NETWORK MOTIFS

UNDERSTANDING BIOLOGY THROUGH MATHEMATICS

presented by Laura Martens & Arthur Heimbrecht

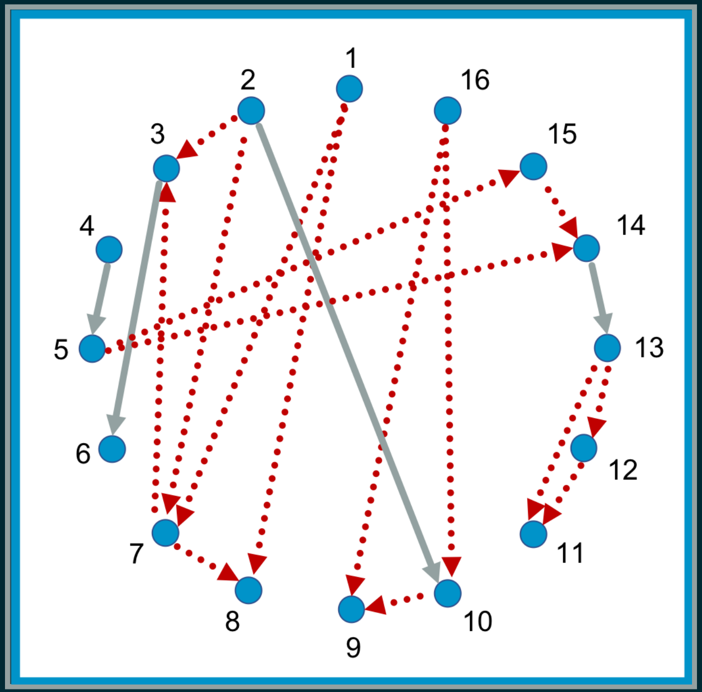
CONTENTS

INTRODUCTION

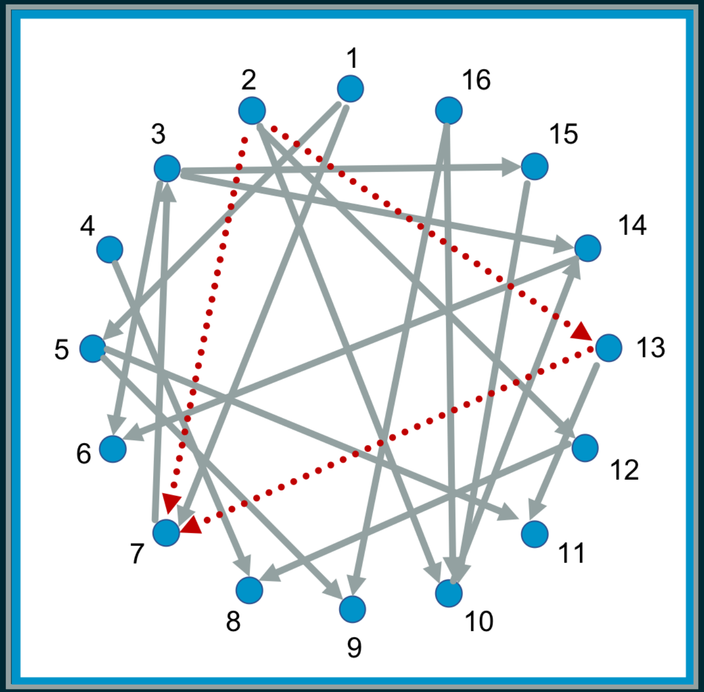
WHAT ARE NETWORK MOTIFS?

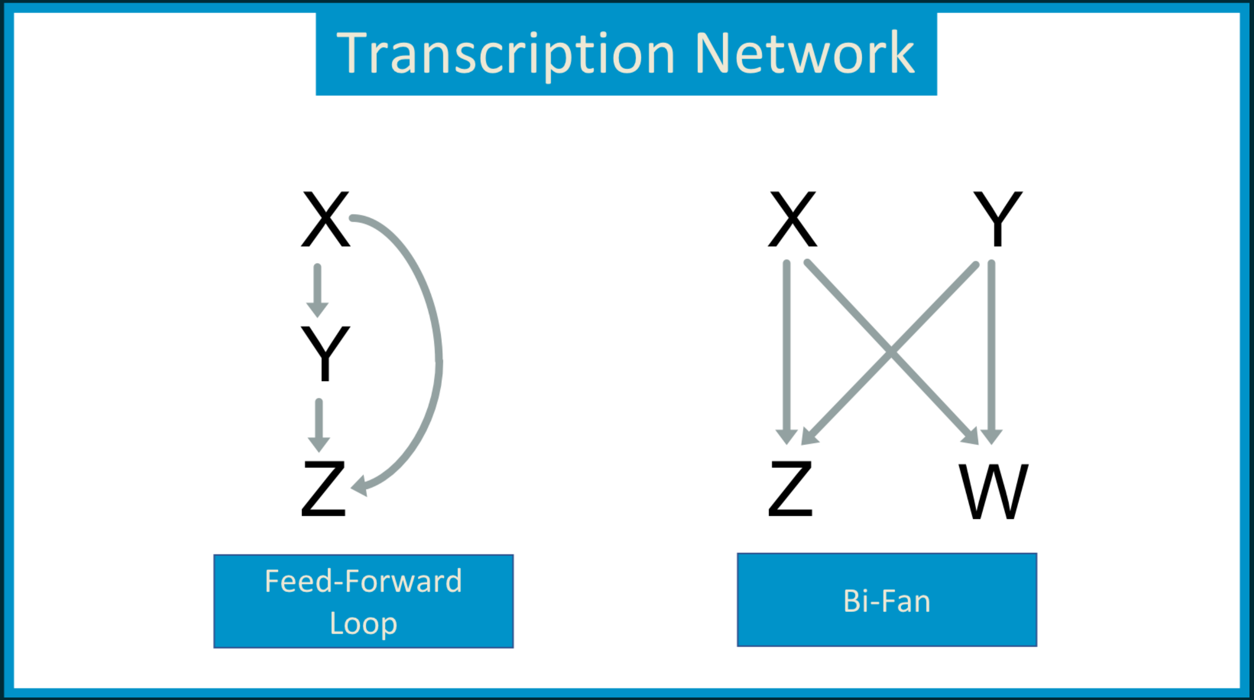
- Basic interaction patterns that recur throughout biological and non-biological networks much more often than in random networks
- Small set of network motifs serve as bulding blocks of large networks
- Each network has a defined function: e.g. filters, pulse generators

