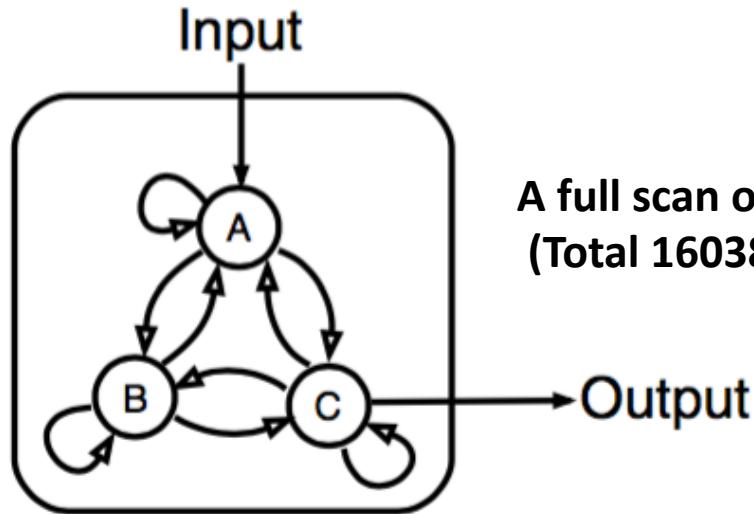
- be sensitive to input change — **Sensitivity**
- maintain output unchanged — **Precision**



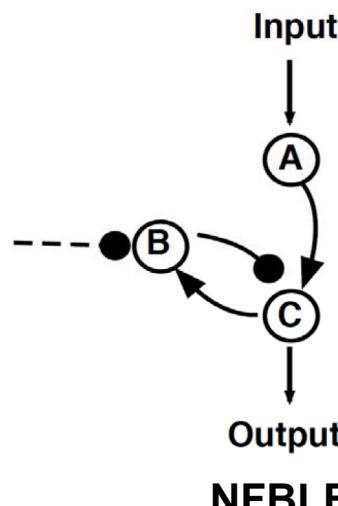
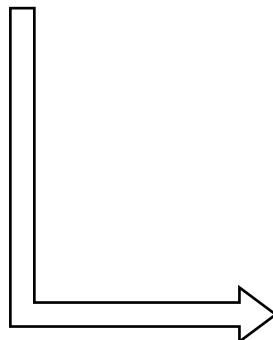
$$\text{Sensitivity} = \left| \frac{(O_{peak} - O_1)/O_1}{(I_2 - I_1)/I_1} \right|$$

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

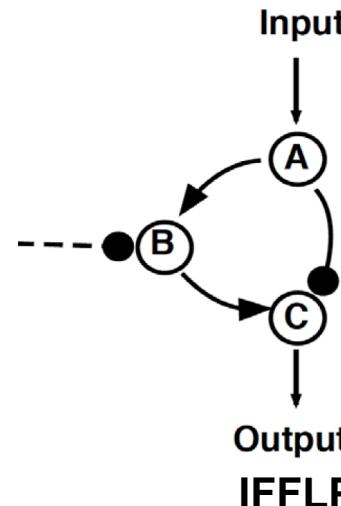
# Design principle of adaptation



A full scan of 3-node network space  
(Total 16038 networks)



NFBLB  
(Negative feedback loop  
with a buffering node)

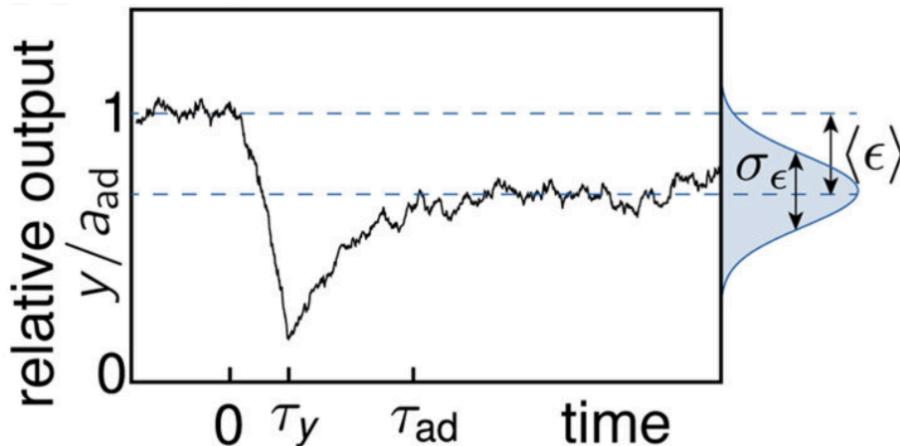


IFFLP  
(Incoherent feedforward loop  
with a proportioner node)

**Two core motifs to achieve adaptation**

# Noise affects the accuracy of adaptation

- Extrinsic noise
  - Fluctuations in environment,  
e.g., ligand concentration, kinetic parameters
- Intrinsic noise
  - Stochasticity of chemical reactions

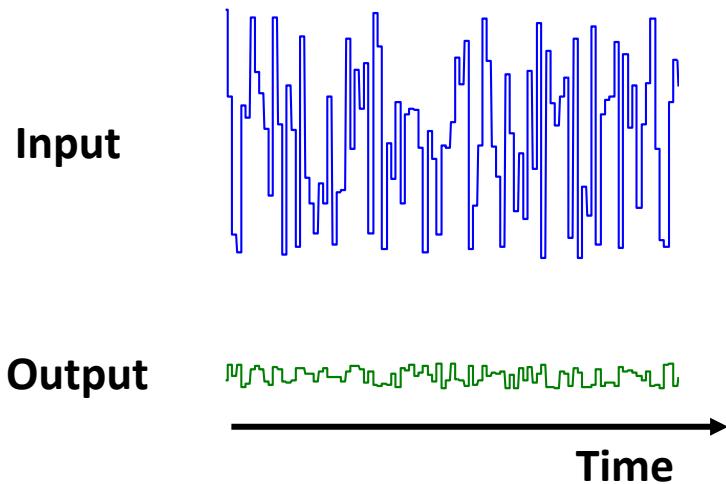


# Quantify noise buffering capability

- Small fluctuation of output

Noise amplification rate (NAR)

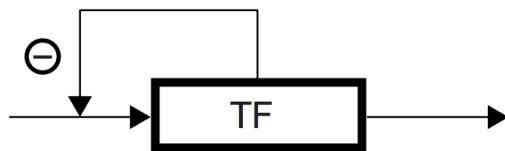
$$NAR = \frac{\text{std}(O)/\langle O \rangle}{\text{std}(I)/\langle I \rangle}$$



# Design principle of noise attenuation

- Negative feedback loop (NF)

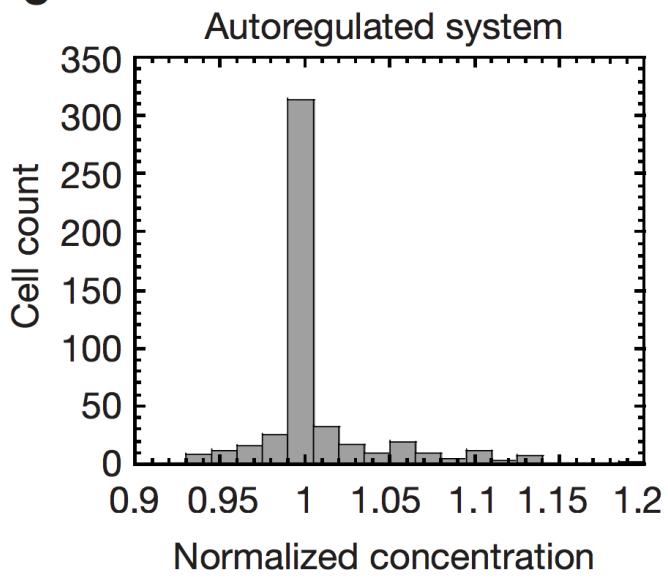
c



d

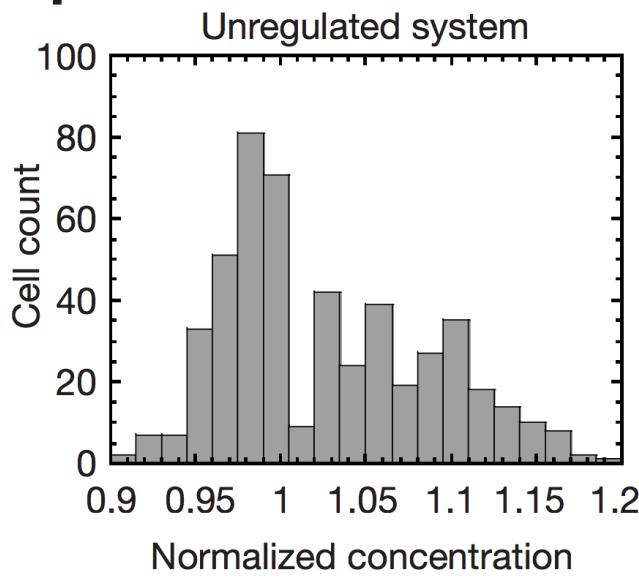


e



**Buffering noise**

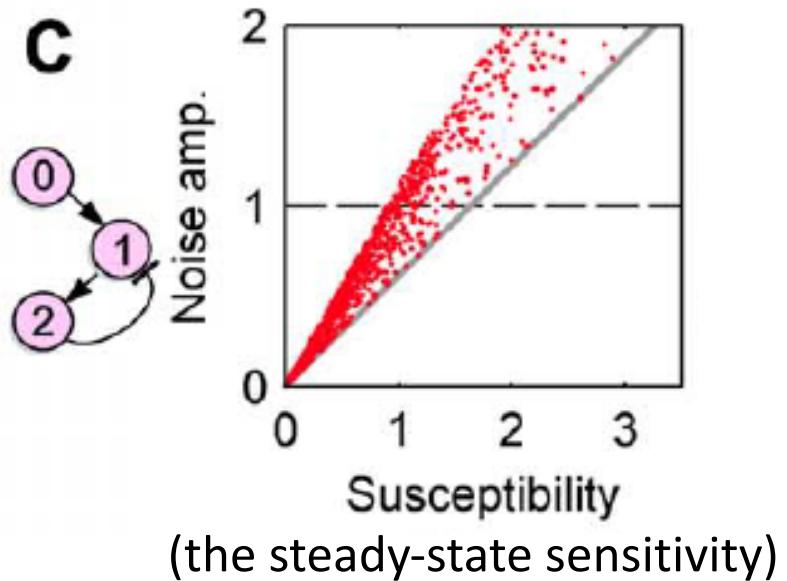
f



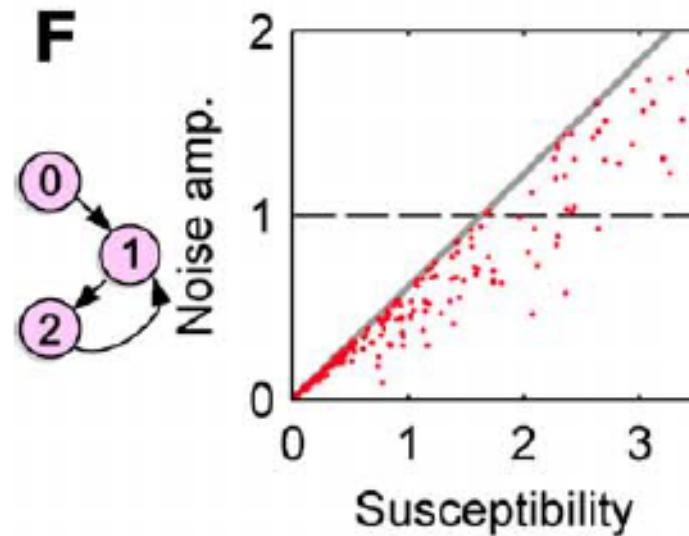
**Not buffering noise**

# Design principle of noise attenuation (cont.)

- Positive feedback loop (PF)



