Noise, speed and cost in biological networks

How to compute **with** genes

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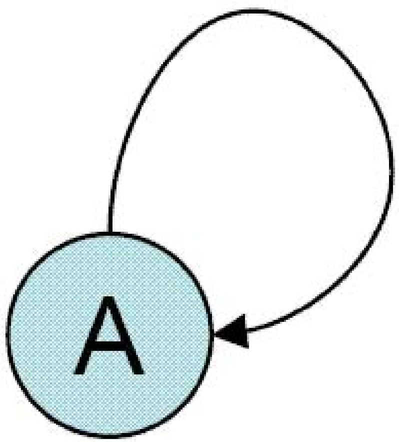
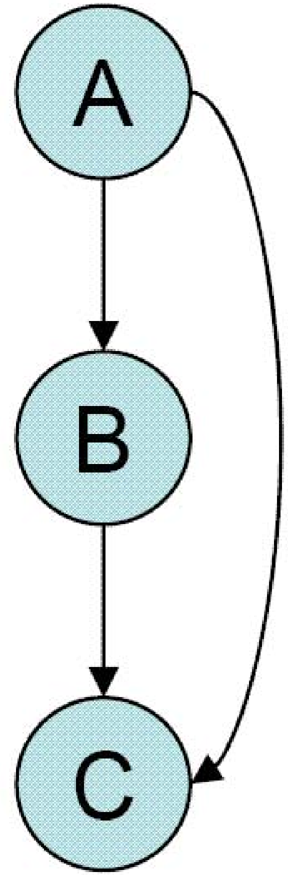
Network motifs in biology