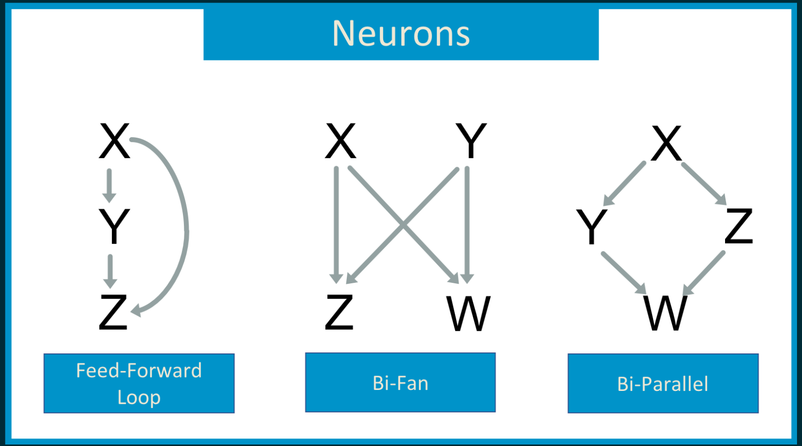
REAL NETWORK



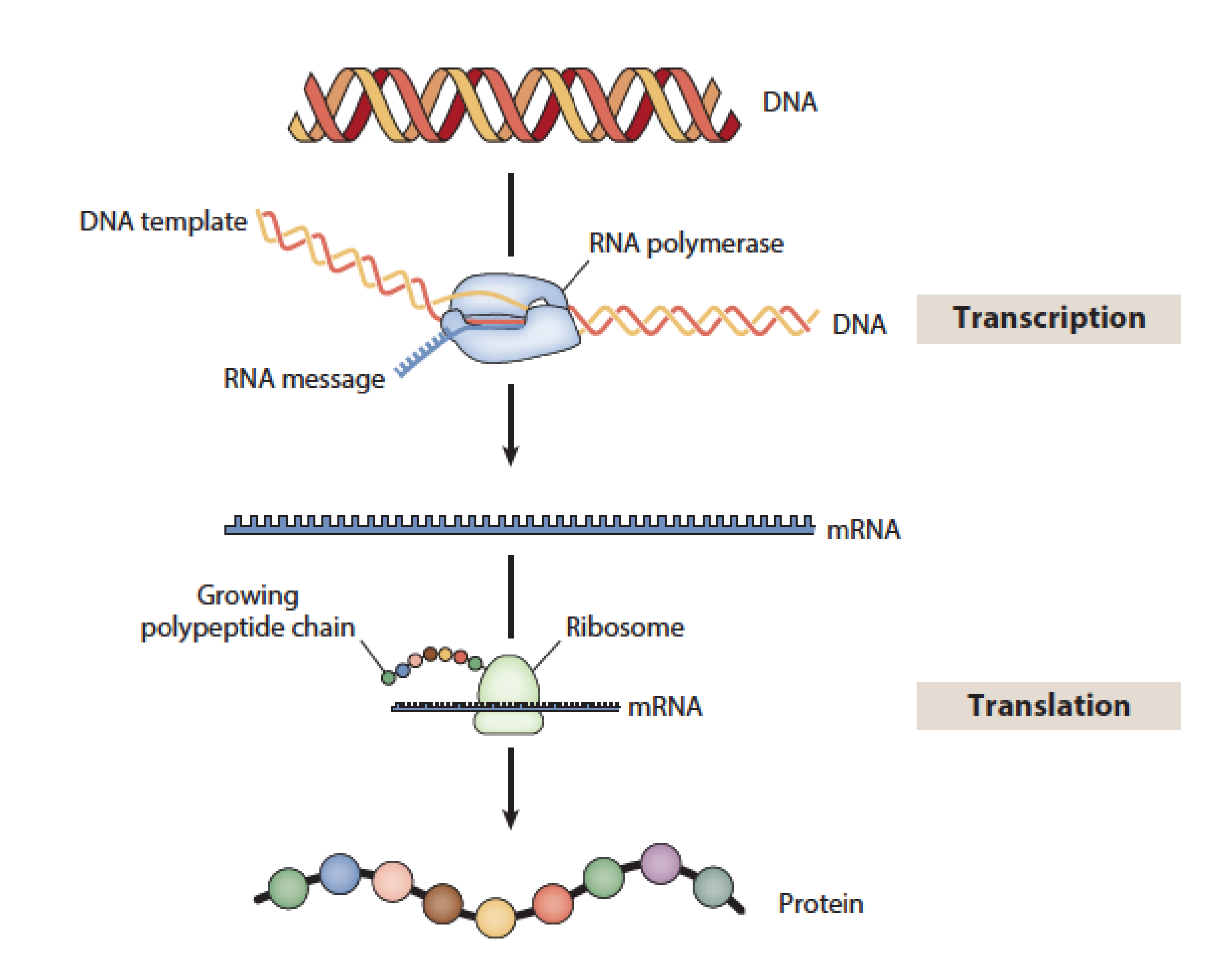
RANDOM NETWORK



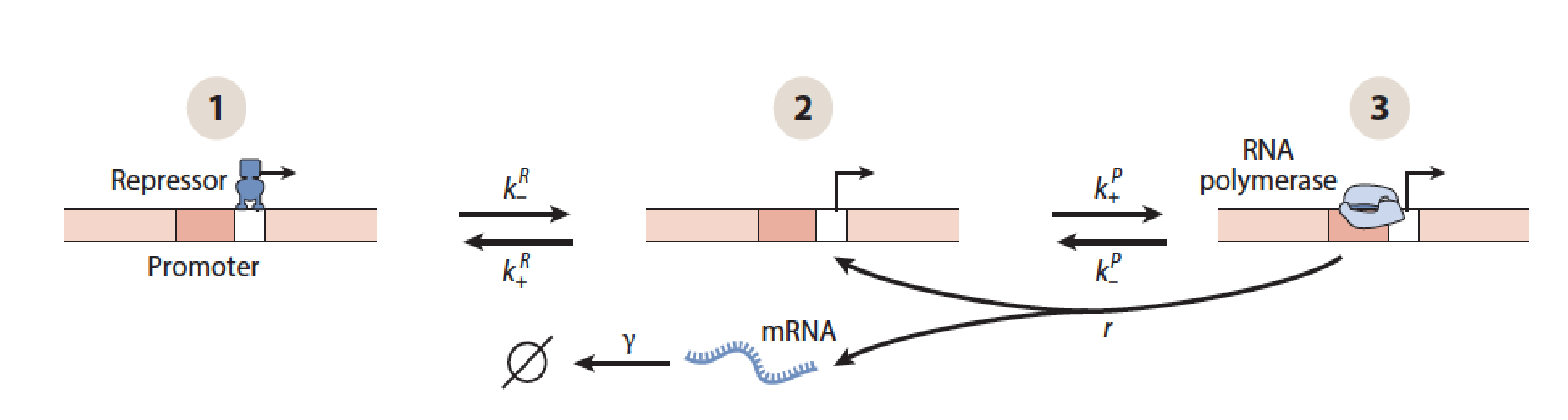

Transcription Network
X
Y
Z
Feed-Forward Loop
X
Y
Z
W
Bi-Fan


Neurons
X
Y
Z
Feed-Forward Loop
X
Y
Z
W
Bi-Fan
X
Y
Z
W
Bi-Parallel

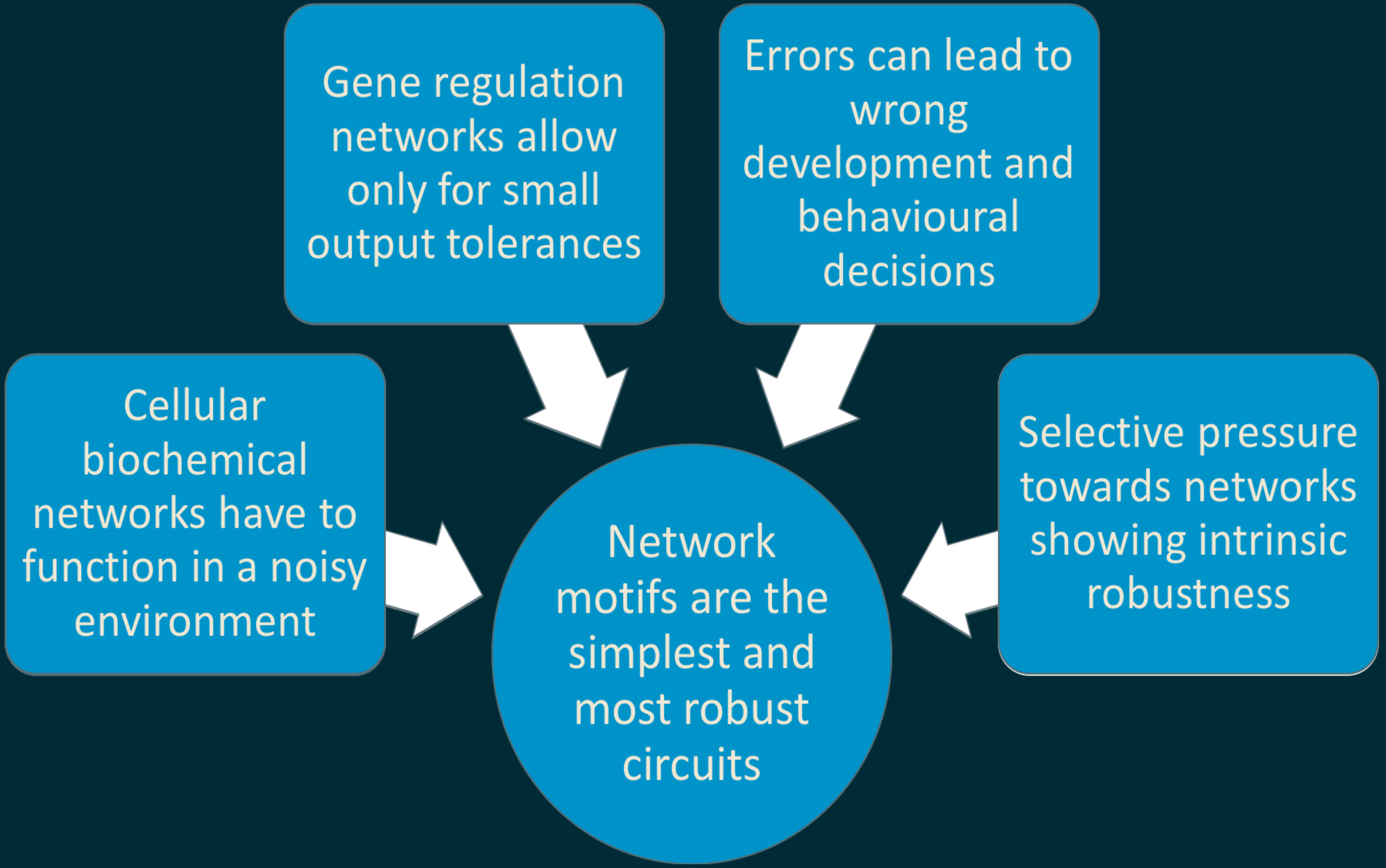
TRANSCRIPTION NETWORKS

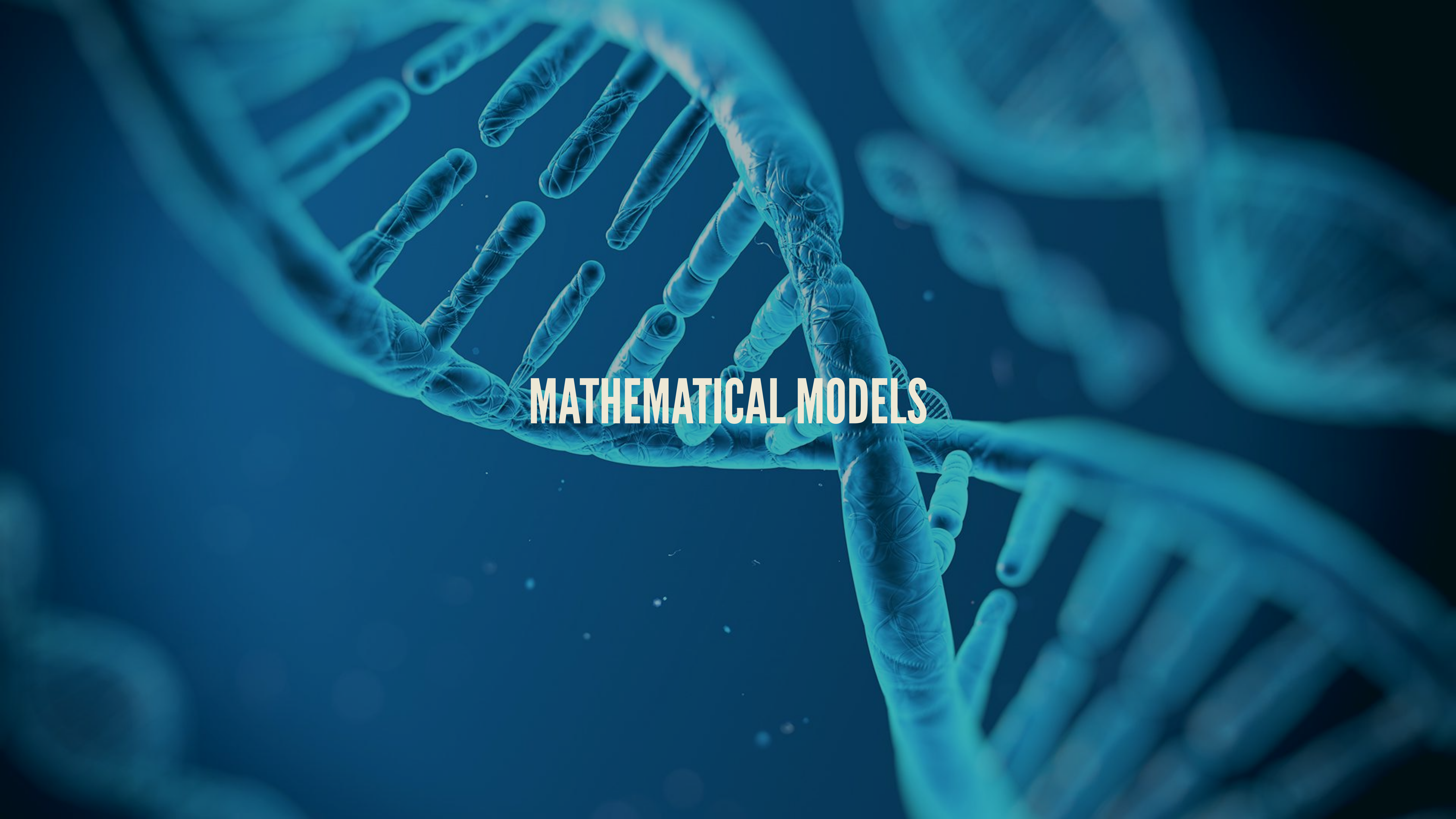


ACTIVATORS AND REPRESSORS



EVOLUTION OF NETWORK MOTIFS

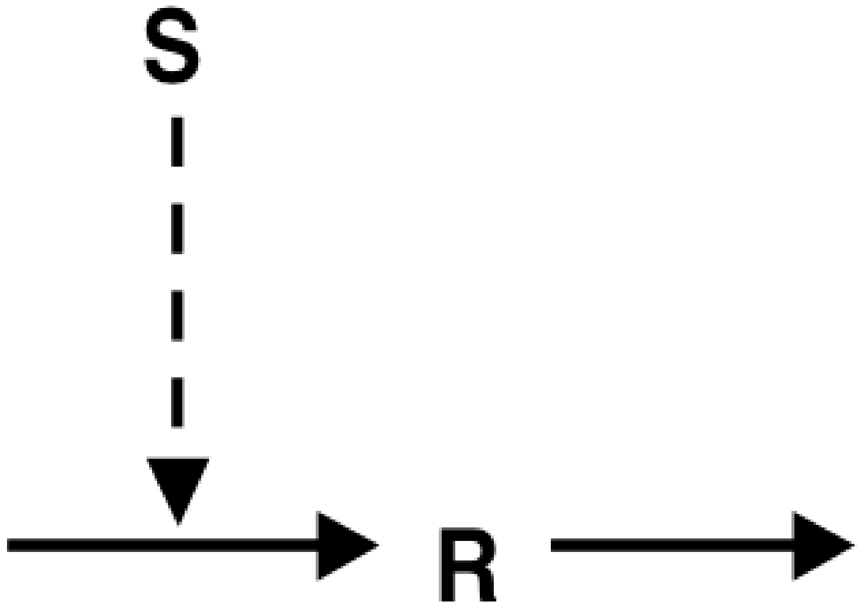

Gene regulation networks allow only for small output tolerances
Errors can lead to wrong development and behavioural decisions
Cellular biochemical networks have to function in a noisy environment
Network motifs are the simplest and most robust circuits
Selective pressure towards networks showing intrinsic robustness


MATHEMATICAL MODELS

CLASSIFYING DEVELOPMENTAL AND SENSORY NETWORKS

- **Sensory networks**
  - Cell "senses" its surroundings/its own state
  - Response is a function of the signal
- **Developmental networks**
  - Response does not depend on the signal if threshold is reached
  - Cell fate decisions are final