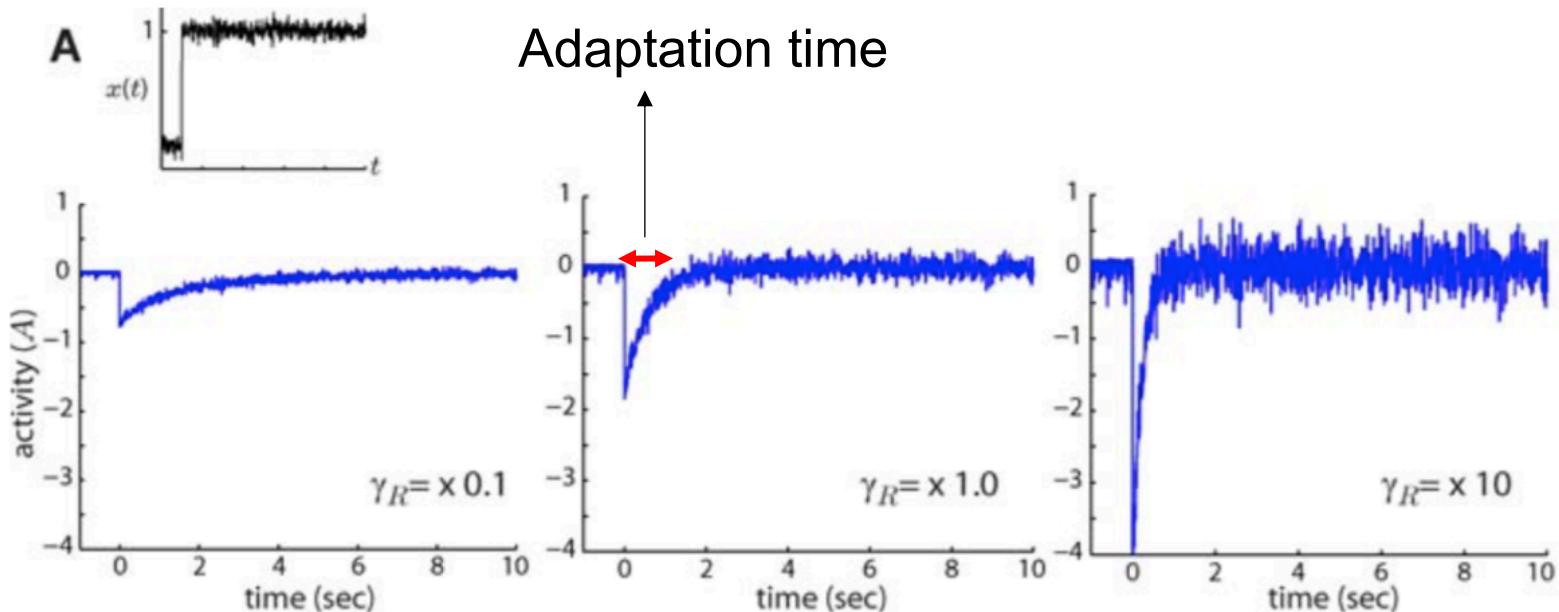
**Buffering noise but  
sacrificing sensitivity**



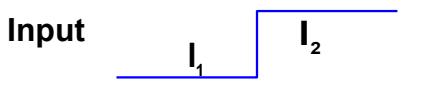
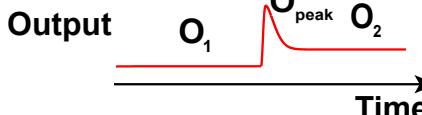
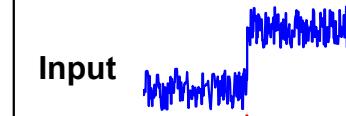
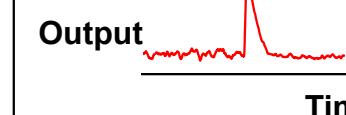
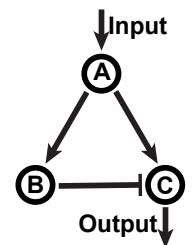
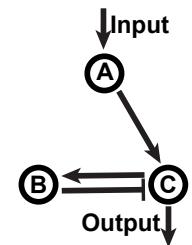
**Buffering noise while  
maintaining sensitivity**

# Noise attenuation & timescale

**Longer adaptation time can achieve lower noise in E. coli signaling pathway**

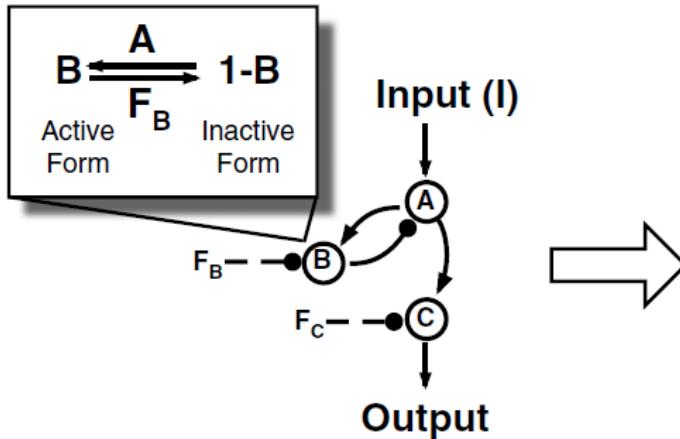


# How to achieve both adaptation and Noise attenuation

| Function | Adaptation   | Noise attenuation  | Adaptation & Noise attenuation   |
|----------|--|--|--|
| Dynamics | <p>Input </p> <p>Output </p>           | <p>Input </p> <p>Output </p> | <p>Input </p> <p>Output </p> |
| Index    | <p>Sensitivity = <math>\left  \frac{(O_{\text{peak}} - O_1) / O_1}{(I_2 - I_1) / I_1} \right </math></p> <p>Precision = <math>\left  \frac{(O_2 - O_1) / O_1}{(I_2 - I_1) / I_1} \right ^{-1}</math></p> | <p>NAR = <math>\frac{\text{std}(O)/\langle O \rangle}{\text{std}(I)/\langle I \rangle}</math></p>  | <p>NAR<br/>↓</p> <p>&amp; Sensitivity<br/>↑</p> <p>&amp; Precision<br/>↑</p>   |
| Motif    |  <p>IFFLP<br/>(Incoherent feedforward loop with a proportioner node)</p>   |  <p>NFBLB<br/>(Negative feedback loop with a buffering node)</p>   | <p>B ↔ A<br/>PF<br/>(Positive Feedback)</p> <p>B → A<br/>NF<br/>(Negative Feedback)</p> <p>?</p>   |

# Searching strategy — begin with three-node networks

- Equations of three-node enzyme network:



$$\frac{dA}{dt} = k_{IA} I \frac{(1 - A)}{(1 - A) + K_{IA}} - k'_{BA} B \frac{A}{A + K'_{BA}}$$
$$\frac{dB}{dt} = k_{AB} A \frac{(1 - B)}{(1 - B) + K_{AB}} - k'_{F_BB} F_B \frac{B}{B + K'_{F_BB}}$$
$$\frac{dC}{dt} = k_{AC} A \frac{(1 - C)}{(1 - C) + K_{AC}} - k'_{F_C C} F_C \frac{C}{C + K'_{F_C C}}$$

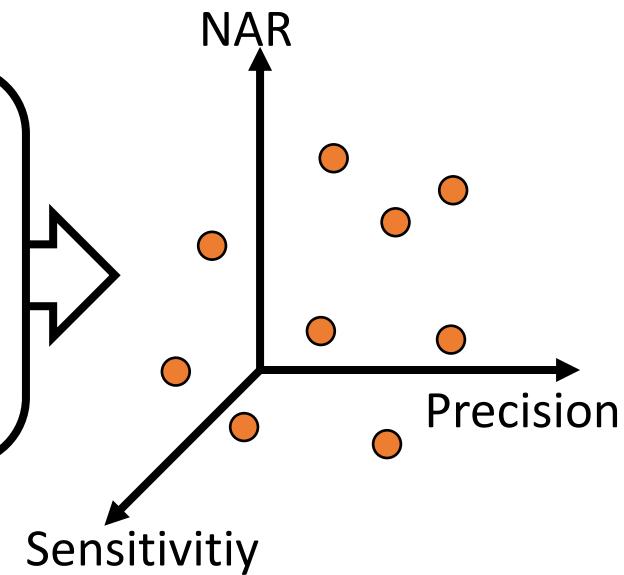
10,000 random parameter sets per network  
**(16,038 networks in total)**

ODE simulation

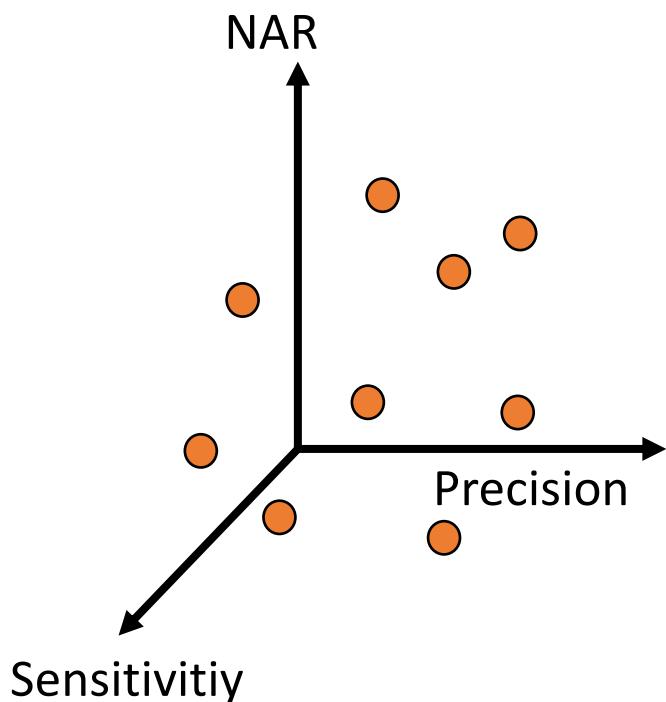
Input ( $I$ ):  $I_1$

Linear Noise Approximation

Input ( $I$ ): (or  $I_2$ )  
plus fluctuations with mean 0 and autocorrelation time  $\tau_0$



# Q value: measuring the robustness of networks



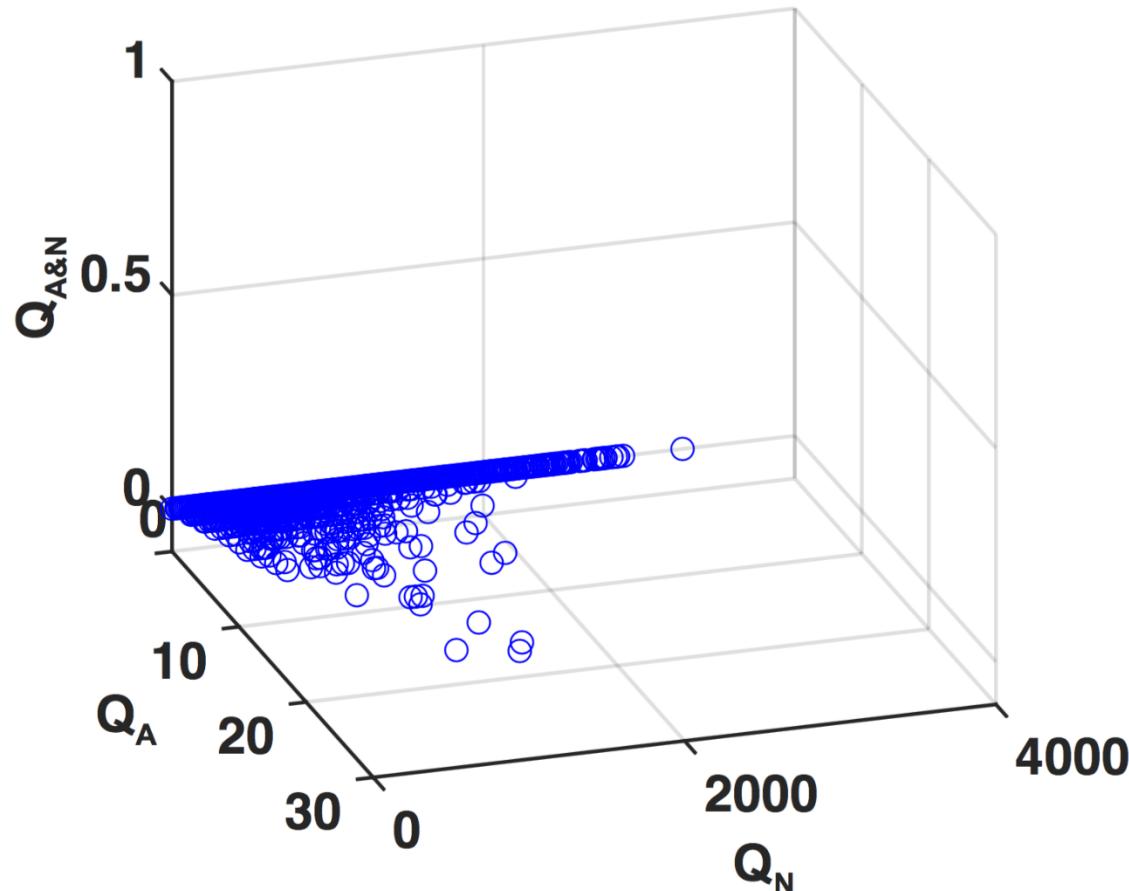
$Q_A$  : number of parameter sets capable of adaptation (Sensitivity>1 & Precision>10)