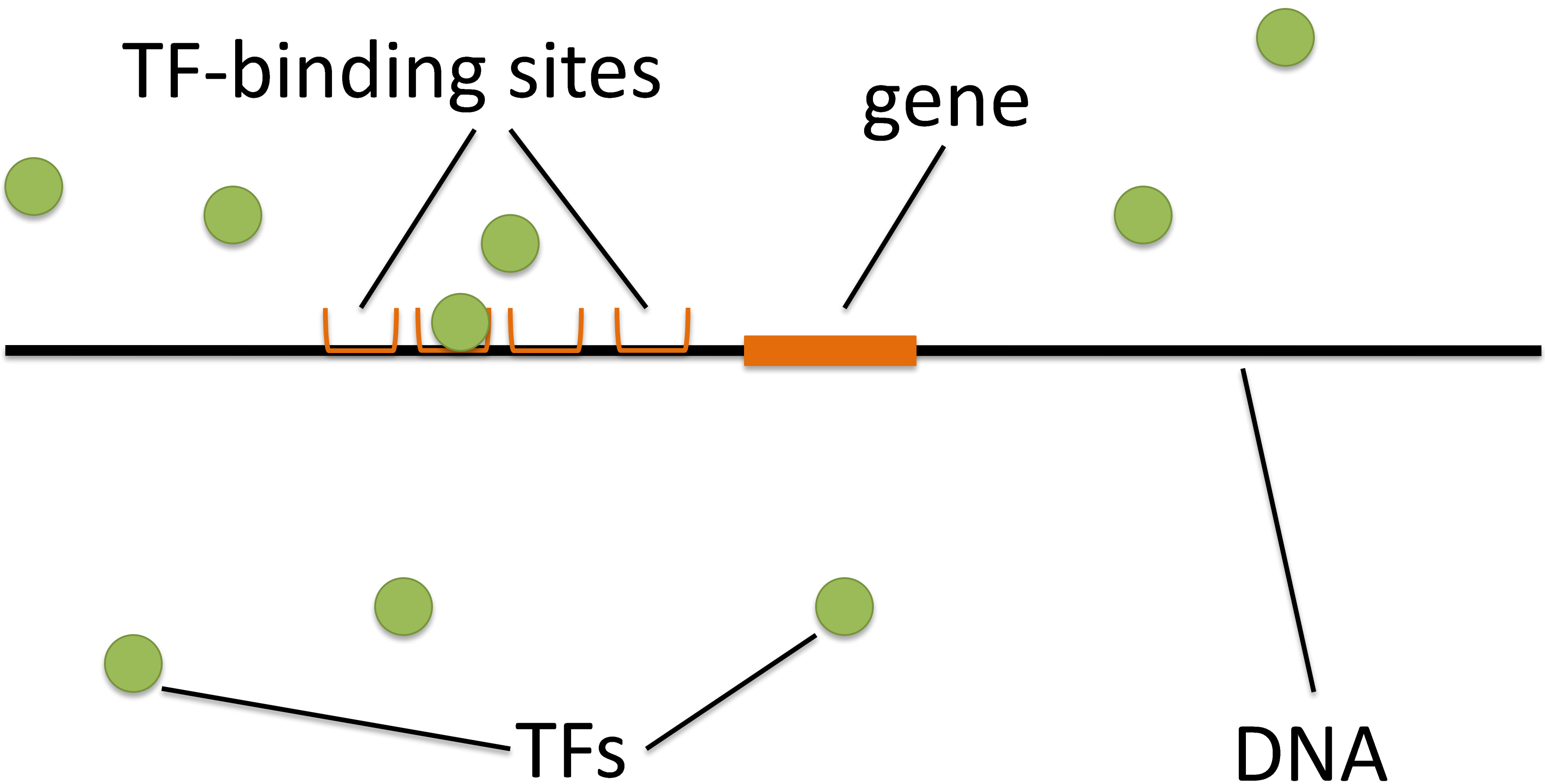


Let us put numbers to the arrows.