PRELIMINARY EXAMPLE

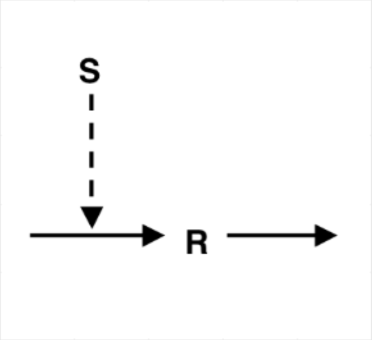


$$\frac{dR}{dt} = \boxed{k_0 + k_1 S} - \boxed{k_2 R}$$

$$R_{SS} = \frac{k_0 + k_1 S}{k_2}$$

PRELIMINARY EXAMPLE

Wire Diagramm



Formulas

$$\frac{dR}{dt} = \boxed{k_0 + k_1 S} - \boxed{k_2 R}$$

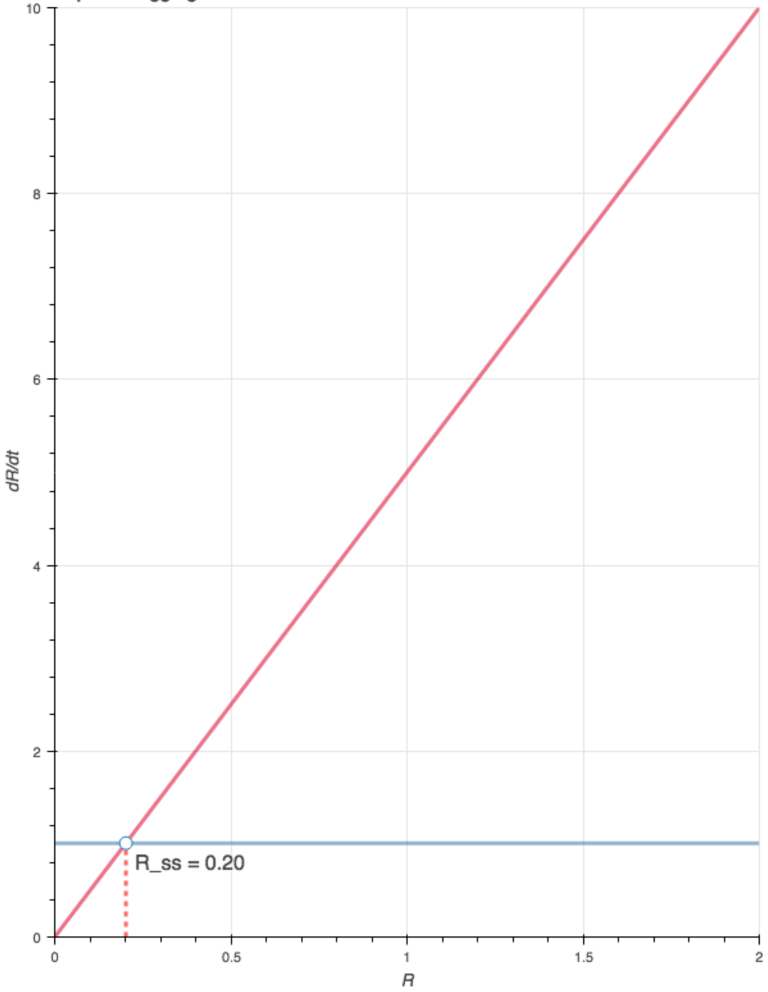
$$R_{SS} = \frac{k_0 + k_1 S}{k_2}$$

S: **1**

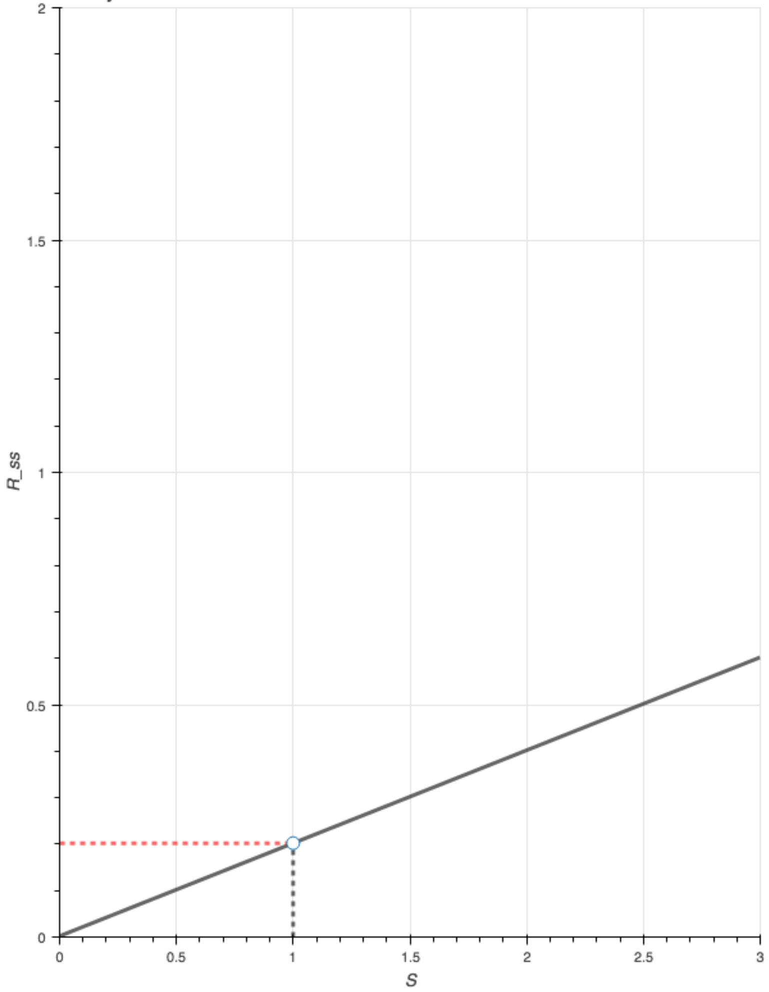
k0: **0.01** k1: **1**

k2: **5**

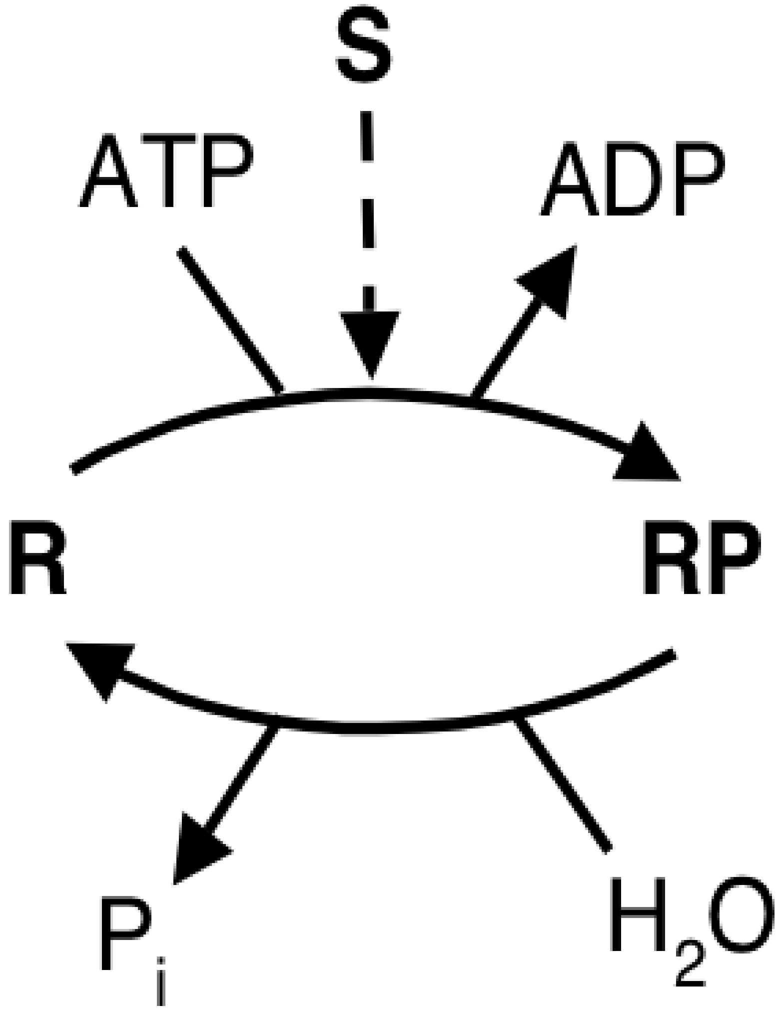
Depletion/Aggregation Rate



Steady State Solutions



BIOLOGICAL EXAMPLE

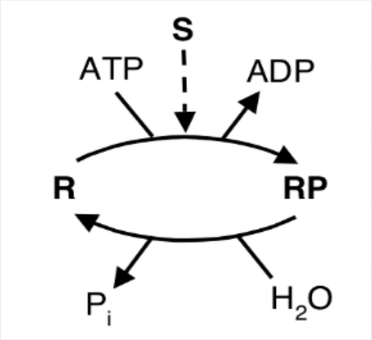


$$\frac{dR_P}{dt} = \boxed{k_1 S(R_T - R_P)} - \boxed{k_2 R_P}$$

$$R_{P,SS} = \frac{R_T S}{(k_2/k_1) + S}$$

BIOLOGICAL EXAMPLE

Wire Diagramm



Formulas

$$\frac{dR_P}{dt} = \boxed{k_1 S (R_T - R_P)} - \boxed{k_2 R_P}$$

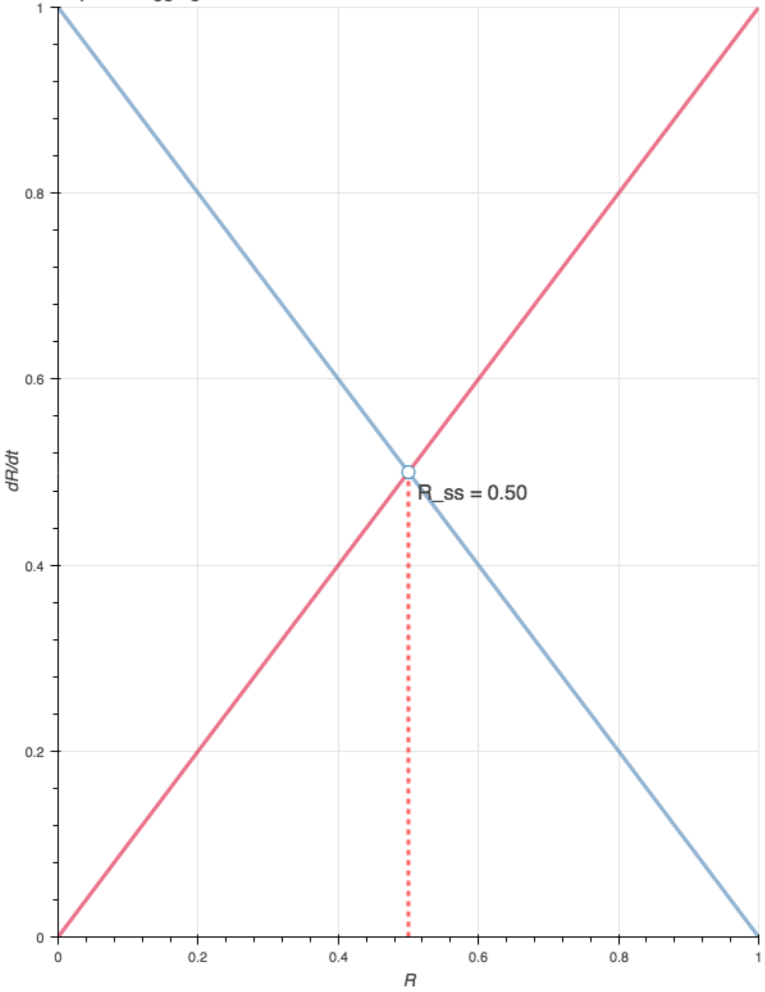
$$R_{P,SS} = \frac{R_T S}{(k_2/k_1) + S}$$