$Q_N$  : number of parameter sets capable of noise attenuation (NAR<0.2)

$Q_{A\&N}$  : number of parameter sets capable of dual function (Sensitivity>1, Precision>10 & NAR<0.2)

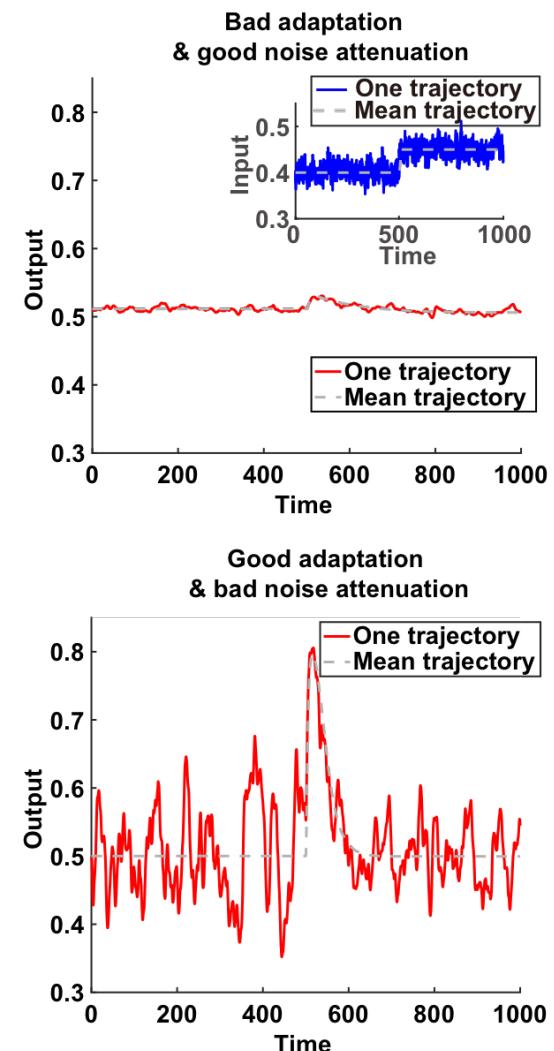
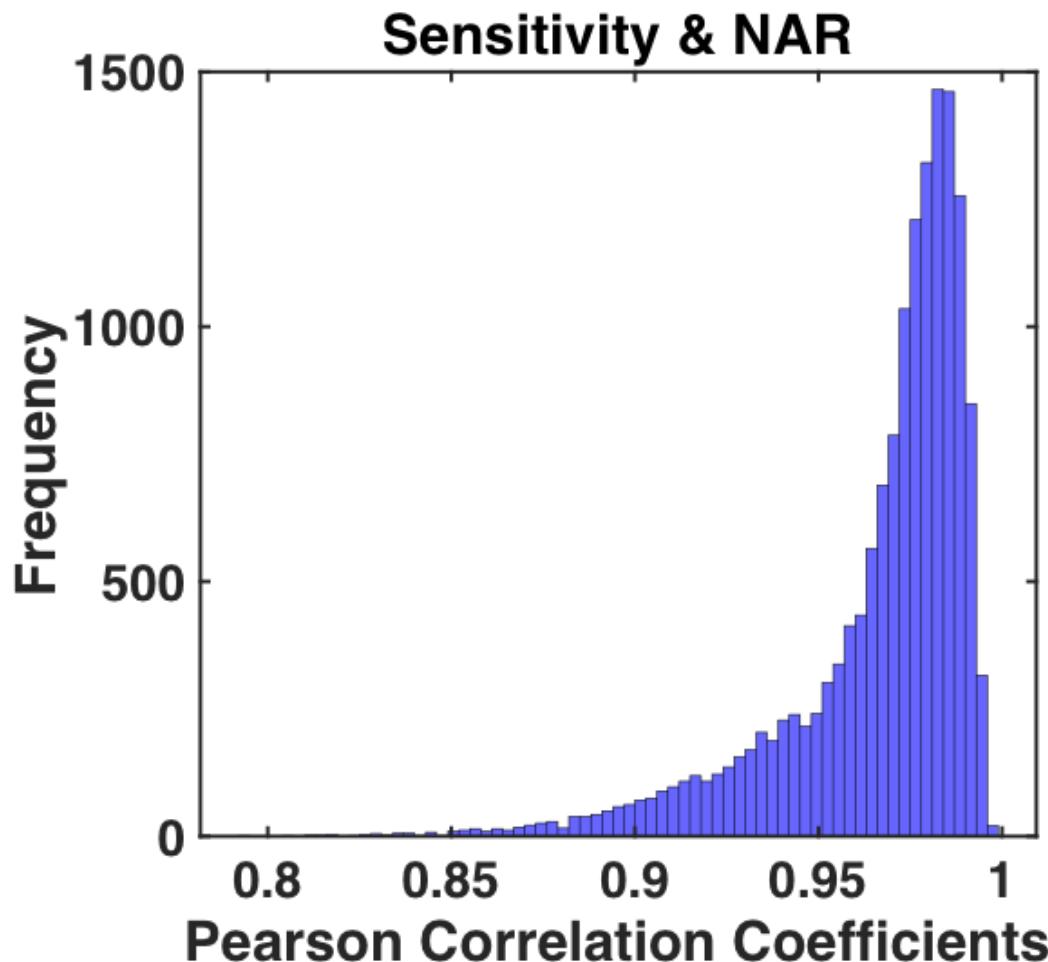
# Result I

- Fail to achieve the dual functions in all 16038 possible three-node networks.
  - Each point is a 10,000 times simulation of different kinetic parameters for each network.

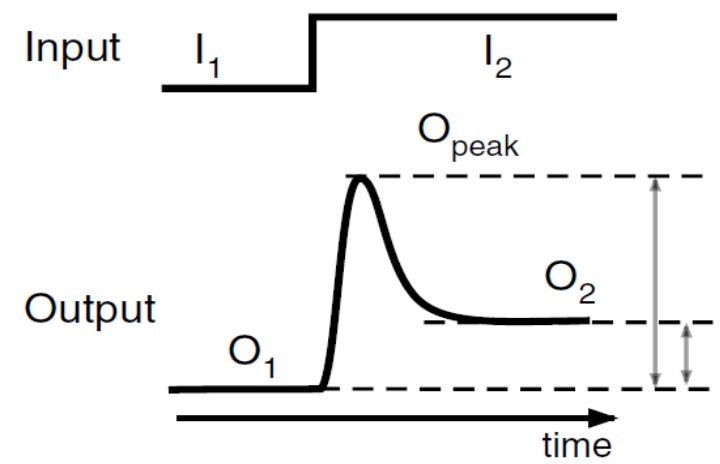
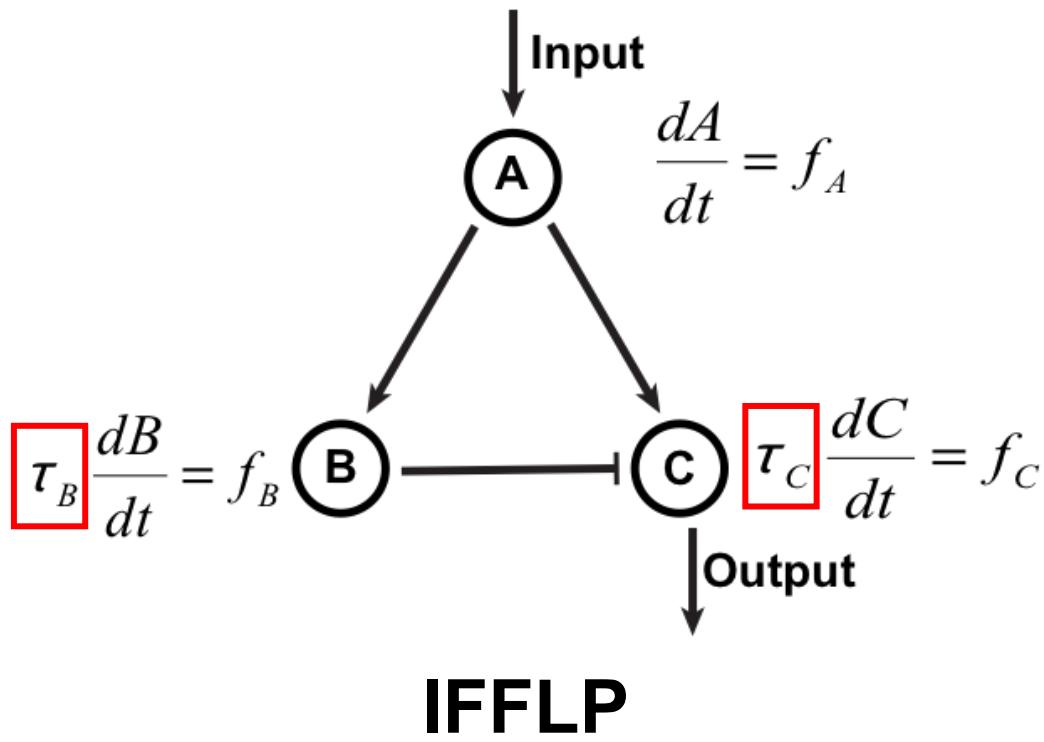


**There exists an intrinsic trade-off between adaptation and noise attenuation:**

— Positive correlation between NAR and sensitivity



# Tune timescale of the network nodes to achieve dual function



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

# Analysis of timescale

Take IFFLP as an example:

## i. Approximation of sensitivity

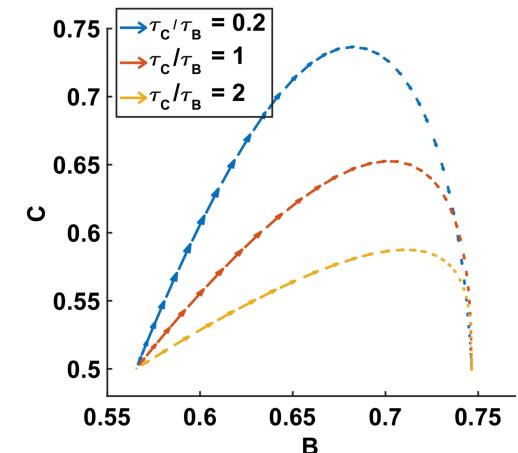
We approximate sensitivity by linearizing the system around steady state ( $\langle A \rangle, \langle B \rangle, \langle C \rangle$ ) :

$$\begin{bmatrix} \frac{d\Delta B}{dt} \\ \frac{d\Delta C}{dt} \end{bmatrix} = \begin{bmatrix} -k_2 & 0 \\ \frac{k_5 \langle C \rangle}{\tau_C \langle B \rangle} & -k_6 \end{bmatrix} \begin{bmatrix} \Delta B \\ \Delta C \end{bmatrix} + \Delta A \begin{bmatrix} \frac{k_1 \langle B \rangle}{\tau_B \langle A \rangle} \\ \frac{k_4 \langle C \rangle}{\tau_C \langle A \rangle} \end{bmatrix}$$

where  $\langle A \rangle, \langle B \rangle, \langle C \rangle$  denote the steady states of  $A, B, C$ .  $k_1 = \frac{\langle A \rangle}{\langle B \rangle} \frac{\partial f_B}{\partial A}$ ,  $k_2 = -\frac{\partial f_B}{\partial B}$ ,  $k_4 = \frac{\langle A \rangle}{\langle C \rangle} \frac{\partial f_C}{\partial A}$ ,  $k_5 = -\frac{\langle B \rangle}{\langle C \rangle} \frac{\partial f_C}{\partial B}$ ,  $k_6 = -\frac{\partial f_C}{\partial C}$ . The condition of perfect adaptation is assumed, that is,  $k_1 k_5 - k_2 k_4 = 0$ . By solving above equations, we get the expression of  $\Delta C(t)$ . Let  $\Delta C'(t) = 0$ , and we obtain the sensitivity:

$$\text{Sensitivity} = \frac{k_4}{k_6} \left( \frac{k_2 \tau_C}{k_6 \tau_B} \right)^{\frac{k_2 \tau_C}{k_6 \tau_B}}.$$

Sensitivity is determined by  $\frac{\tau_C}{\tau_B}$  and smaller  $\frac{\tau_C}{\tau_B}$  causes larger sensitivity.