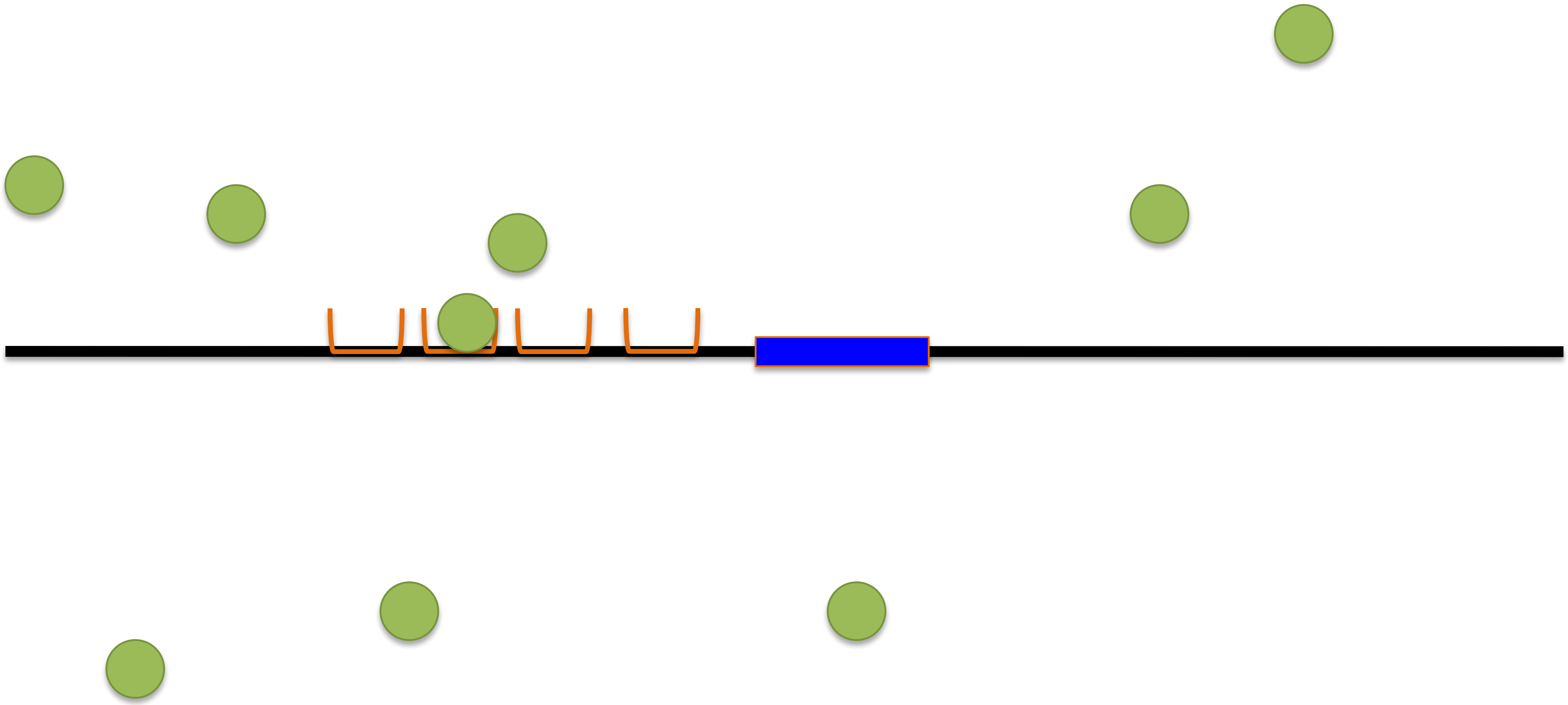
Why do parameters have the values they have?