S: **1**

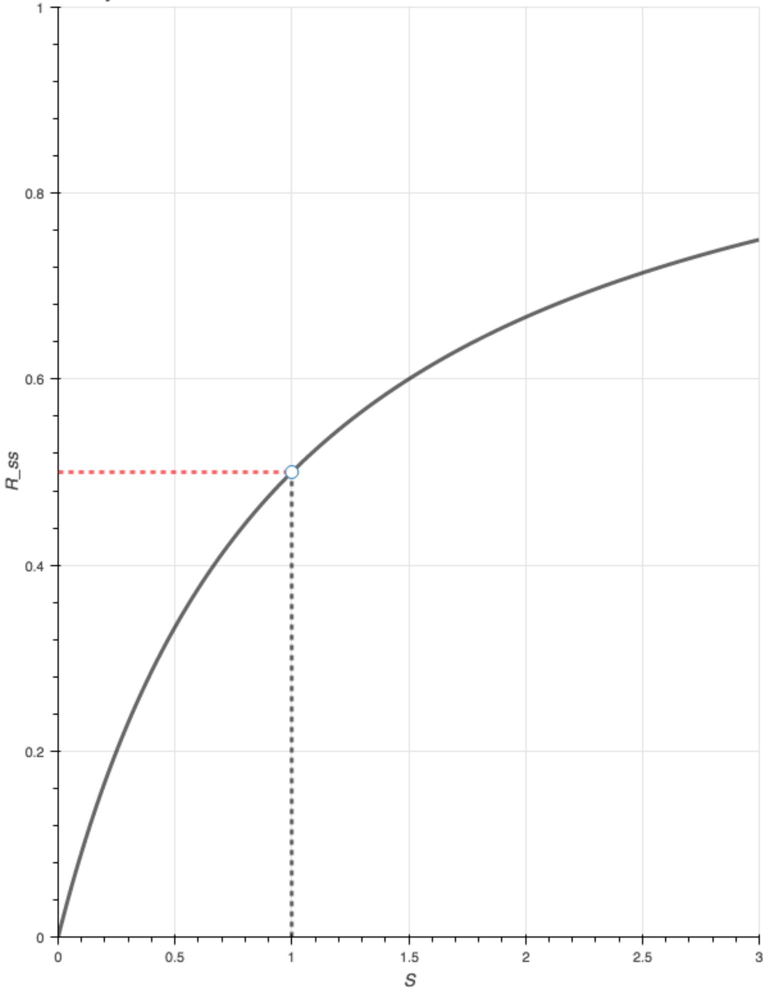
R_T: **1** k1: **1**

k2: **1**

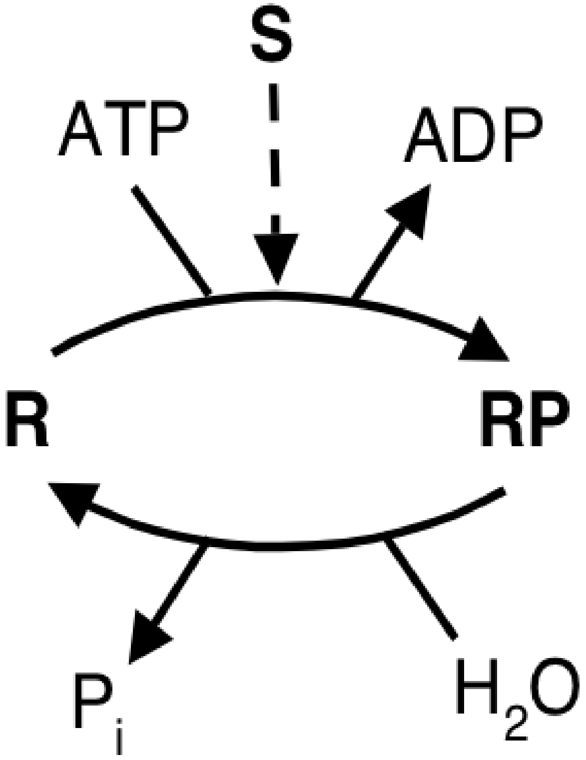
Depletion/Aggregation Rate



Steady State Solutions



BUZZER

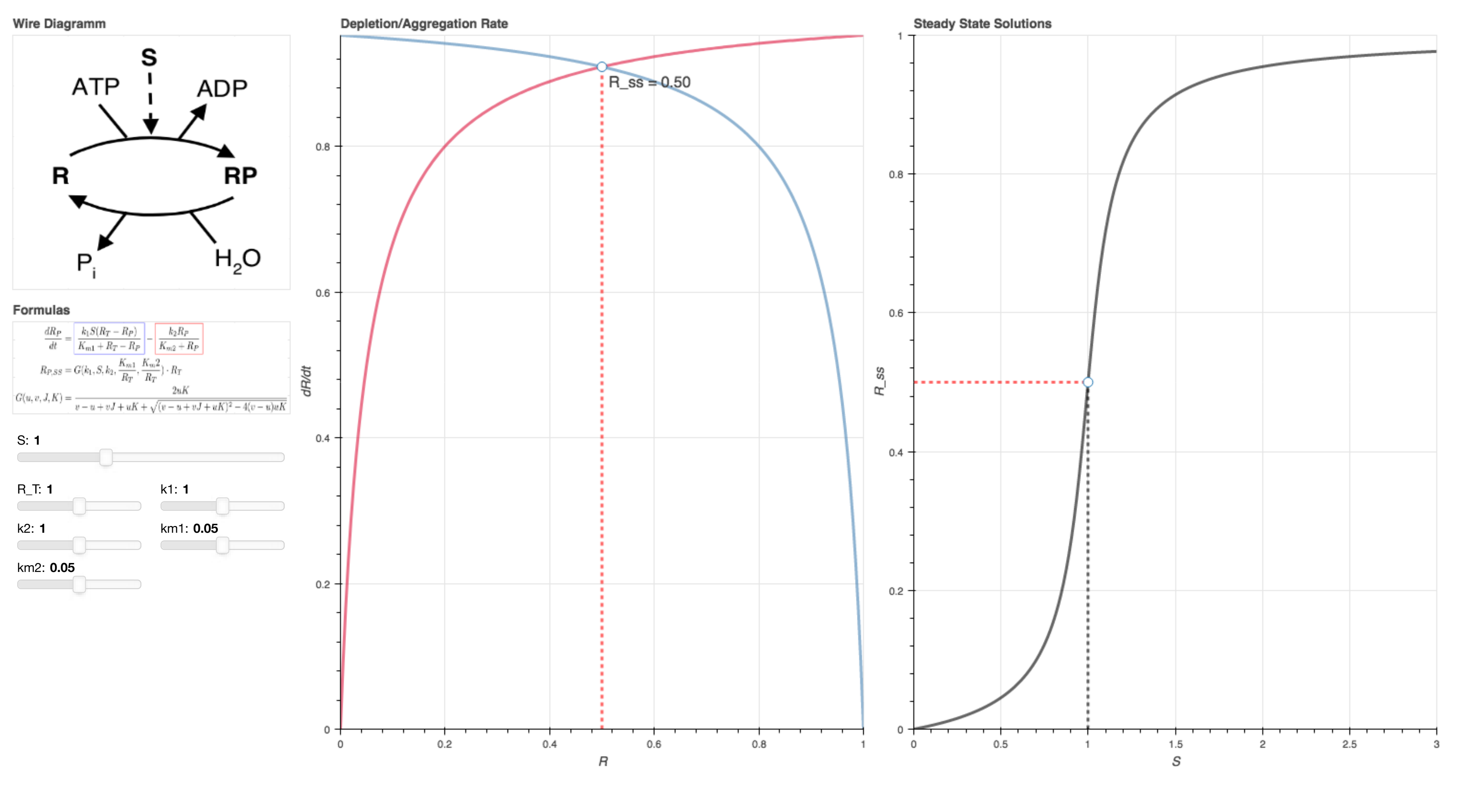


$$\frac{dR_P}{dt} = \boxed{\frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P}} - \boxed{\frac{k_2 R_P}{K_{m2} + R_P}}$$

$$R_{P,SS} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_m 2}{R_T}) \cdot R_T$$

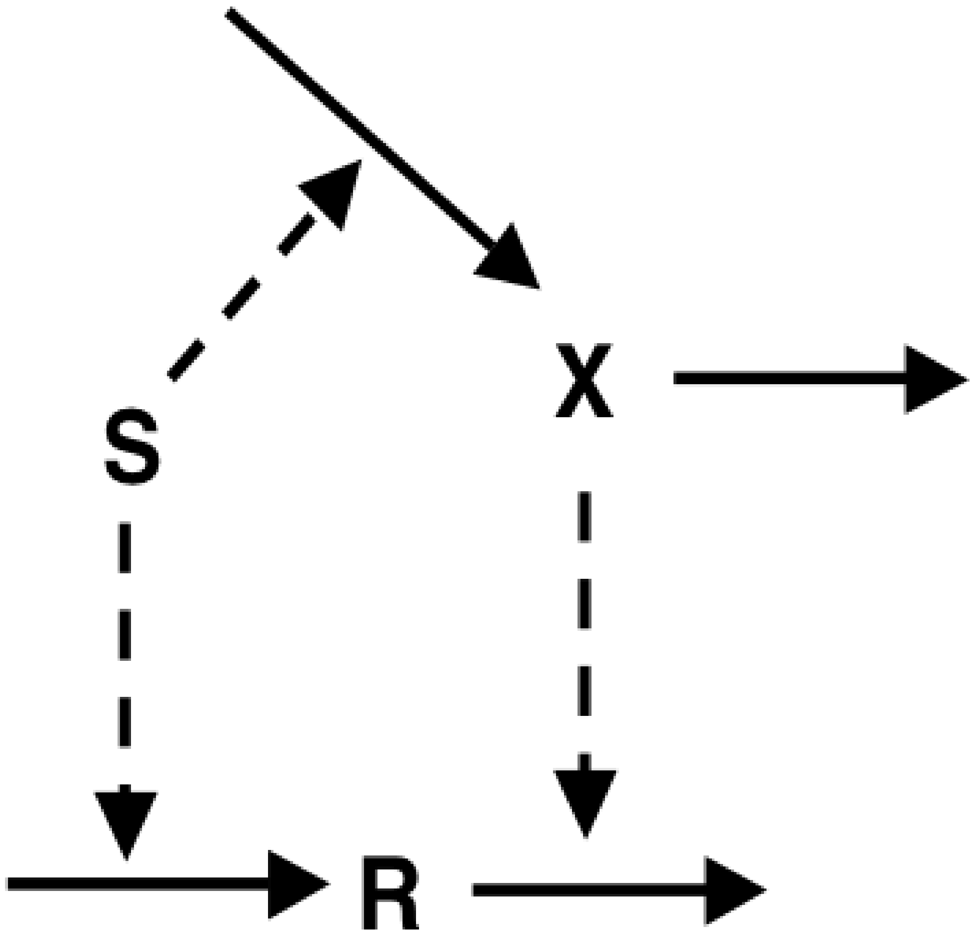
$$G(u, v, J, K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v - u)uK}}$$

BUZZER



Wire Diagramm
S
ATP
ADP
R
RP
P_i
H_2O
Formulas
$\frac{dR_P}{dt} = \boxed{\frac{k_1 S(R_T - R_P)}{K_{m1} + R_T - R_P}} - \boxed{\frac{k_2 R_P}{K_{m2} + R_P}}$
$R_{P,SS} = G(k_1, S, k_2, \frac{K_{m1}}{R_T}, \frac{K_m2}{R_T}) \cdot R_T$
$G(u, v, J, K) = \frac{2uK}{v - u + vJ + uK + \sqrt{(v - u + vJ + uK)^2 - 4(v - u)uK}}$
S: 1
R_T: 1
k1: 1
k2: 1
km1: 0.05
km2: 0.05
Depletion/Aggregation Rate
R_ss = 0.50
dR/dt
R
Steady State Solutions
R_ss
S

SNIFFER



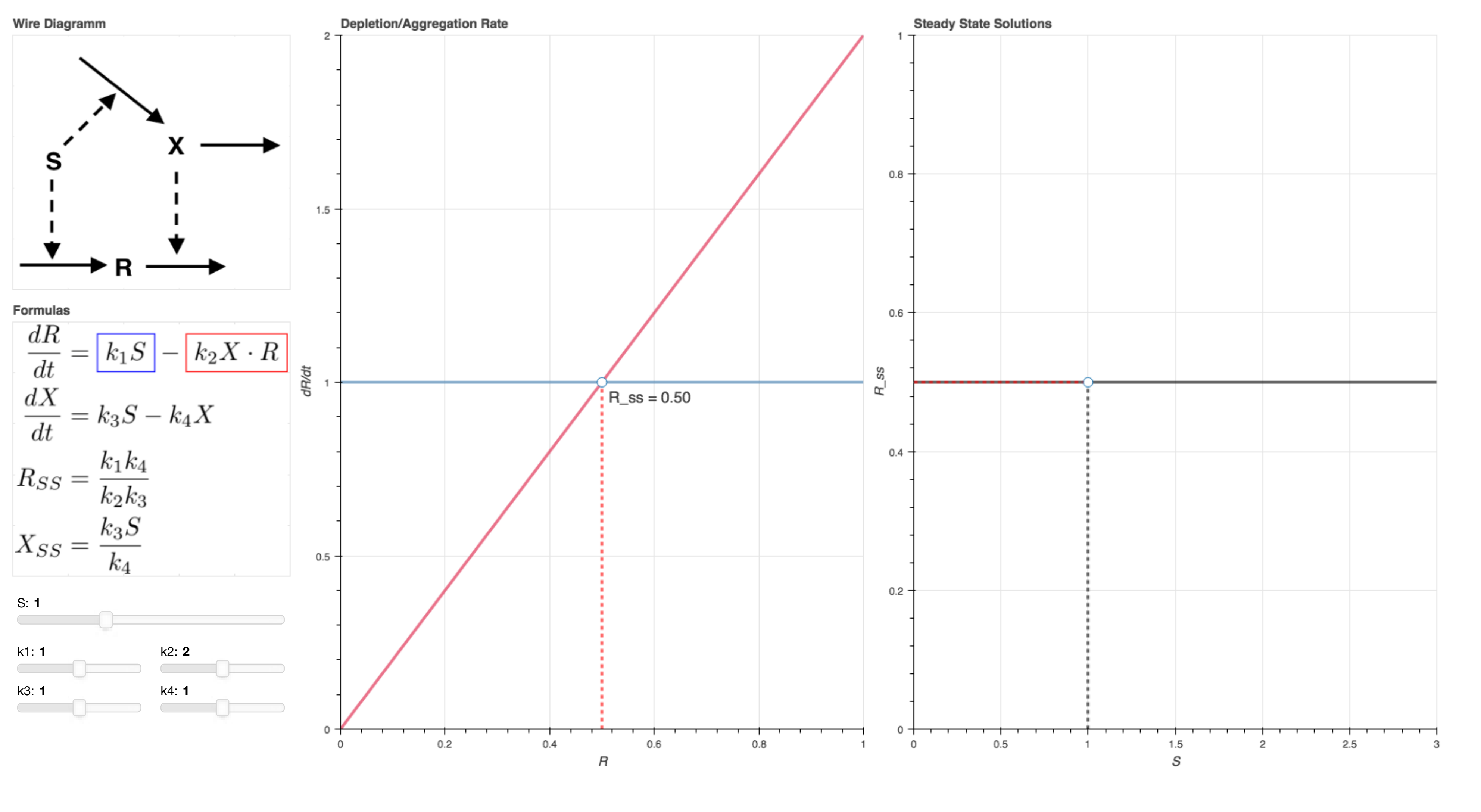
$$\frac{dR}{dt} = \boxed{k_1 S} - \boxed{k_2 X \cdot R}$$

$$\frac{dX}{dt} = k_3 S - k_4 X$$

$$R_{SS} = \frac{k_1 k_4}{k_2 k_3}$$

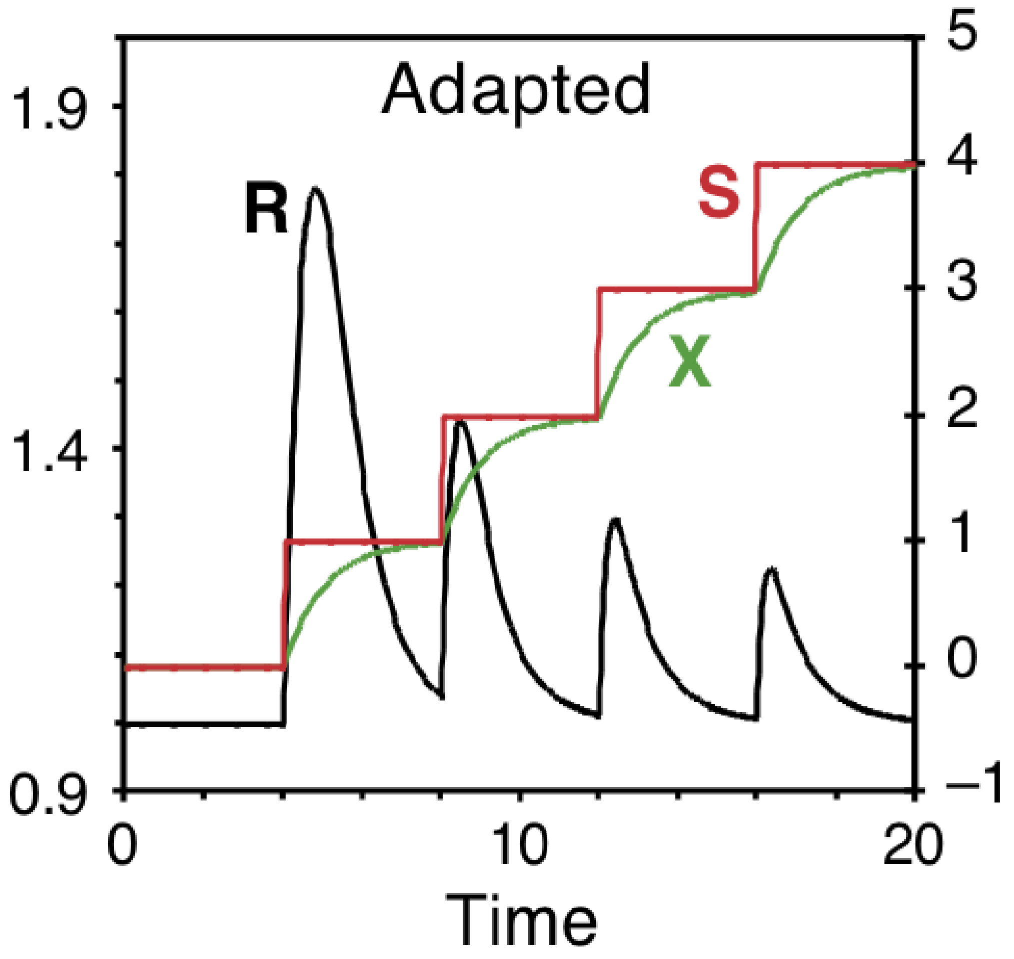
$$X_{SS} = \frac{k_3 S}{k_4}$$

SNIFFER



Wire Diagramm
S
X
R
Formulas
$\frac{dR}{dt} = \boxed{k_1 S} - \boxed{k_2 X \cdot R}$
$\frac{dX}{dt} = k_3 S - k_4 X$
$R_{SS} = \frac{k_1 k_4}{k_2 k_3}$
$X_{SS} = \frac{k_3 S}{k_4}$
S: 1
k1: 1
k2: 2
k3: 1
k4: 1
Depletion/Aggregation Rate
dR/dt
R
R_ss = 0.50
0
0.2
0.4
0.6
0.8
1
0.5
1.5
2
Steady State Solutions
R_ss
S
0
0.2
0.4
0.6
0.8
1
0.5
1.5
2
2.5
3