## ii. Approximation of NAR

We use linear noise approximation (LNA) to derive NAR. We assume the fluctuation of  $A$  is an Ornstein-Uhlenbeck process with time scale  $\tau_0 = 1/\omega$  and variance  $\eta_0^2$ . Then we can calculate

$$M = (M_{ij}) = \begin{pmatrix} -\omega & 0 & 0 \\ k_1/\tau_B & -k_2/\tau_B & 0 \\ k_4/\tau_C & -k_5/\tau_C & -k_6/\tau_C \end{pmatrix}$$

and

$$D = \begin{pmatrix} 2\eta_0^2\omega & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

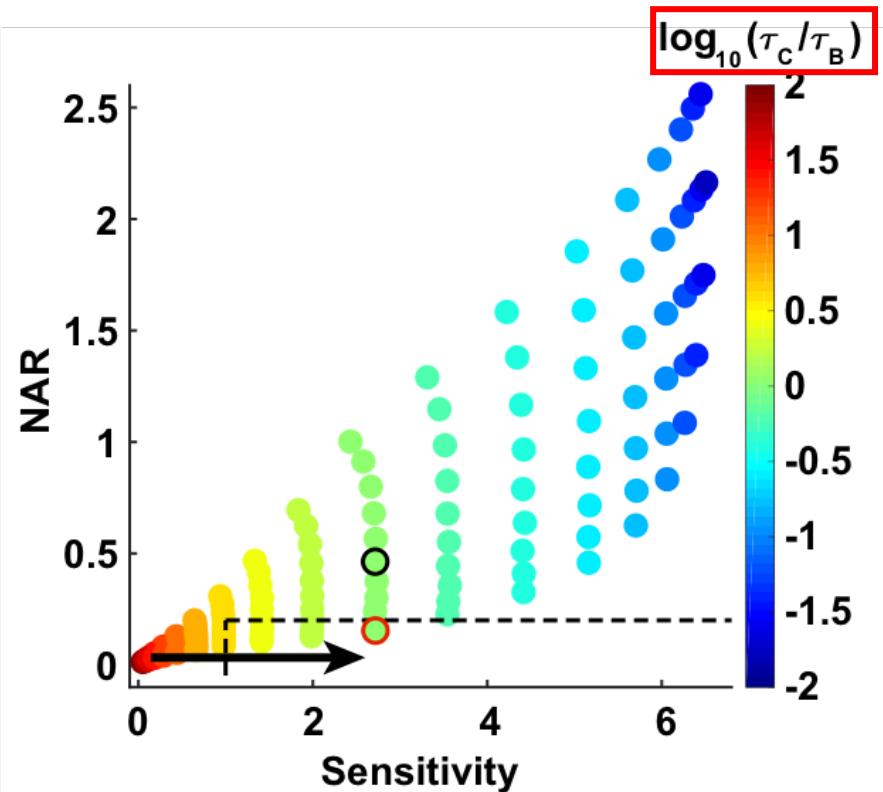
By solving  $M\eta + \eta M^T + D = 0$ , we get the expression of NAR :

$$NAR = \sqrt{\frac{(k_1 k_5 - k_2 k_4)^2 \left( k_2 \left( \frac{\tau_B}{\tau_C} \right) \frac{1}{\tau_B} + k_6 \left( \frac{\tau_B}{\tau_C} \right)^2 \frac{1}{\tau_B} + \left( \frac{\tau_B}{\tau_C} \right) \omega \right) + k_2 k_6 k_4^2 \left( \frac{\tau_B}{\tau_C} \right)^2 \omega}{k_2 k_6 \left( k_2 + k_6 \left( \frac{\tau_B}{\tau_C} \right) \right) \left( \frac{k_2}{\tau_B} + \omega \right) \left( k_6 \left( \frac{\tau_B}{\tau_C} \right) + \omega \tau_B \right)}}.$$

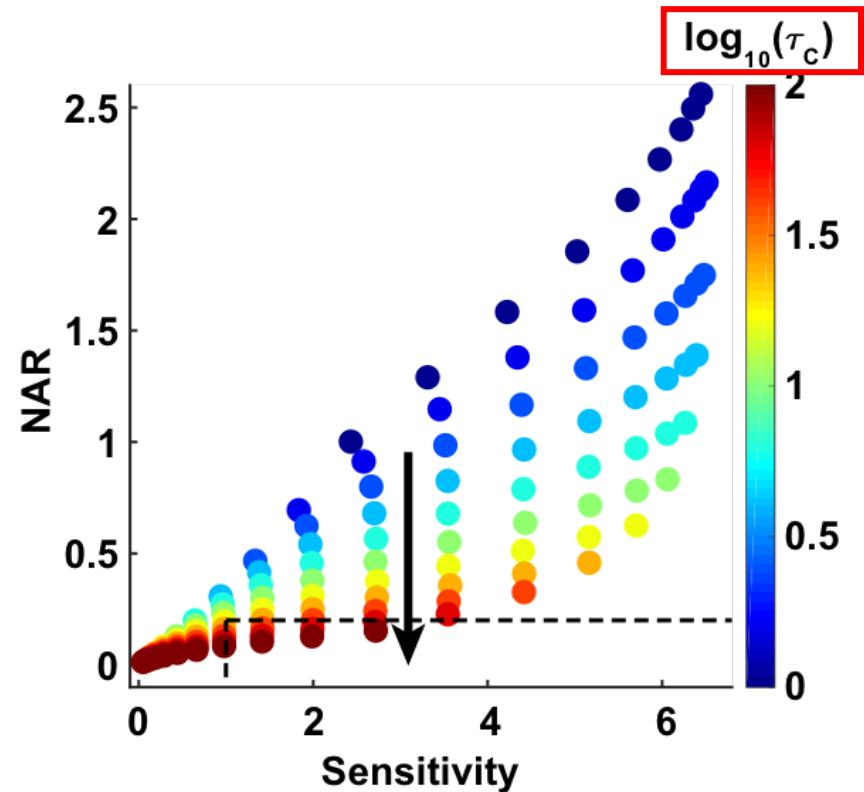
When  $\frac{\tau_C}{\tau_B}$  is fixed, larger  $\tau_C$  (or  $\tau_B$ ) causes smaller NAR.

# Fine-tuning timescales in three-node networks can partially mediate the trade-off between sensitivity and NAR

For IFFLP

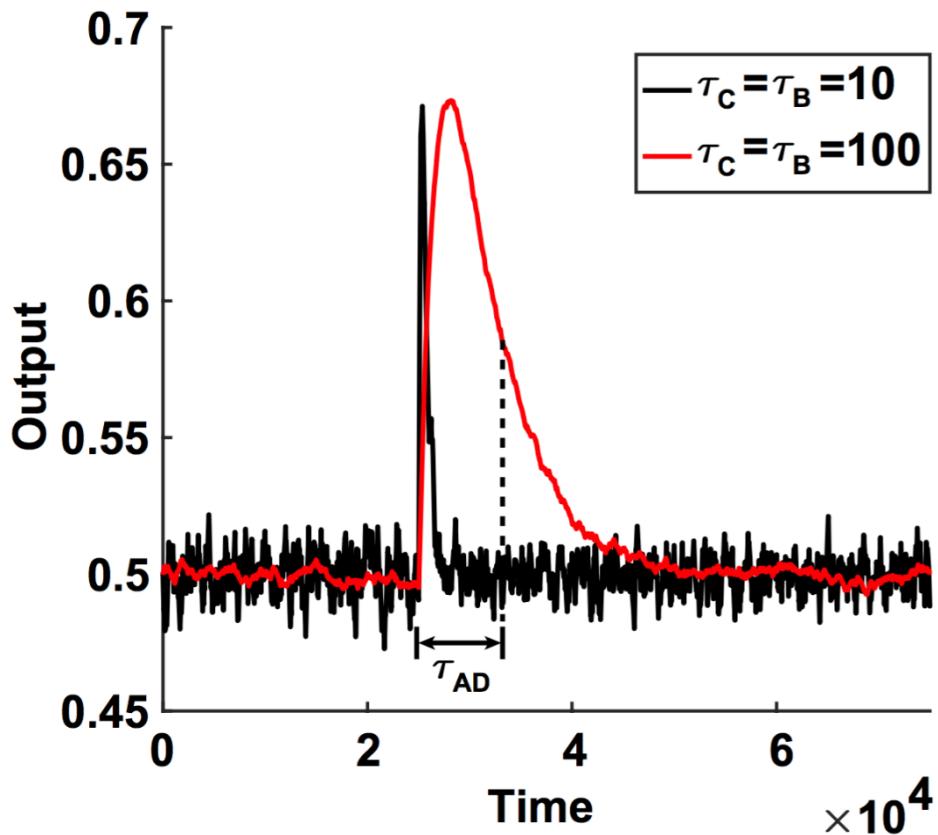


Decrease  $\tau_C/\tau_B$  to ensure high sensitivity



Increase  $\tau_C$  to ensure small NAR ( $\tau_C/\tau_B$  fixed)

# Fine-tuning timescales improves dual function with costs



## Two costs:

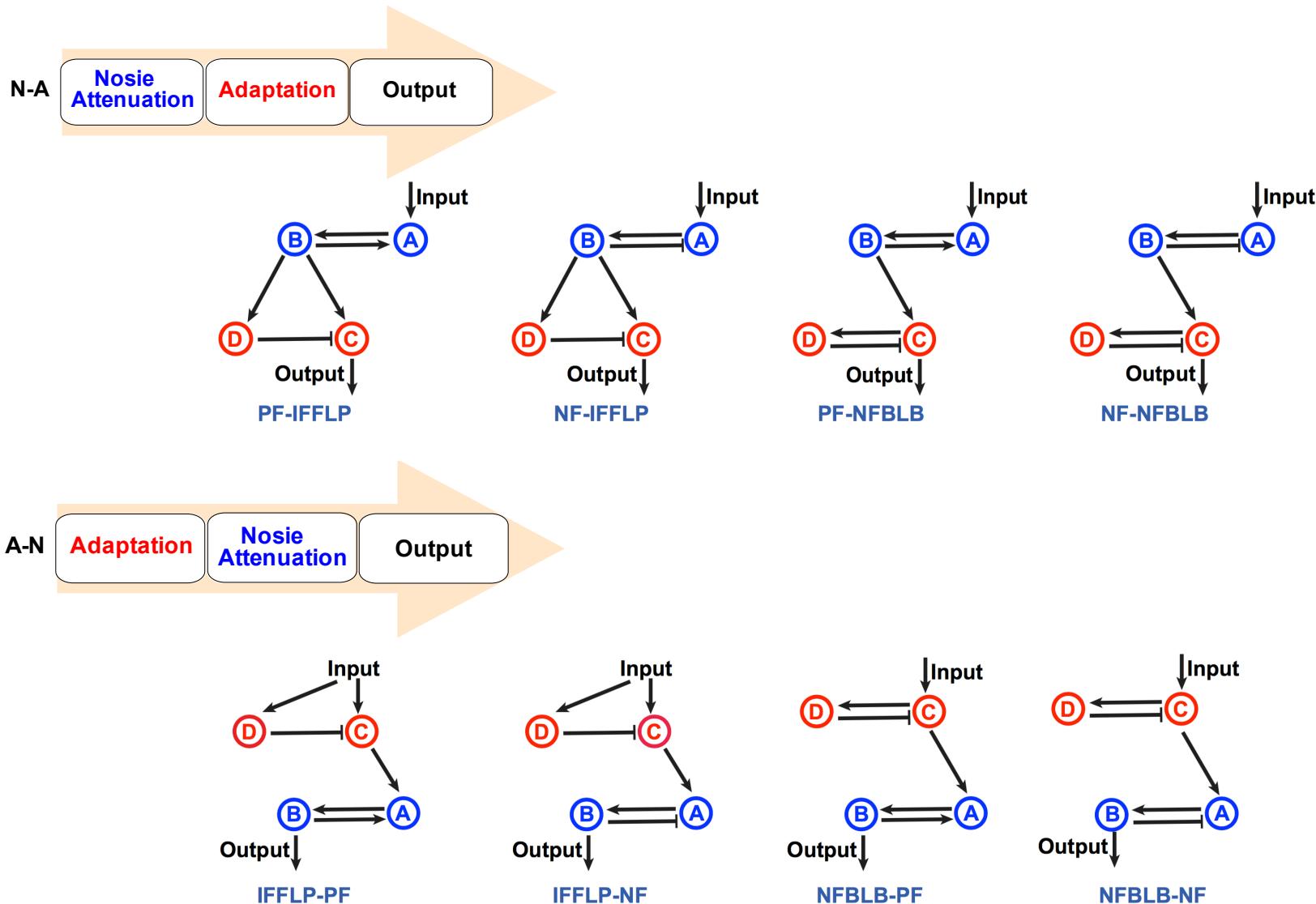
- i. prolong adaptation time ( $\tau_{AD}$ )
- ii. expand the search space of kinetic parameters