SNIFFER



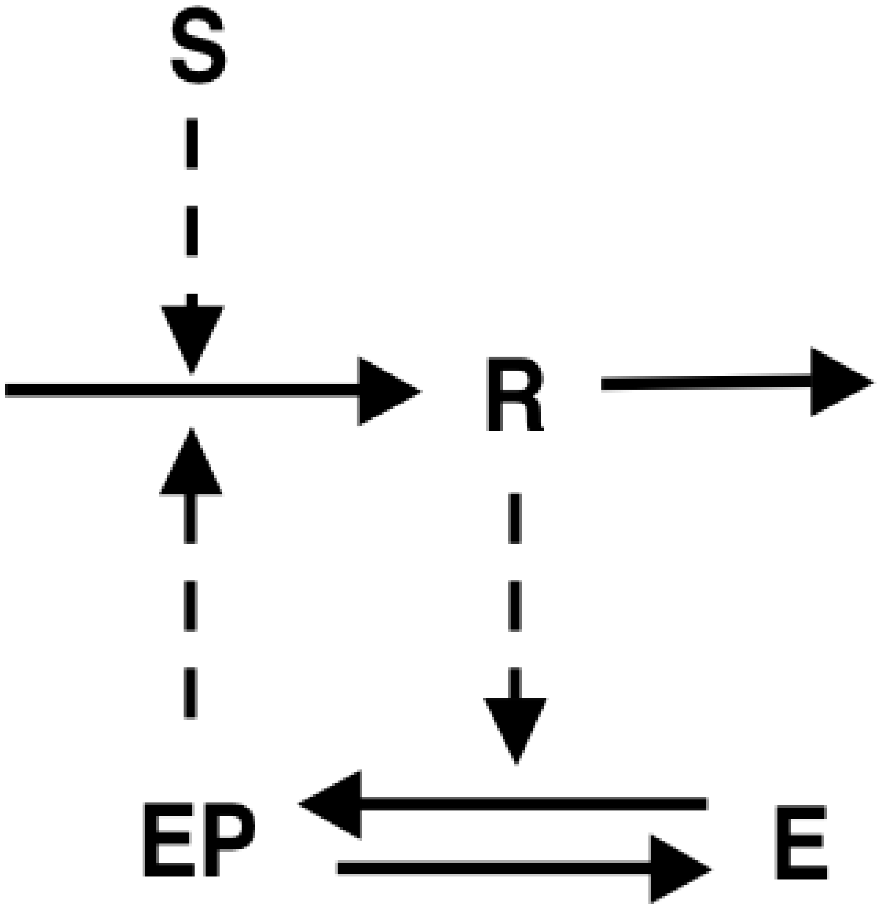
$$\frac{dR}{dt} = \boxed{k_1 S} - \boxed{k_2 X \cdot R}$$

$$\frac{dX}{dt} = k_3 S - k_4 X$$

$$R_{SS} = \frac{k_1 k_4}{k_2 k_3}$$

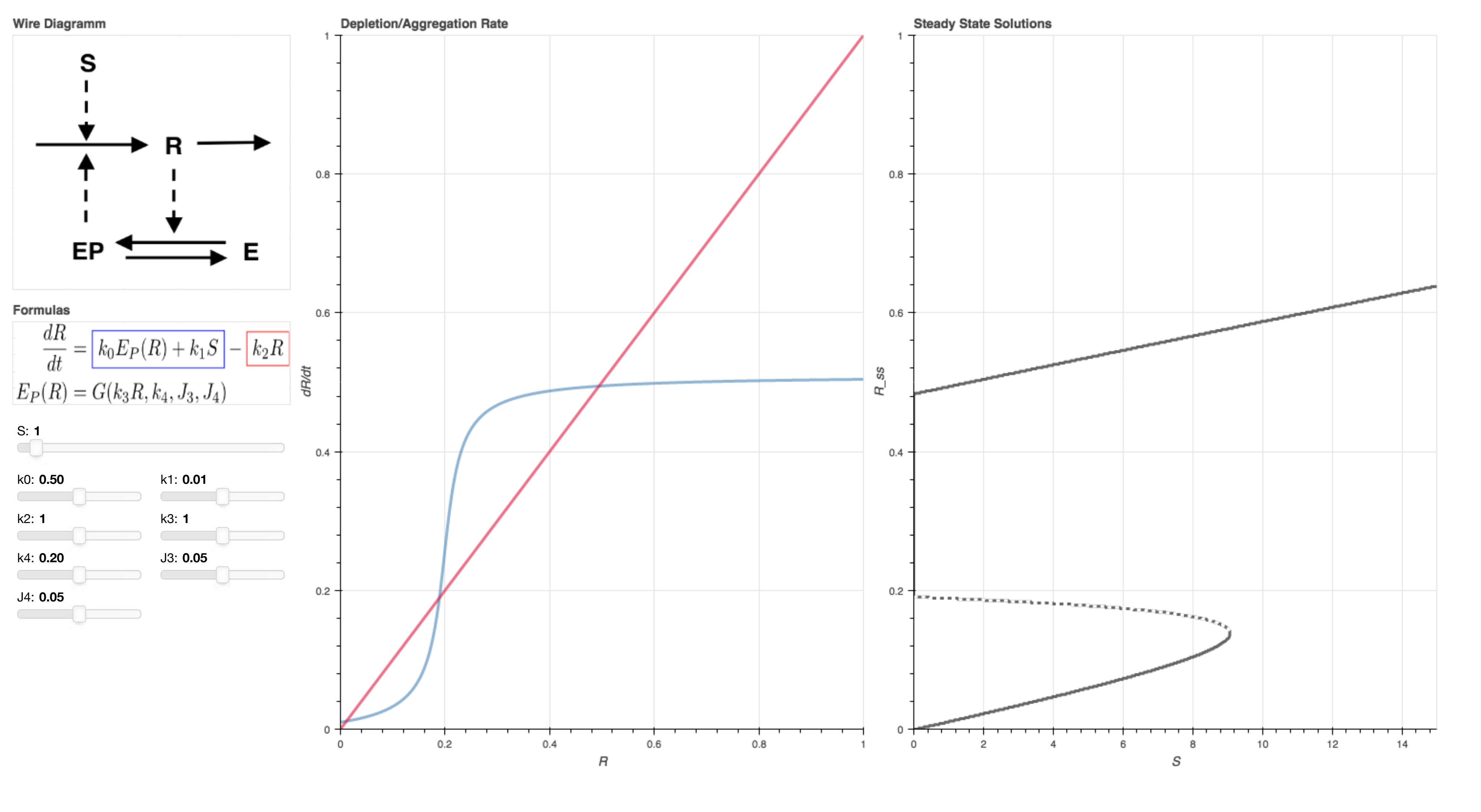
$$X_{SS} = \frac{k_3 S}{k_4}$$

IRREVERSIBLE SWITCH



$$\frac{dR}{dt} = \boxed{k_0 E_P(R) + k_1 S} - \boxed{k_2 R}$$
$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

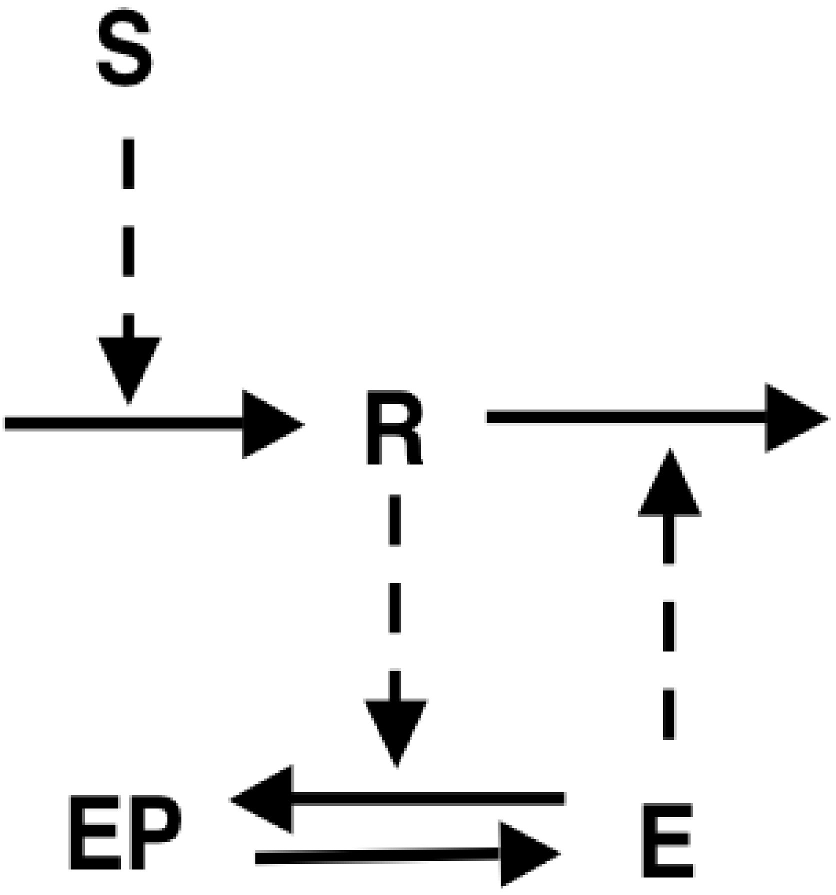
IRREVERSIBLE SWITCH



REVERSIBLE SWITCH

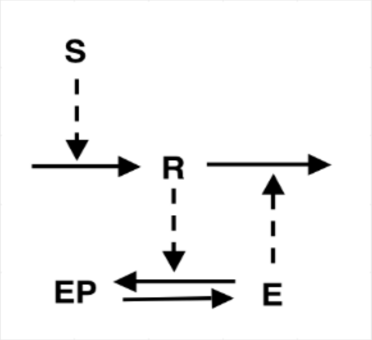
$$\frac{dR}{dt} = \boxed{k_0 + k_1 S} - \boxed{(k_2 R + k_2' E_P(R) \cdot R)}$$

$$E_P(R) = G(k_3, k_4 R, J_3, J_4)$$



REVERSIBLE SWITCH

Wire Diagramm



Formulas

$$\frac{dR}{dt} = \boxed{k_0 + k_1 S} - \boxed{(k_2 R + k_2' E_P(R) \cdot R)}$$

$$E_P(R) = G(k_3, k_4 R, J_3, J_4)$$

S: **1**

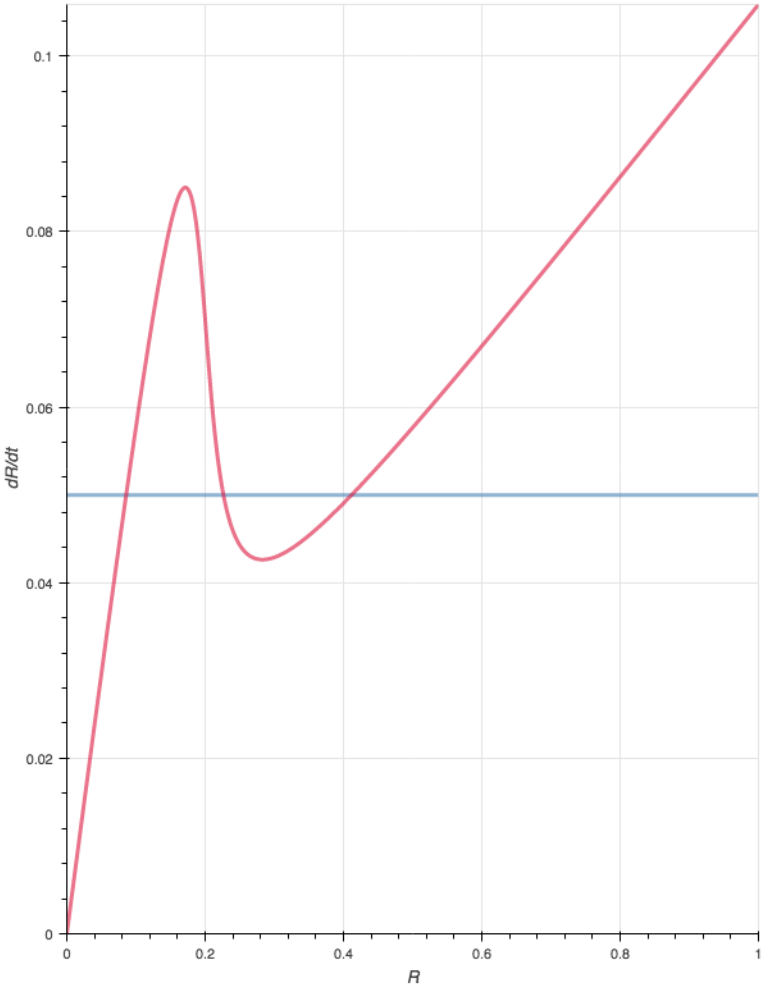
k0: **0**　k1: **0.05**

k2: **0.10**　k2_: **0.50**

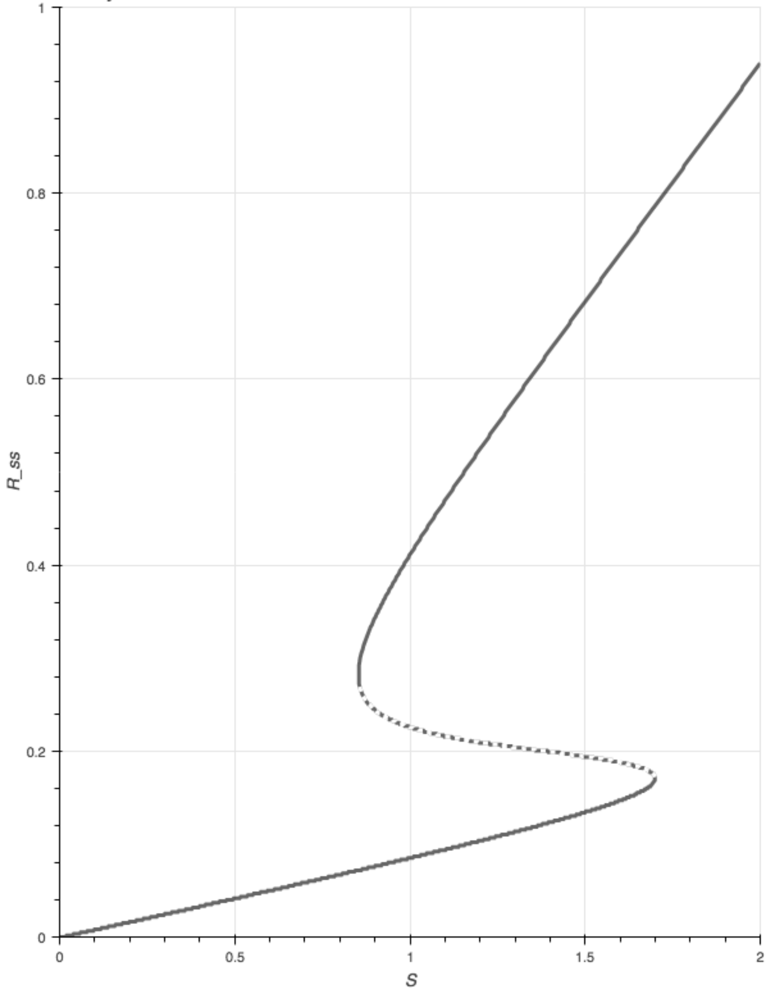
k3: **0.10**　k4: **0.50**

J3: **0.05**　J4: **0.05**

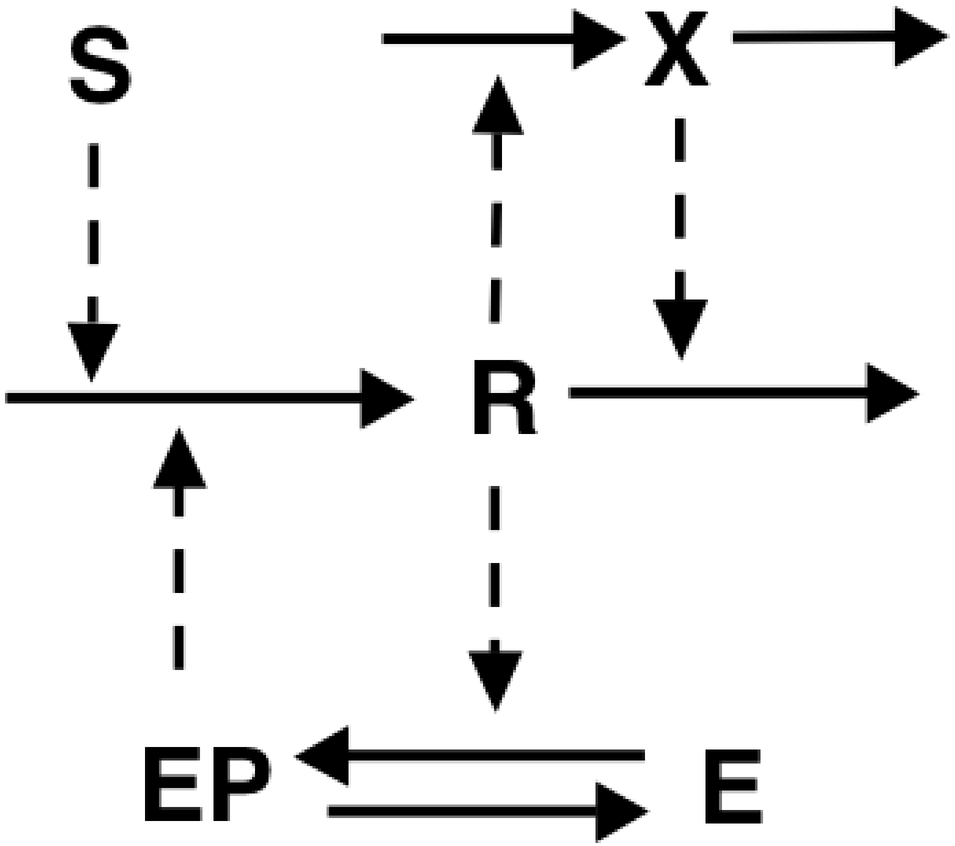
Depletion/Aggregation Rate



Steady State Solutions



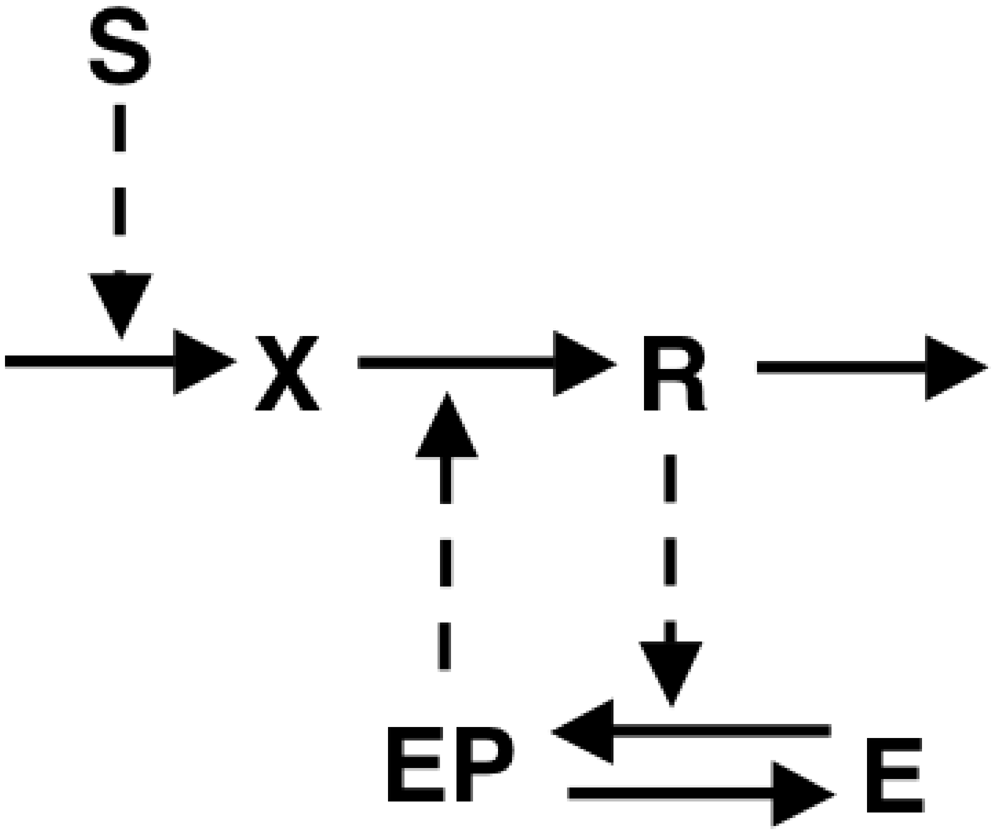
POSITIVE FEEDBACK OSCILLATOR



$$\frac{dR}{dt} = \boxed{k_0 E_P(R) + k_1 S - k_2 R - k_2' X \cdot R}$$
$$\frac{dX}{dt} = \boxed{k_5 R - k_6 X}$$
$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

POSITIVE FEEDBACK OSCILLATOR

NEGATIVE FEEDBACK OSCILLATOR



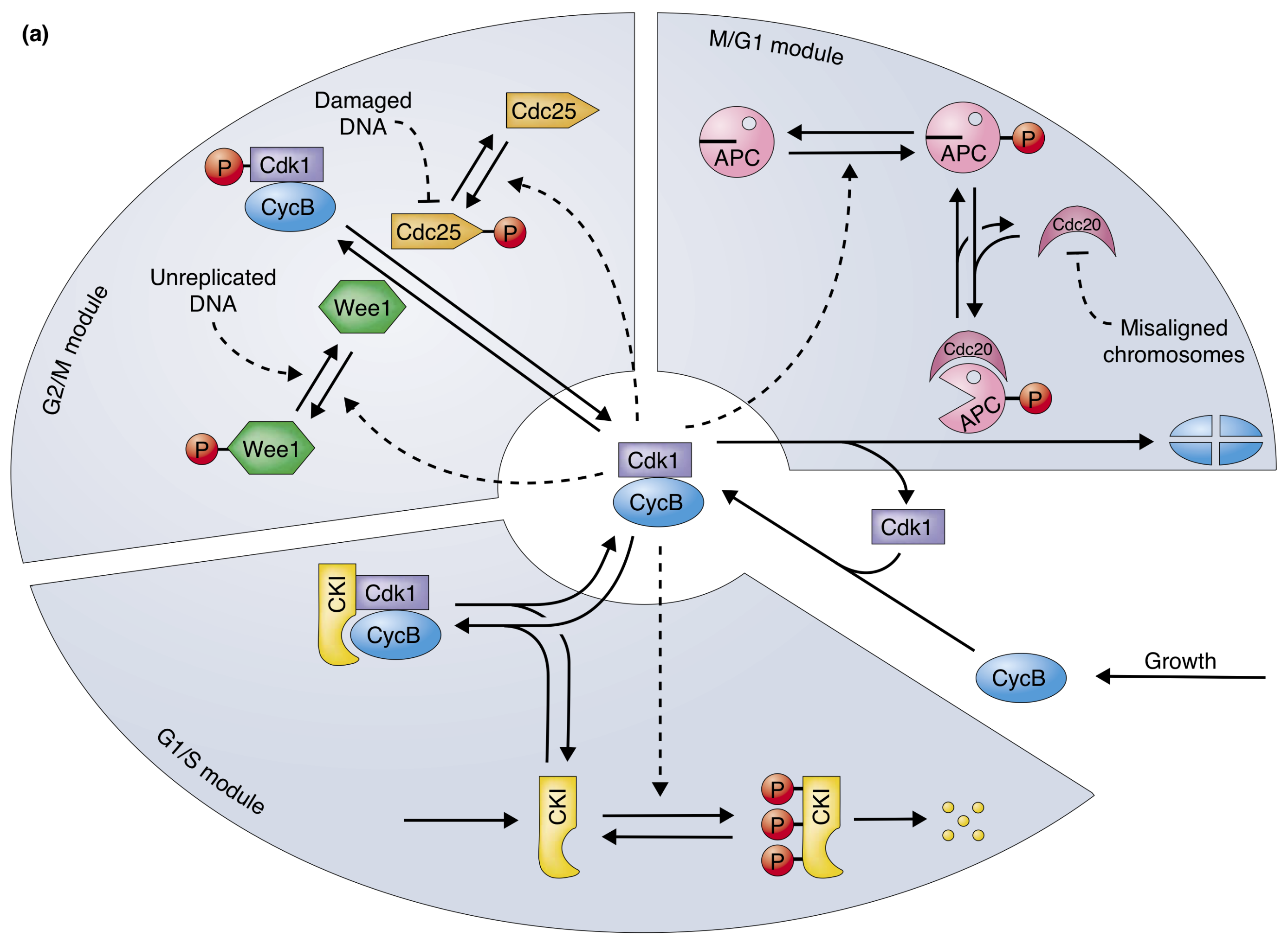
$$\frac{dR}{dt} = \boxed{[k_0' + k_0 E_P(R)] \cdot X - k_2 R}$$