## Investigate dual function in four-node networks

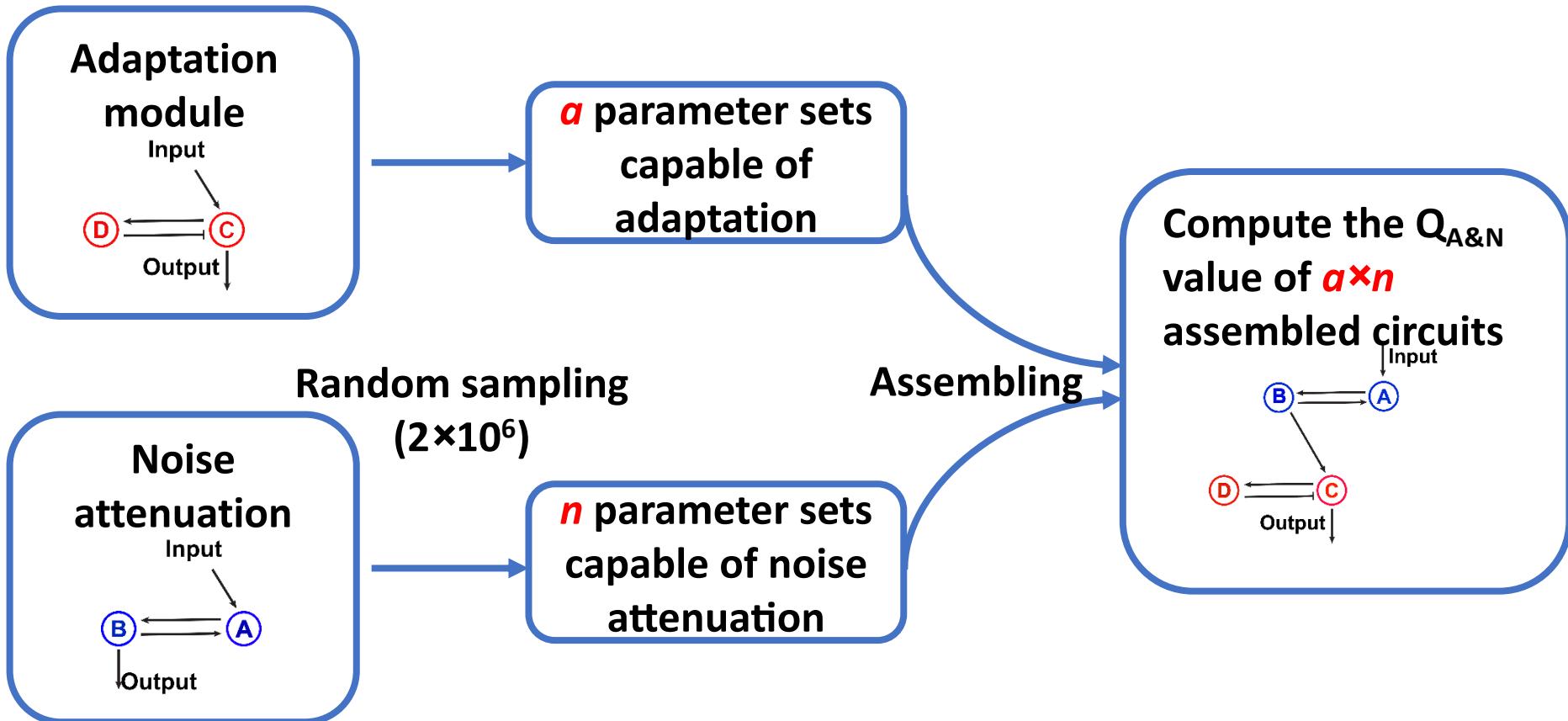
- We extend three-node networks to four-node networks.
- Enumeration of all four-node networks is computationally too expensive:
  1. huge number of 4-node networks (19,805,472):  
1,200 times more than that of 3-node networks (16,038)
  2. much extended parameter space to be sampled.

# Module combination in four-node networks

adaptation module (A) and noise attenuation module (N)

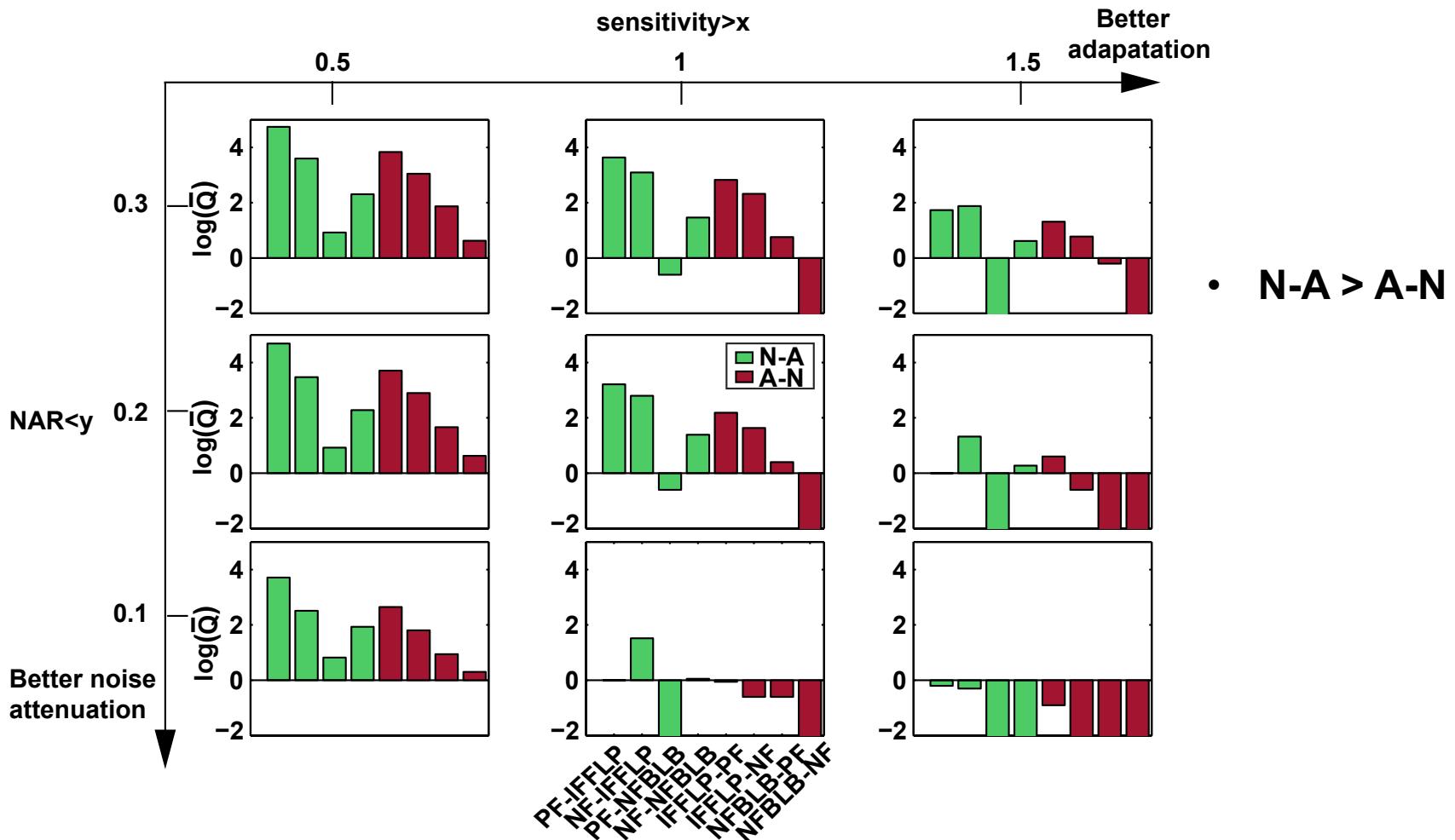


# Robustness (Q value) of combined four-node networks



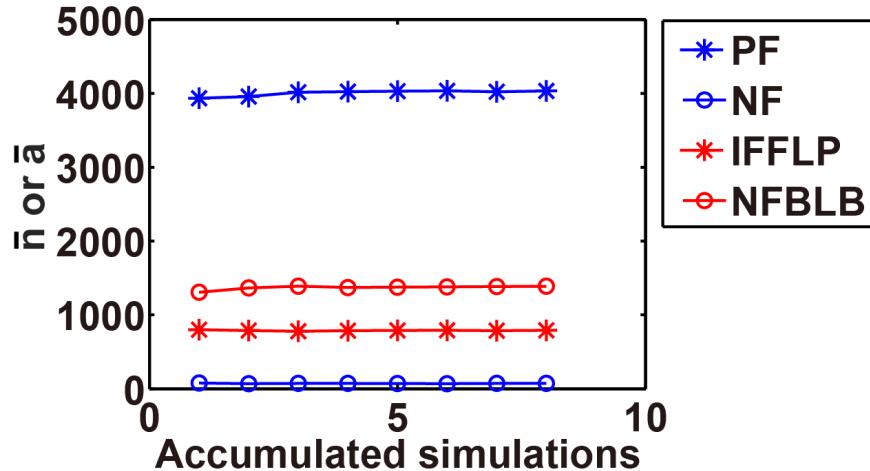
# Results II

- Combinations of function-specific modules in four-node networks can achieve dual function