$$\frac{dX}{dt} = \boxed{k_1 S - [k_0' + k_0 E_P(R)] \cdot X}$$

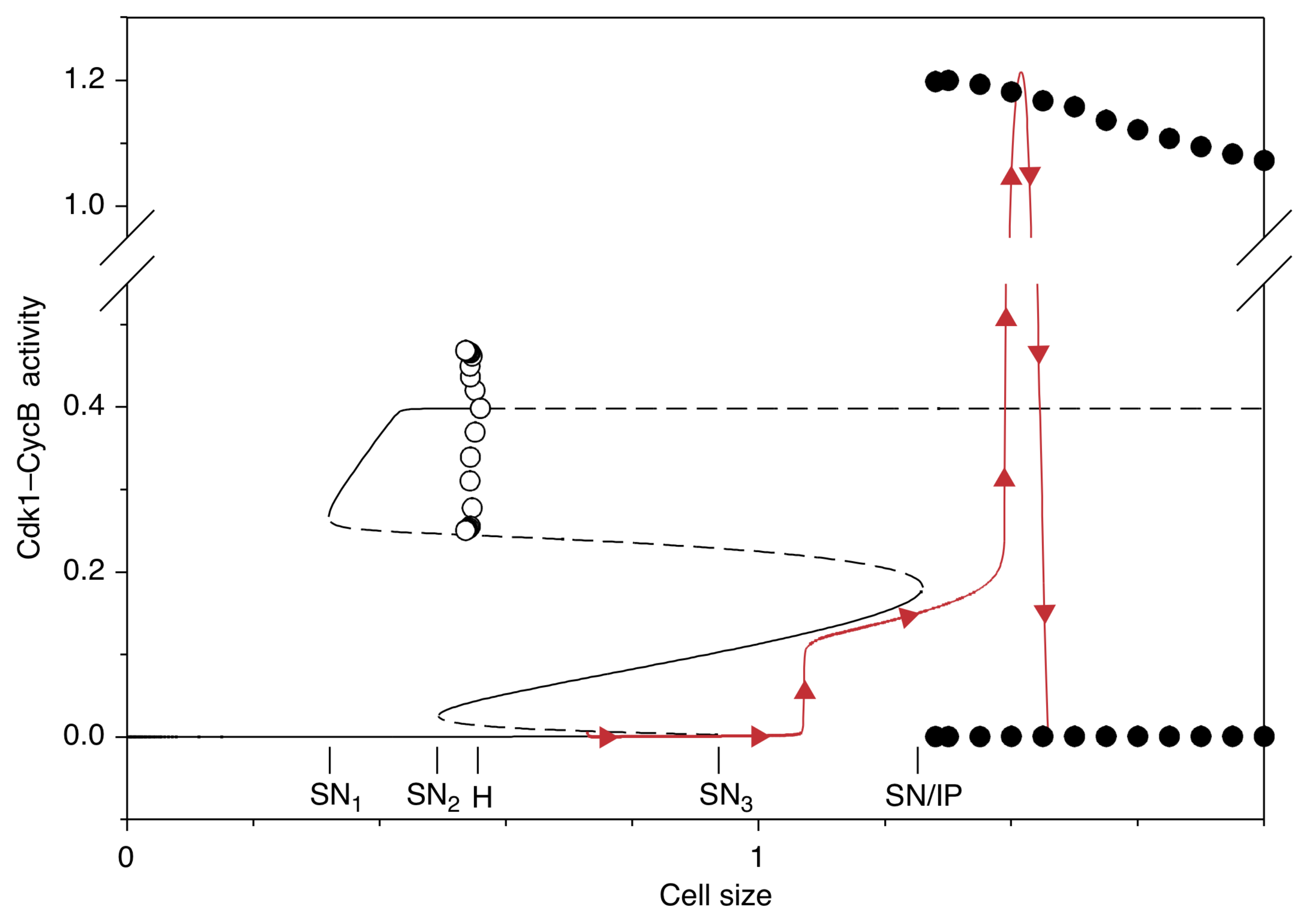
$$E_P(R) = G(k_3 R, k_4, J_3, J_4)$$

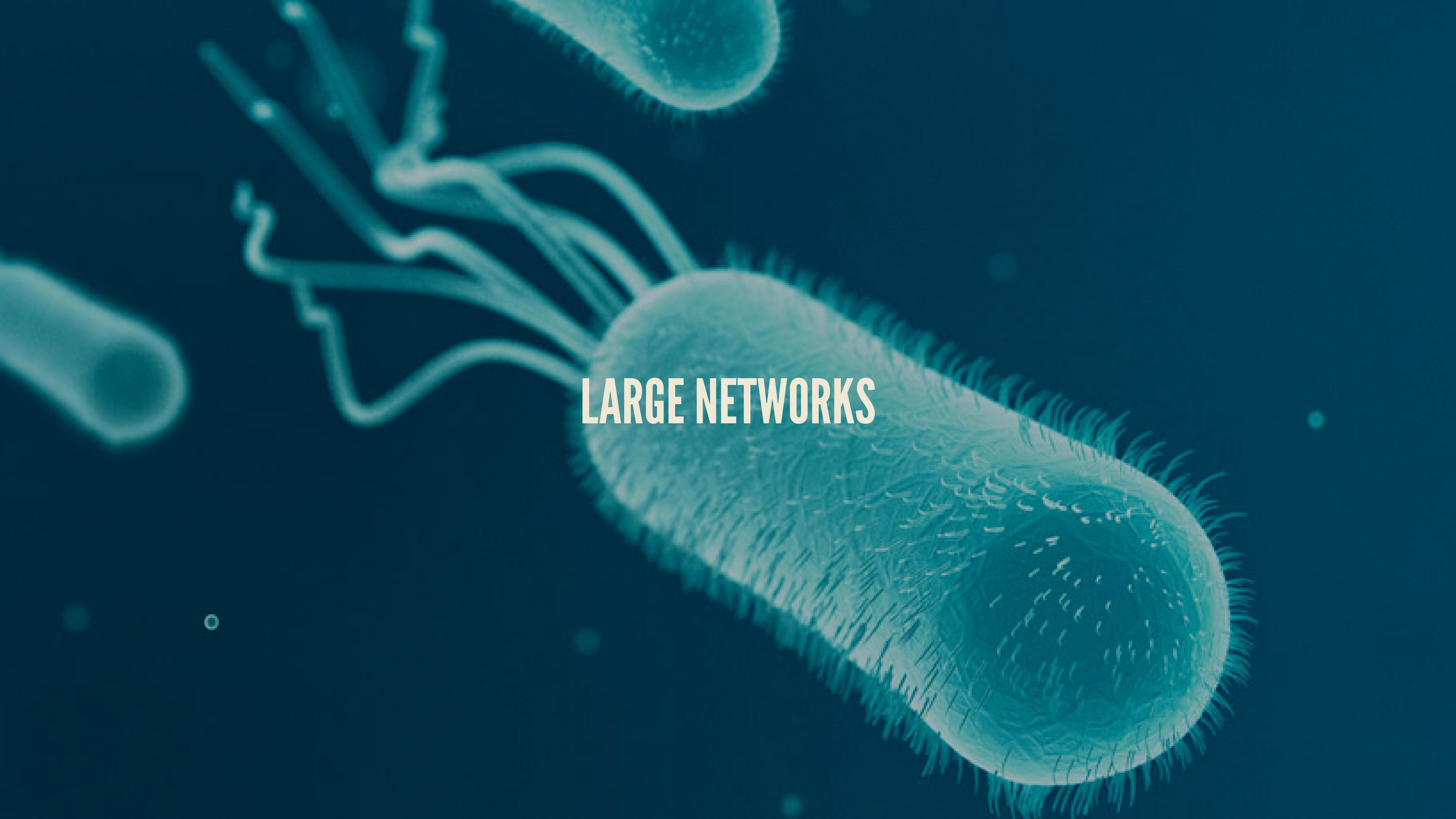
NEGATIVE FEEDBACK OSCILLATOR

LARGE NETWORK EXAMPLE



LARGE NETWORK EXAMPLE





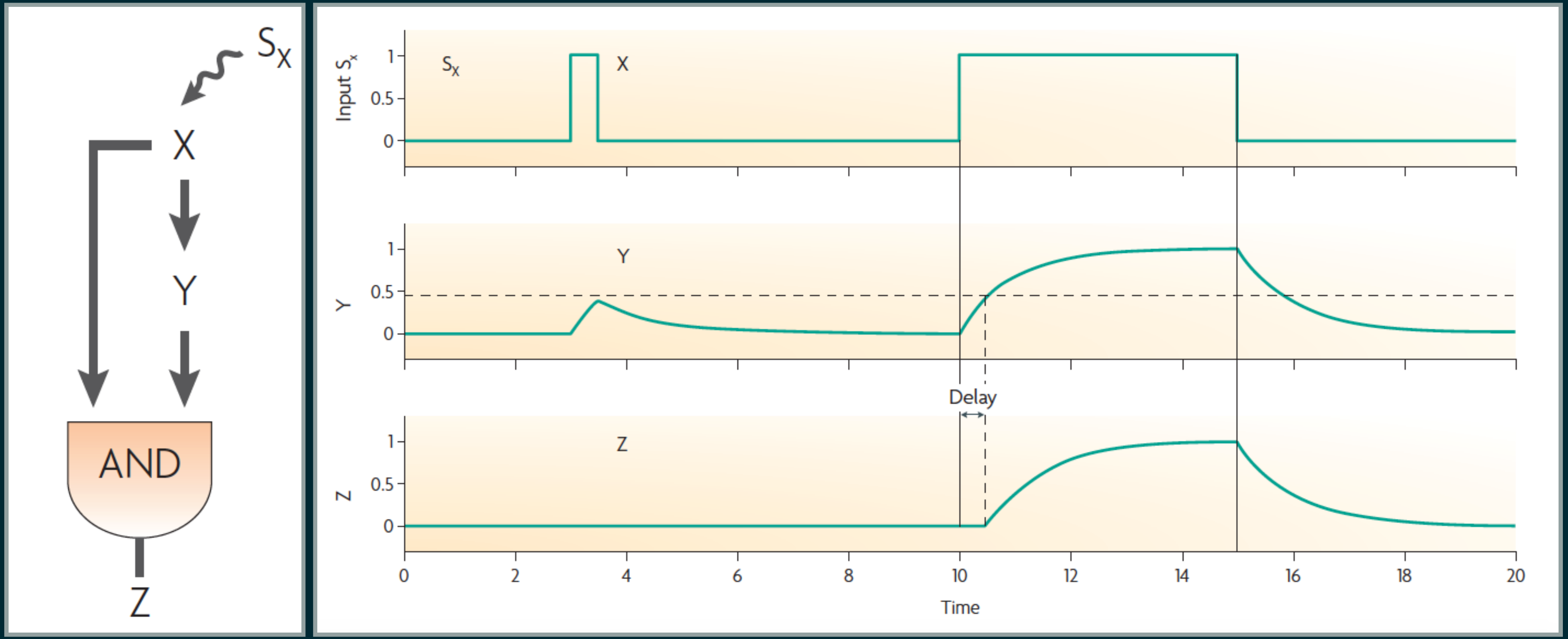
LARGE NETWORKS

LOGIC OPERATORS

There are different ways how X and Y can be integrated to regulate the Z promoter

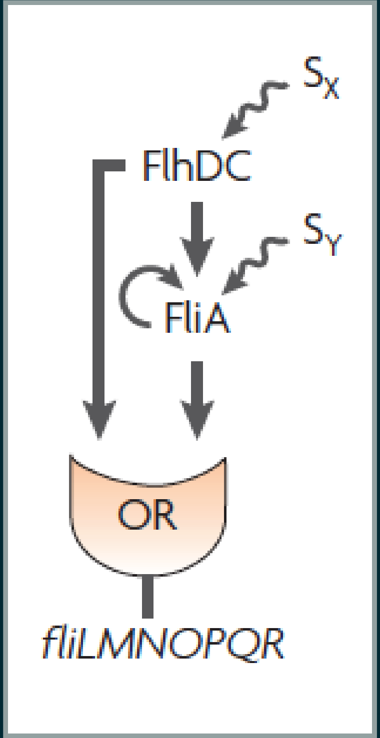
Two common input functions are the **AND** gate and **OR** gate.

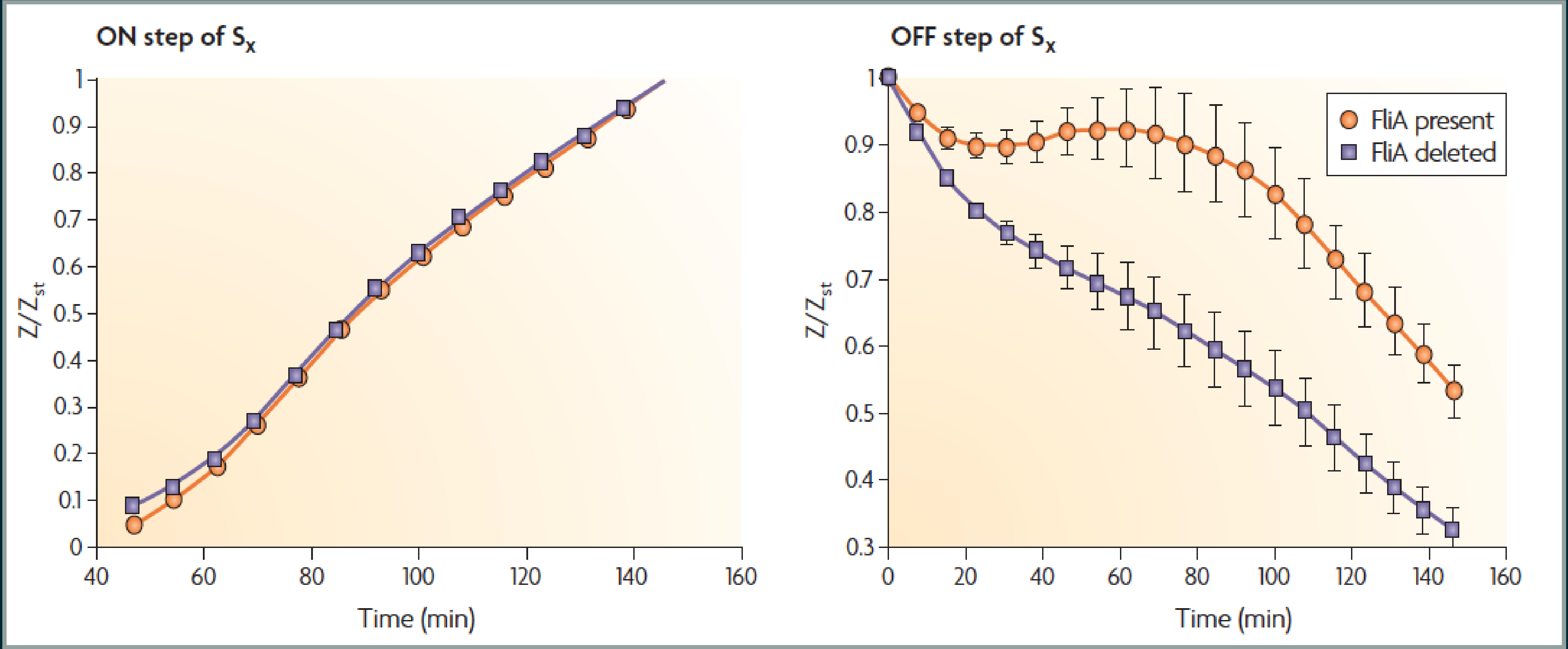
AND GATE



S_X
X
Y
AND
Z
Input S_x
1
0.5
0
S_X
X
Y
Delay
Z
0
2
4
6
8
10
12
14
16
18
20
Time

OR GATE


S_X
FlhDC
S_Y
FliA
OR
fliLMNOPQR


ON step of S_X
OFF step of S_X
Z/Z_{st}
Time (min)
FliA present
FliA deleted

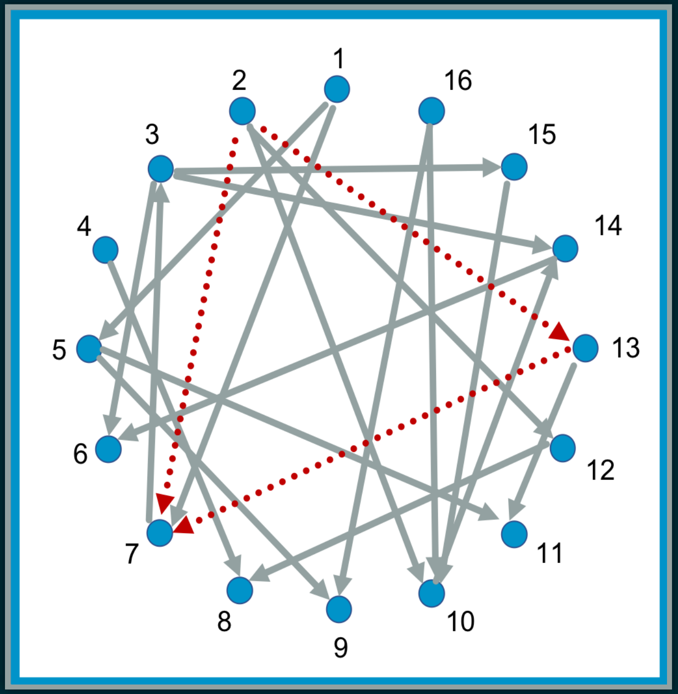
DETECTION OF NETWORK MOTIFS

Theoretically and Experimentally

FINDING NETWORK MOTIFS THEORETICALLY

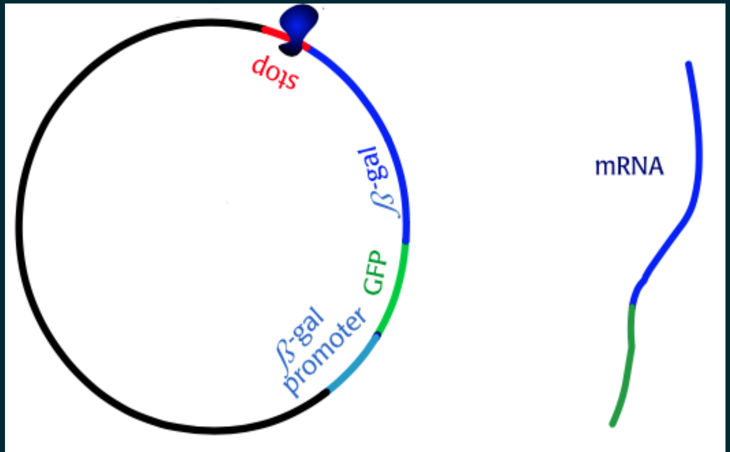
Algorithm to detect network motifs:

- Create a network with same number of nodes as the real network
- Assign the same number of incoming and outgoing edges to each node
  as has the corresponding node in the real network
- Scan network for all possible n-node subgraphs and record the number
  of occurrences of each subgraph
- Compare probabilities → cut-off probability



STUDY NETWORK MOTIFS EXPERIMENTALLY

- Measure the transcriptional activity of promoters by means of reporter genes
- Widely used: Green Fluorescent Protein (GFP)
- Promoter activation is detected by increased fluorescent signal
- Fast-folding GFP variants become fluorescent within minutes after transcription initiation



CONCLUSION

CONCLUSION

- Complex biological networks contain a limited set of network motifs
- Networks can be broken down into smaller understandable motifs
- Certain network motifs have been selected again and again in evolution
- Mathematical modeling has helped to define functions of network motifs
- How do network motifs work in large networks?
- Further research on other networks

THANK YOU FOR LISTENING!

LITERATURE

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- Tyson, John J., Katherine C. Chen, and Bela Novak. "Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell." *Current opinion in cell biology* 15.2 (2003): 221-231.
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- Kalir, Shiraz, Shmoolik Mangan, and Uri Alon. "A coherent feed–forward loop with a SUM input function prolongs flagella expression in Escherichia coli." *Molecular systems biology* 1.1 (2005).
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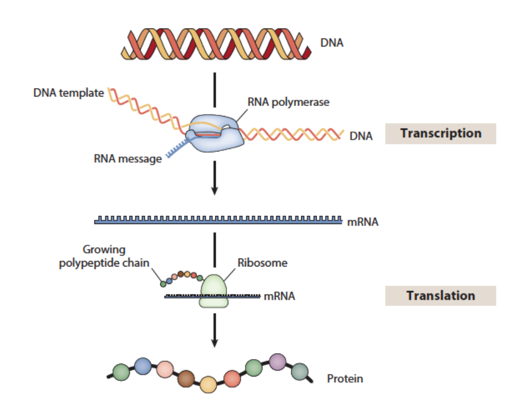
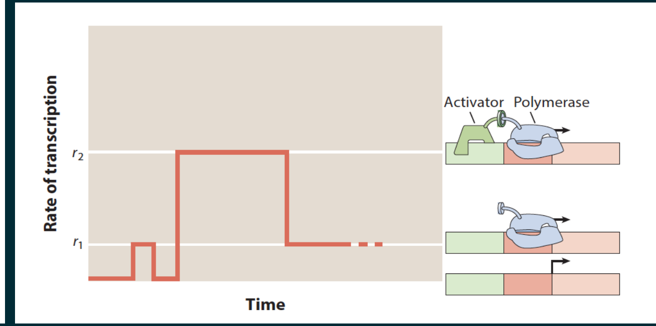
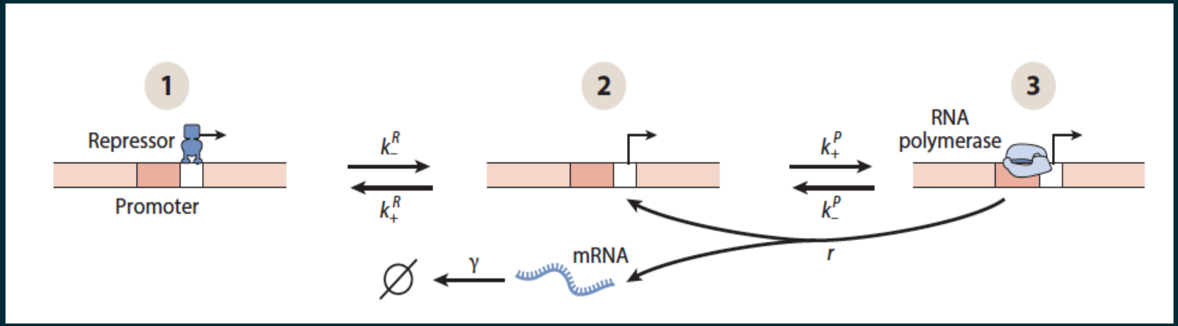
- Uri Alon. "Network Motifs." URL: https://www.weizmann.ac.il/mcb/UriAlon/research/network-motifs (19.06.2018)

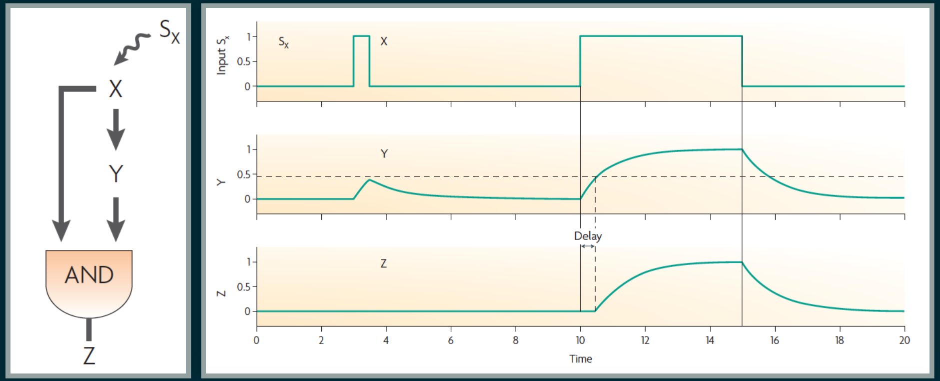
PICTURES

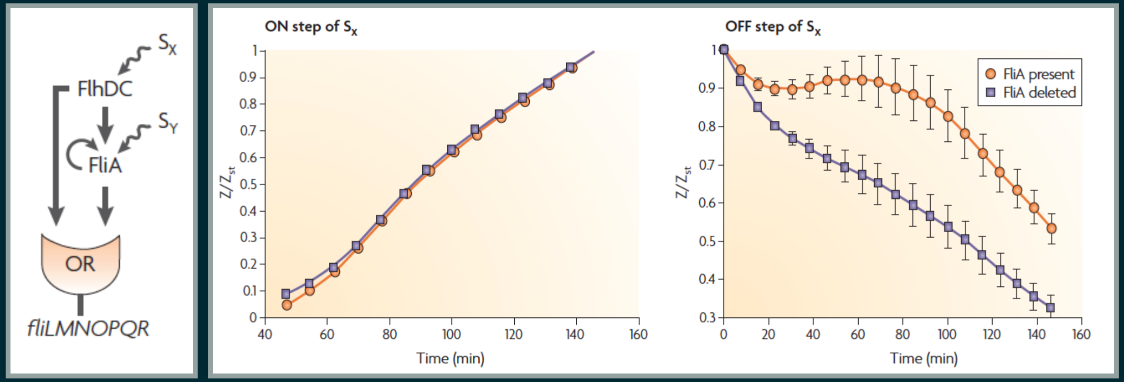




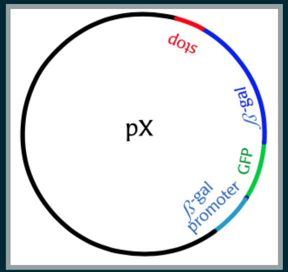


Phillips, Rob. "Napoleon is in equilibrium." *Annu. Rev. Condens. Matter Phys.* 6.1 (2015): 85-111.





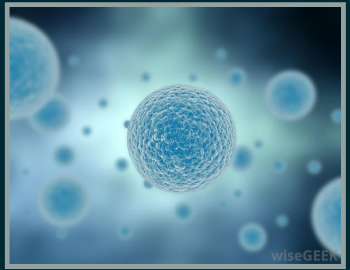
Alon, Uri. "Network motifs: theory and experimental approaches." *Nature Reviews Genetics* 8.6 (2007): 450



- https://www.gettyimages.de/-video/green-jellyfish?sort=most-popular&offlinecontent=include&phrase=green-%20jellyfish

- http://www.dnaftb.org/34/problem.html

- http://tracks.arte.tv/fr/surveillance-deni-de-facies



- https://www.utahpeoples-post.com/2016/10/human-cell-atlas/

- http://tracks.arte.tv/fr/surveillance-deni-de-facies

- https://www.sciencenewsfor-students.org/article/bacteria-help-water-effortlessly-go-flow