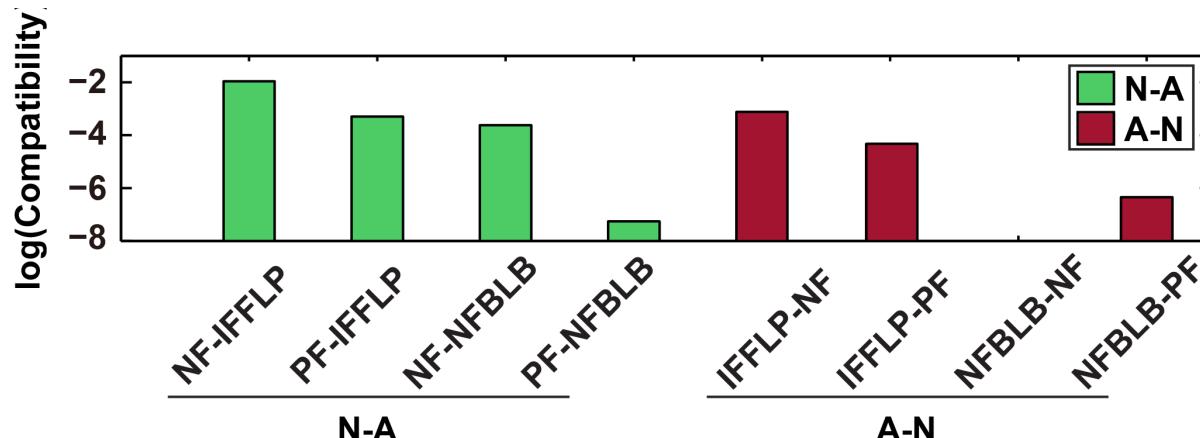


## Two factors affect successful combination

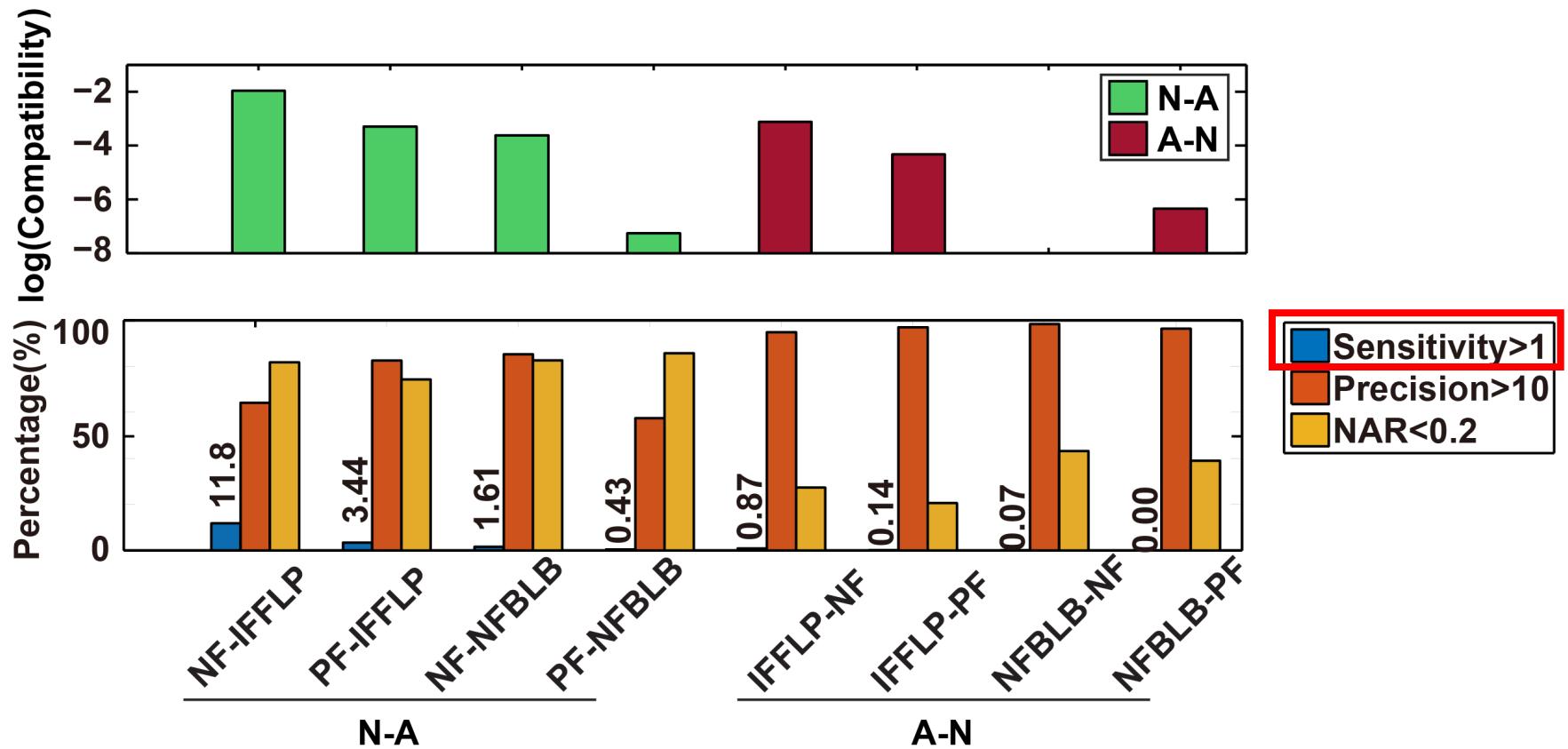
- The robustness of each module ( $a$  or  $n$ )



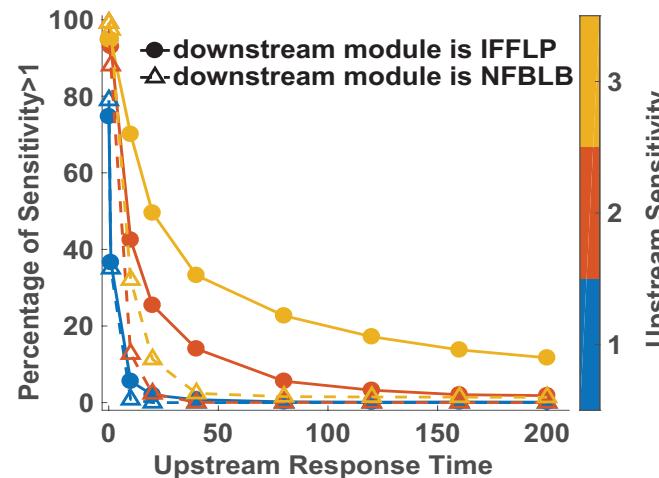
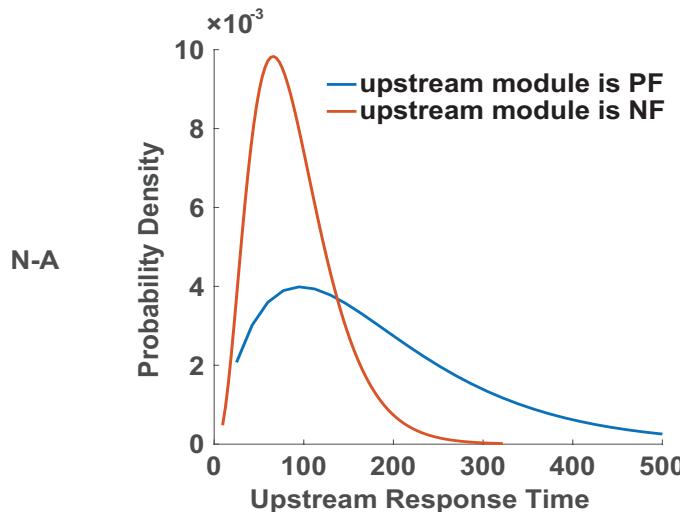
- The compatibility between modules ( Compatibility $\triangleq \frac{Q}{a \times n}$  )



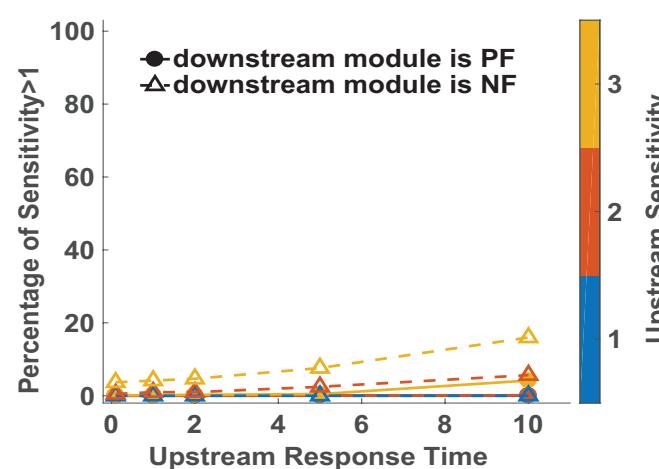
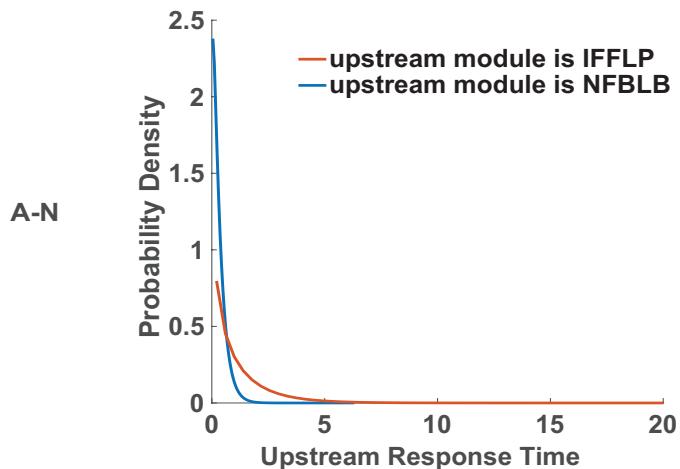
- Compatibility is limited by sensitivity**



- Sensitivity is affected by response time of upstream module

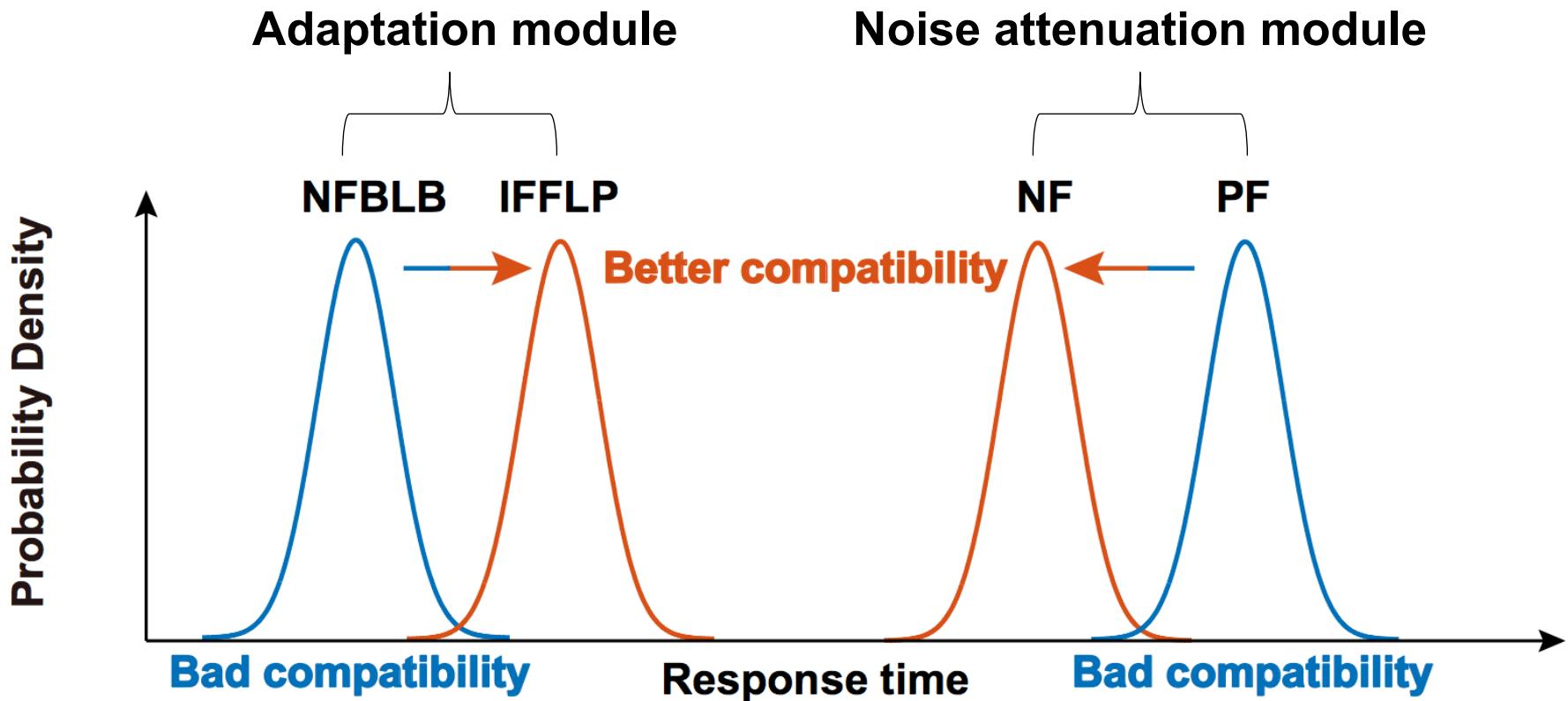


Shorter upstream response time benefits sensitivity: NF>PF & IFFLP>NFBLB

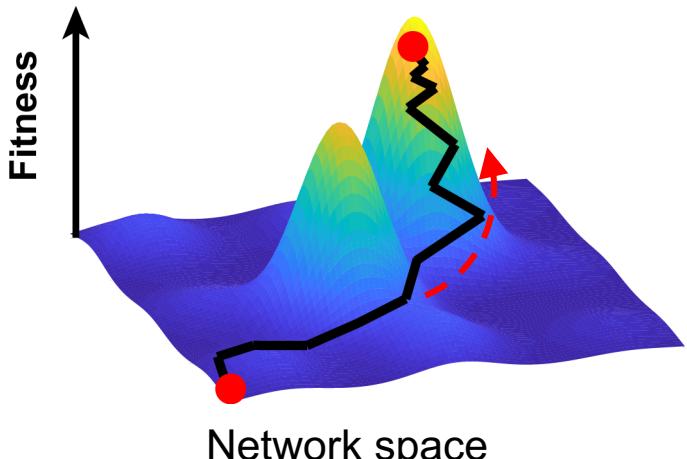
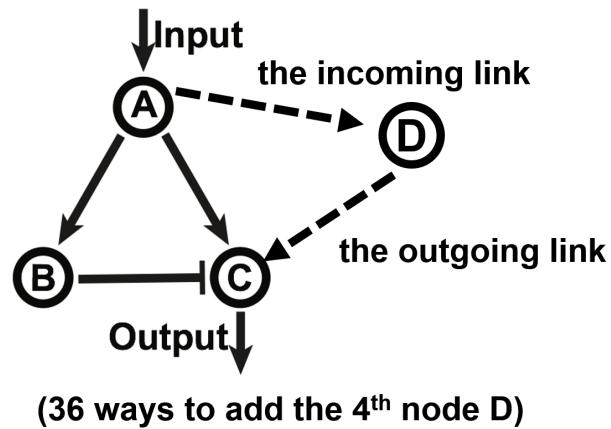


Longer upstream response time benefits sensitivity: IFFLP>NFBLB & NF>PF

# Response time of modules is a key factor for successful combination



# Evolution algorithm is used to explore a larger four-node network space



**A trajectory evolving toward higher fitness**

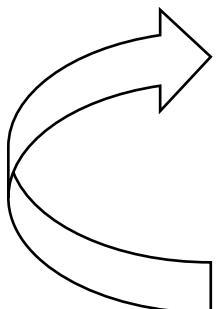
## Initialization

Randomly sample an initial collection of 1000 circuits with 36 different topologies



## Mutation

Add a mutation copy by randomly selecting and perturbing one parameter



## Selection

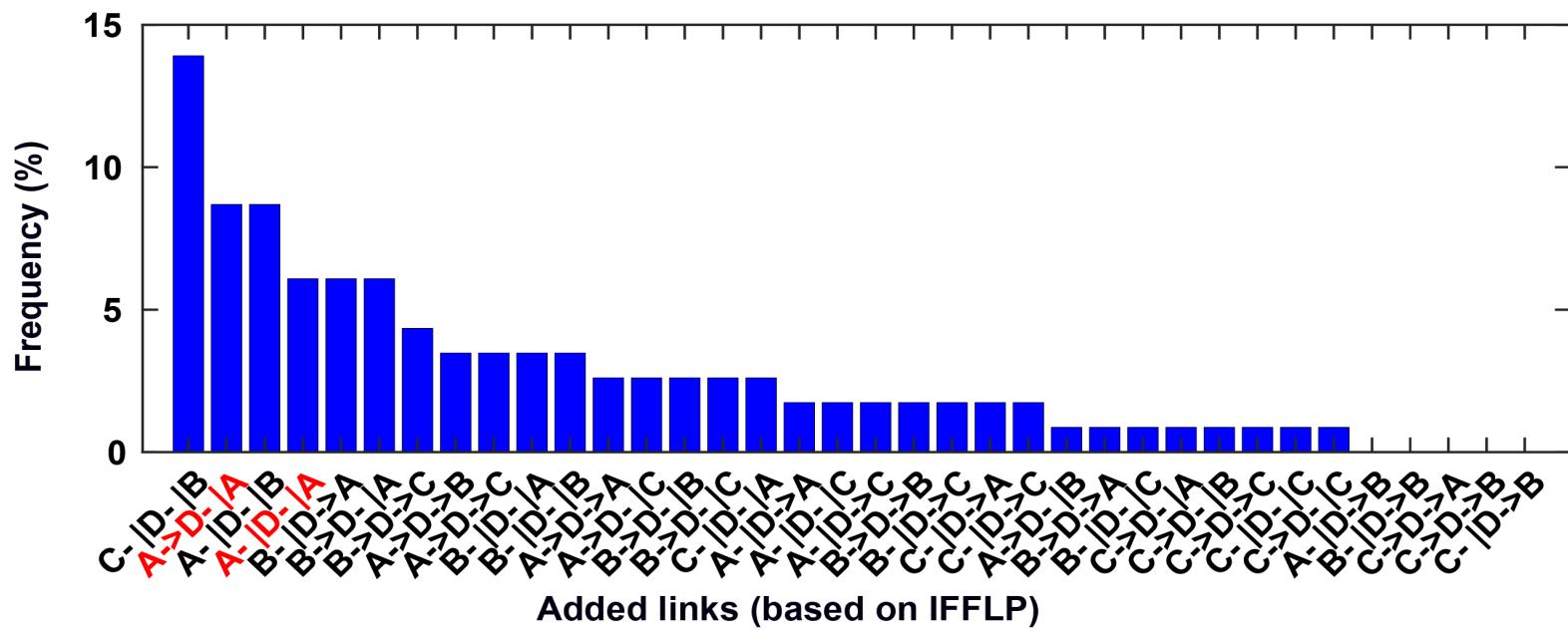
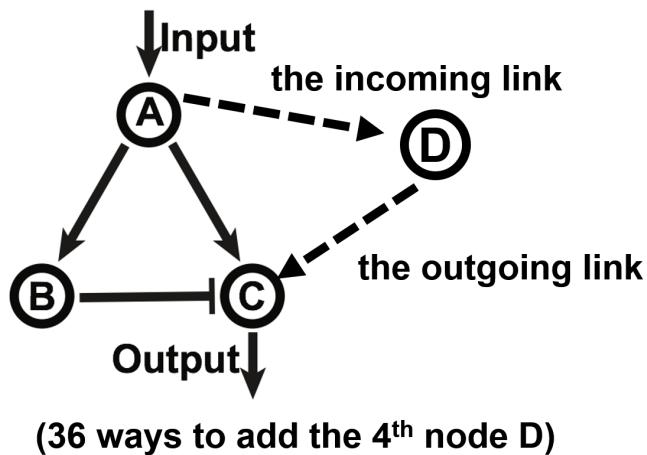
Restore to its original size by selecting the high-fitness circuits



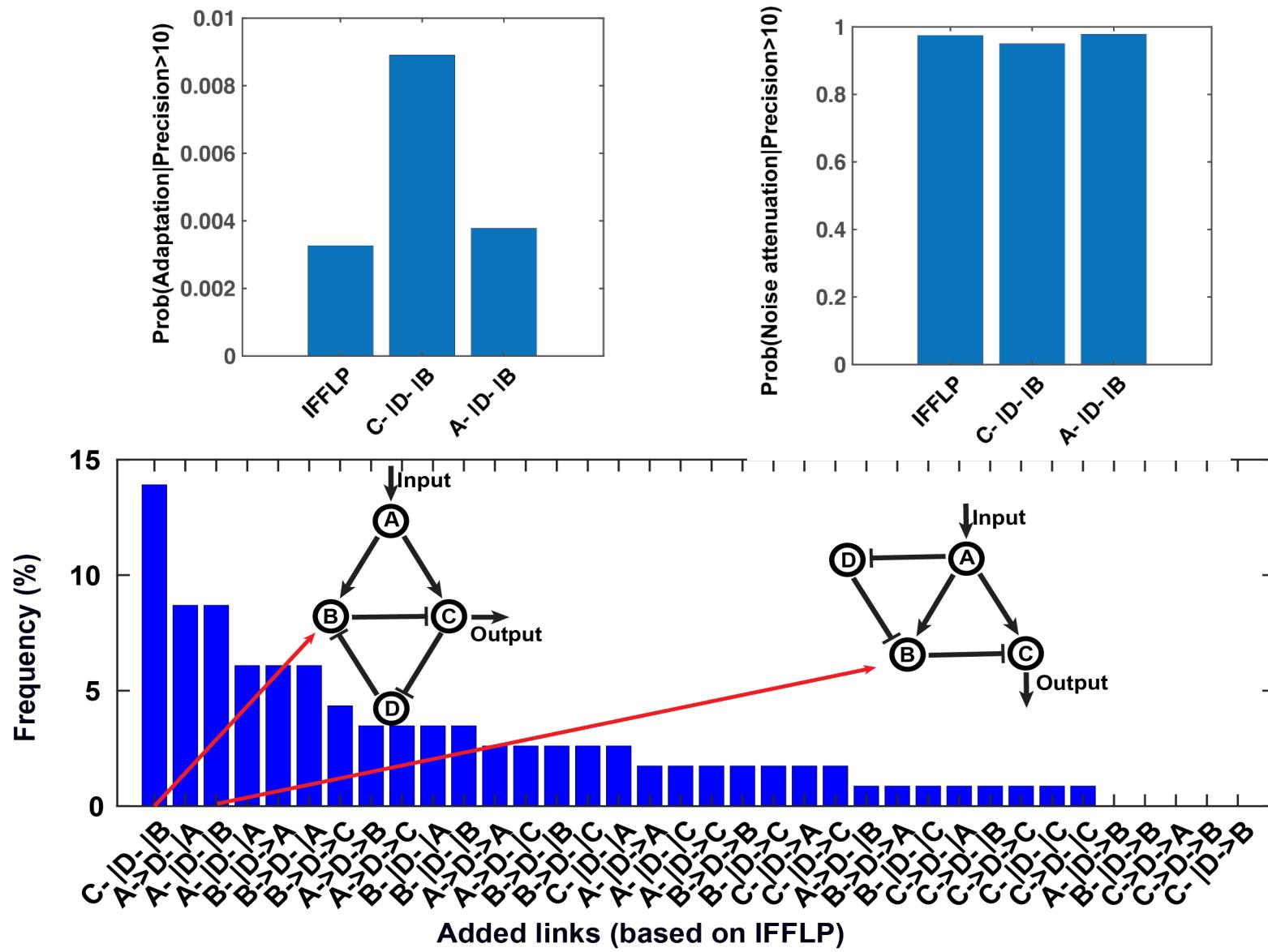
## Termination condition

One dual function circuit emerges or the maximum number of iterations is reached

# N-A networks are advantageous even within a larger network space



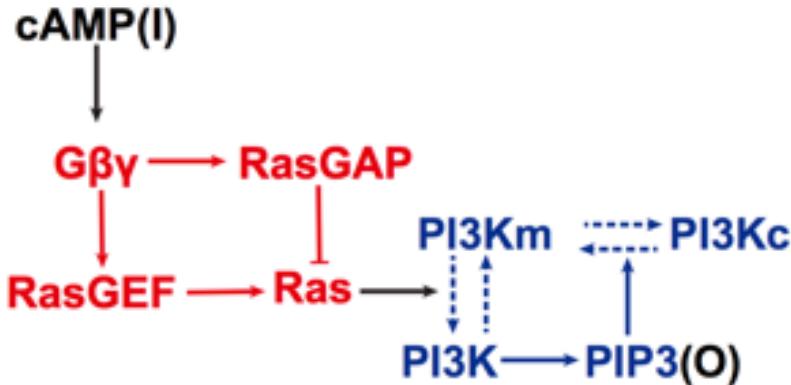
# New dual-function four-node networks emerge



# Biological networks are modularized to achieve dual function

| System   | Network  | Category |
|--|--|----------|
| Chemotaxis in Dictyostelium<br>(Kimmel and Parent, 2003; Sasaki et al., 2004; Park et al., 2004; Han et al., 2006 ; Takeda et al., 2012)   | <pre> graph TD     cAMP[I] --&gt; GbetaGamma[Gβγ]     GbetaGamma --&gt; RasGAP[RasGAP]     GbetaGamma --&gt; RasGEF[RasGEF]     RasGAP --&gt; Ras[Ras]     RasGEF --&gt; Ras     Ras --&gt; PI3K[PI3K]     PI3K --&gt; PIP3O[PIP3(O)]     PIP3O --&gt; RacGEF[RacGEF]     RacGEF --&gt; Rac[Rac]     Rac --&gt; Factin[F-actin]   </pre> | IFFLP-PF |
| UV-induced p53 activation in mammalian cells<br>(Bode and Dong, 2004; Batchelor et al., 2011; Ohashi et al., 2014; Zhang and Lozano, 2017) | <pre> graph TD     UV[I] --&gt; TopBP1[TopBP1]     TopBP1 --&gt; ATR[ATR]     ATR --&gt; Chk1[Chk1]     Chk1 --&gt; Mdm2[Mdm2]     Chk1 --&gt; Wip1[Wip1]     Mdm2 --&gt; p53O[p53(O)]     Wip1 --&gt; p53O   </pre>   | PF-NFBLB |
| Tumorigenesis<br>(O'Donnell et al., 2005; Zhang et al., 2014a; Tago et al., 2015)  | <pre> graph TD     Arf[I] --&gt; DDX5[DDX5]     DDX5 --&gt; cMyc[c-Myc]     cMyc --&gt; miR20[miR-20]     cMyc --&gt; miR17[miR-17-5p]     miR20 --&gt; E2F1O[E2F1(O)]     miR17 --&gt; E2F1O   </pre>   | PF-IFFLP |
| Coagulation and fibrinolysis in blood system<br>(Jackson and Nemerson, 1980; Beltrami and Jesty, 1995; Cesarman-Maus and Hajjar, 2005)     | <pre> graph TD     tPA[tPA] --&gt; plasmin[plasmin]     plasmin --&gt; fibrinO[fibrin(O)]     tPA --&gt; thrombin[thrombin]     thrombin --&gt; Xa[Xa]     Xa --&gt; Va[Va]     Va --&gt; VIIIa[VIIIa]     VIIIa --&gt; Xa     Xa --&gt; VIIIa   </pre>  | PF-NFBLB |
| Sensory organ precursor determination in Drosophila<br>(Li et al., 2009)   | <pre> graph TD     EGF[I] --&gt; EGFR[EGFR]     EGFR --&gt; PntP1[Pnt-P1]     PntP1 --&gt; Senseless[Senseless]     Senseless --&gt; Atonal[Atonal]     Atonal --&gt; miR7[miR-7]     miR7 --&gt; EsplC[E(spl)C(O)]   </pre>   | PF-IFFLP |

# *Dictyostelium discoideum* chemotaxis



$$\frac{dG_{\beta\gamma}}{dt} = k_1 \cdot cAMP \cdot (G_{\beta\gamma 0} - G_{\beta\gamma}) - kd_1 \cdot G_{\beta\gamma}$$

$$\frac{dRasGEF}{dt} = k_2 \cdot G_{\beta\gamma} - kd_2 \cdot RasGEF$$

$$\frac{dRasGAP}{dt} = k_3 \cdot G_{\beta\gamma} - kd_3 \cdot RasGAP$$

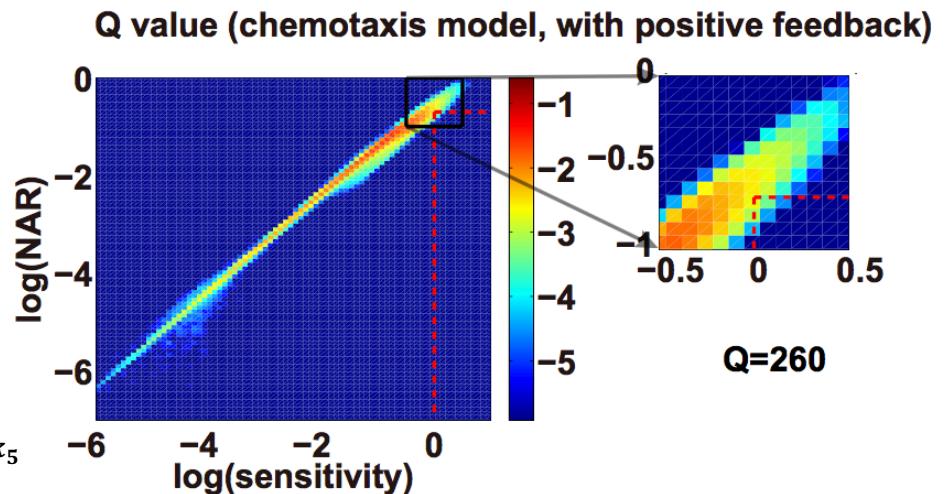
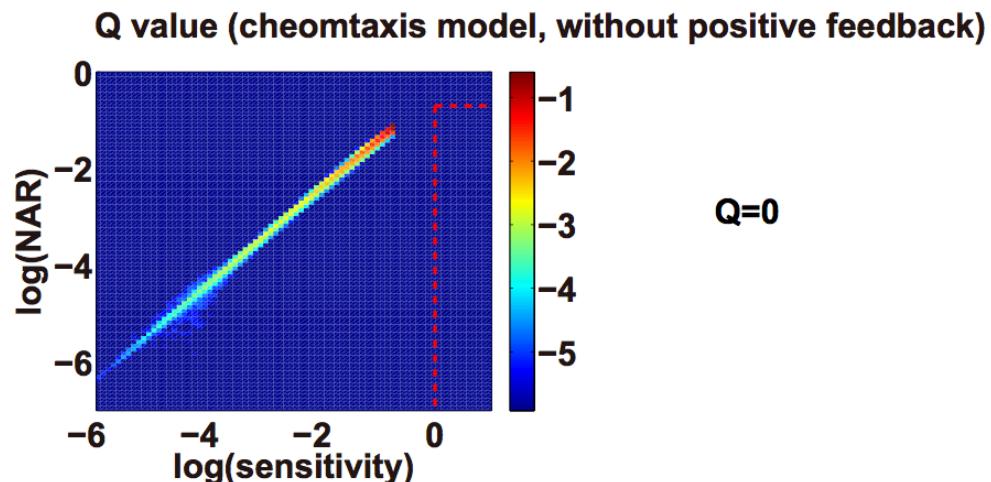
$$\frac{dRas}{dt} = k_4 \cdot RasGEF \cdot (Ras_0 - Ras) - kd_4 \cdot RasGAP \cdot Ras$$

$$\frac{dPI3K}{dt} = k_5 \cdot Ras \cdot PI3K_m - kd_5 \cdot PI3K$$

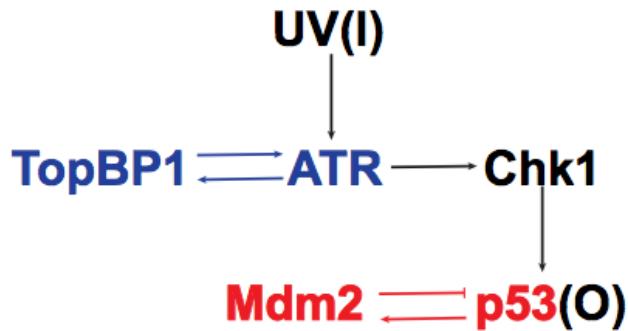
$$\frac{dPI3K_m}{dt}$$

$$= k_7 \cdot (PI3K_0 - PI3K_m - PI3K) \cdot (PIP3 + k_{70}) - kd_7 \cdot PI3K_m - k_5 \cdot Ras \cdot PI3K_m + kd_5 \cdot PI3K$$

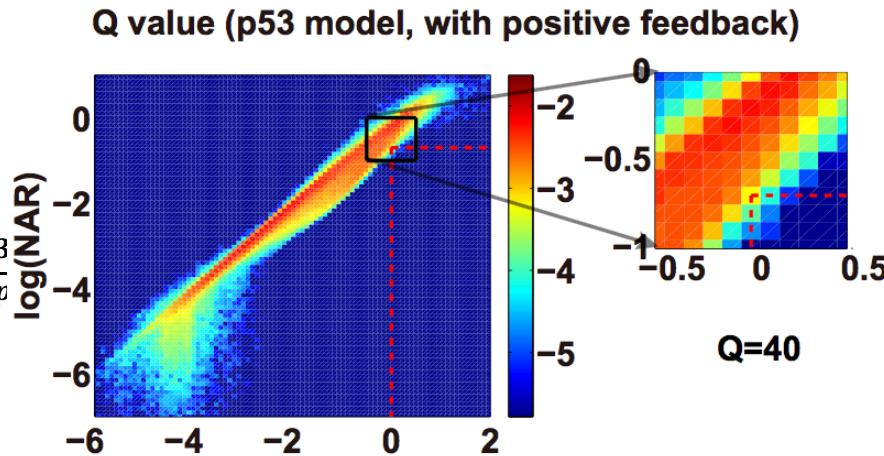
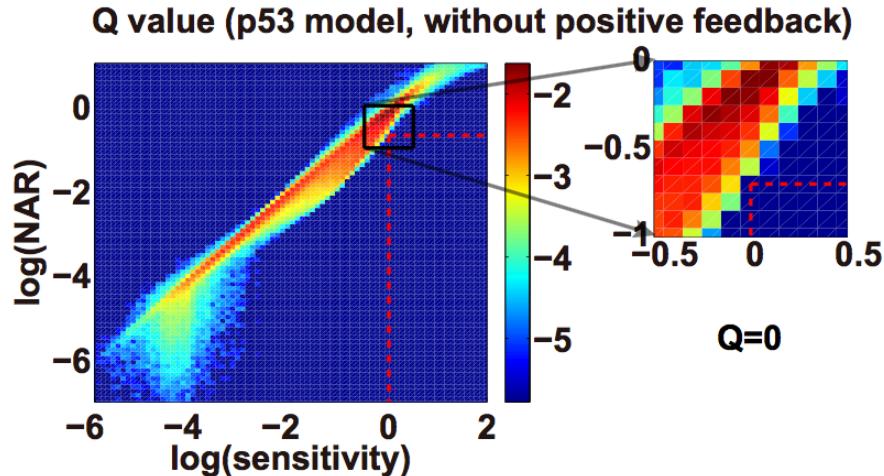
$$\frac{dPIP3}{dt} = k_6 \cdot PI3K \cdot \frac{P_0 - PIP3}{P_0 - PIP3 + K_6} - kd_6 \cdot PIP3.$$



# p53 dynamics



$$\begin{aligned}
 \frac{dATR}{dt} &= k_1 \cdot cAMP \cdot (TopBP1 + l_1) \cdot (ATR_0 - ATR) - kd_1 \cdot ATR \\
 \frac{dTopBP1}{dt} &= k_2 \cdot Chk1 \cdot (TopBP1_0 - TopBP1) - kd_2 \cdot TopBP1 \\
 \frac{dChk1}{dt} &= k_3 \cdot ATR \cdot \frac{Chk1_0 - Chk1}{K_3 + Chk1_0 - Chk1} - kd_3 \cdot \frac{Chk1}{Kd_3 + Chk1} \\
 \frac{dp53}{dt} &= kg_4 - kd_4 \cdot p53 + k_4 \cdot Wip1 \cdot \frac{p53^*}{K_4 + p53^*} - k_5 \cdot Chk1 \cdot \frac{p53}{K_5 + p} \\
 \frac{dp53^*}{dt} &= k_5 \cdot Chk1 \cdot \frac{p53}{K_5 + p53} - k_4 \cdot Wip1 \cdot \frac{p53^*}{K_4 + p53^*} - kd_5 \cdot Mdm2 \\
 \frac{dMdm2}{dt} &= k_6 \cdot \frac{p53^*}{K_6 + p53^*} - kd_6 \\
 \frac{dWip1}{dt} &= k_7 \cdot \frac{p53^*}{K_7 + p53^*} - kd_7 \cdot \frac{Wip1}{Kd_7 + Wip1}
 \end{aligned}$$



Next week ...

- **Lecture 2: Michalis-Menten kinetics**

Reading –

[Alon] Appendix A;

[Keener&Sneyd] Chapter 1.