Simplest possible model system

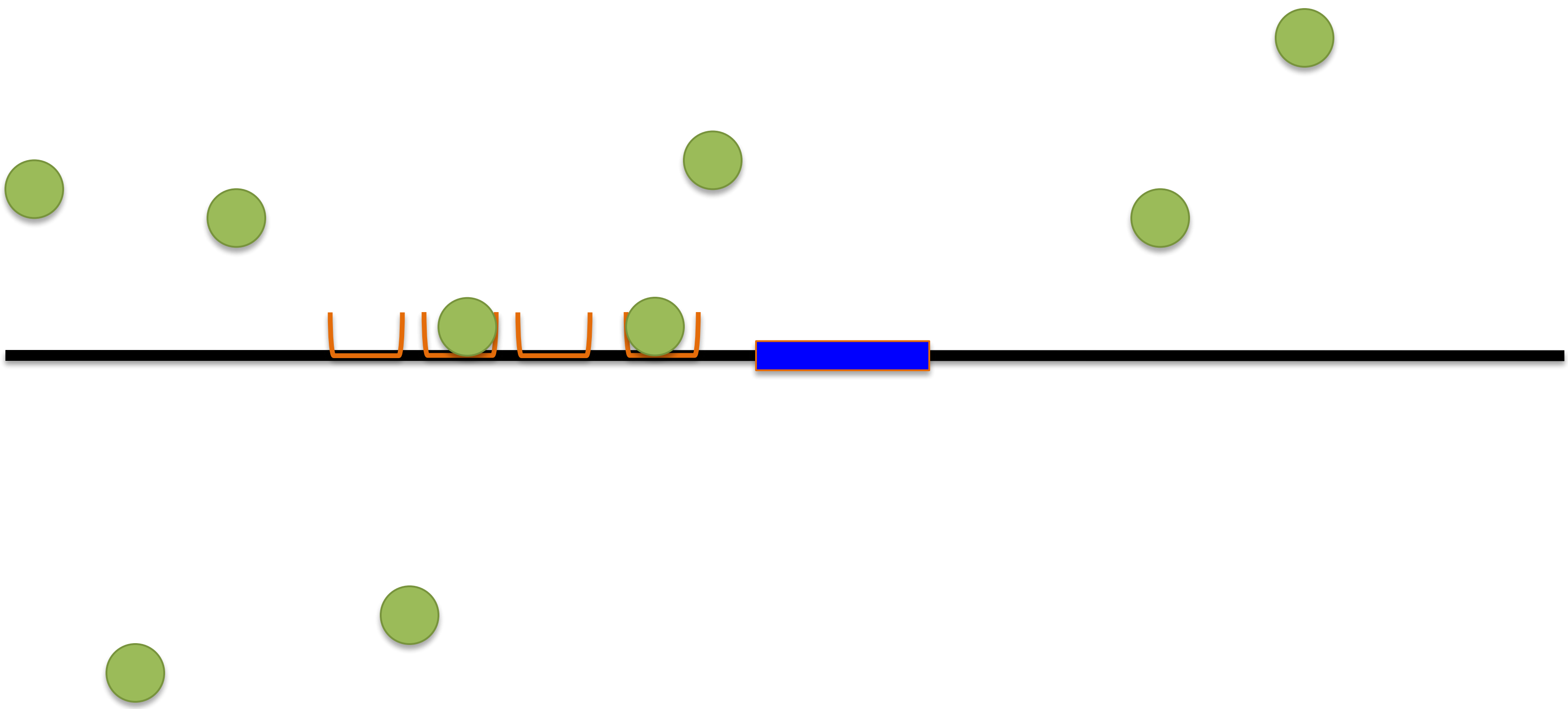
The system: A single gene



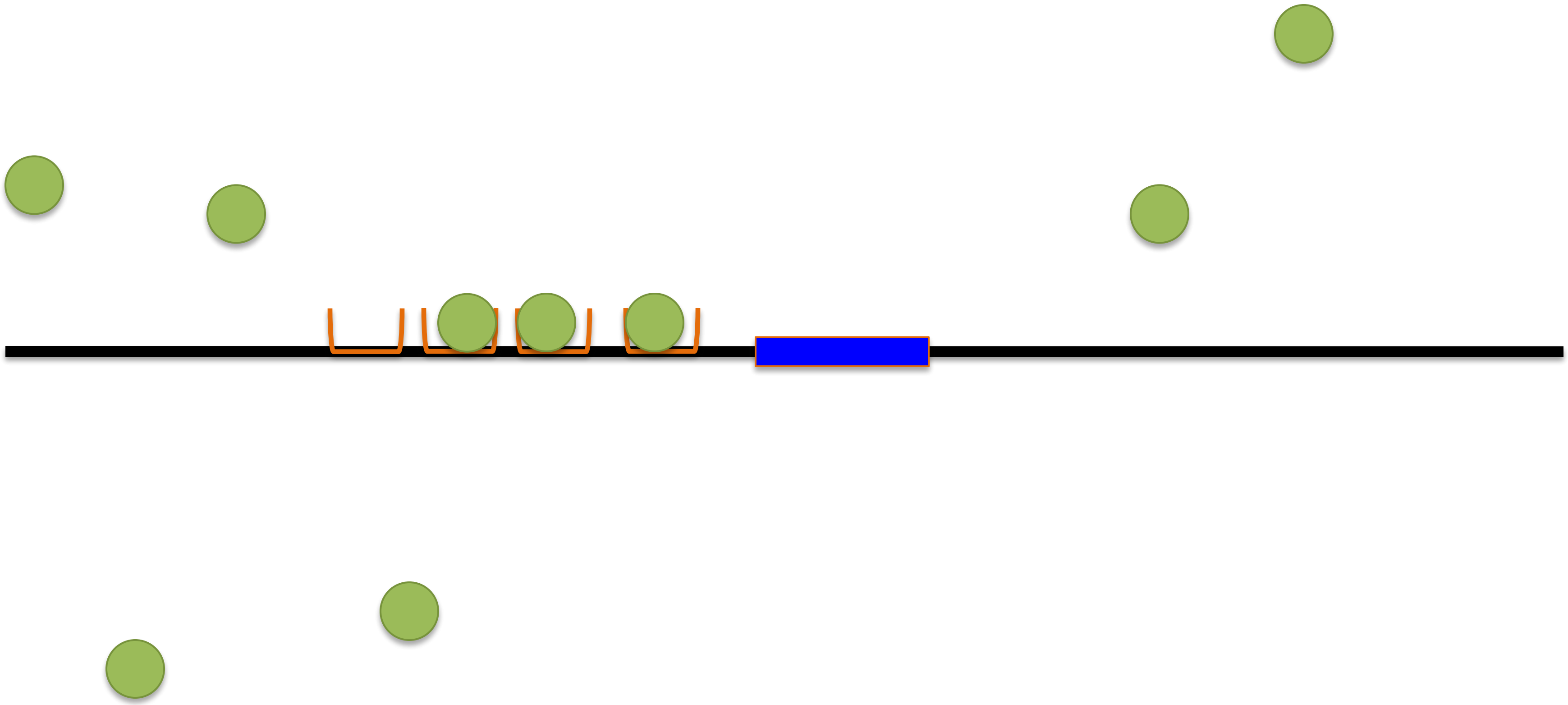
The system



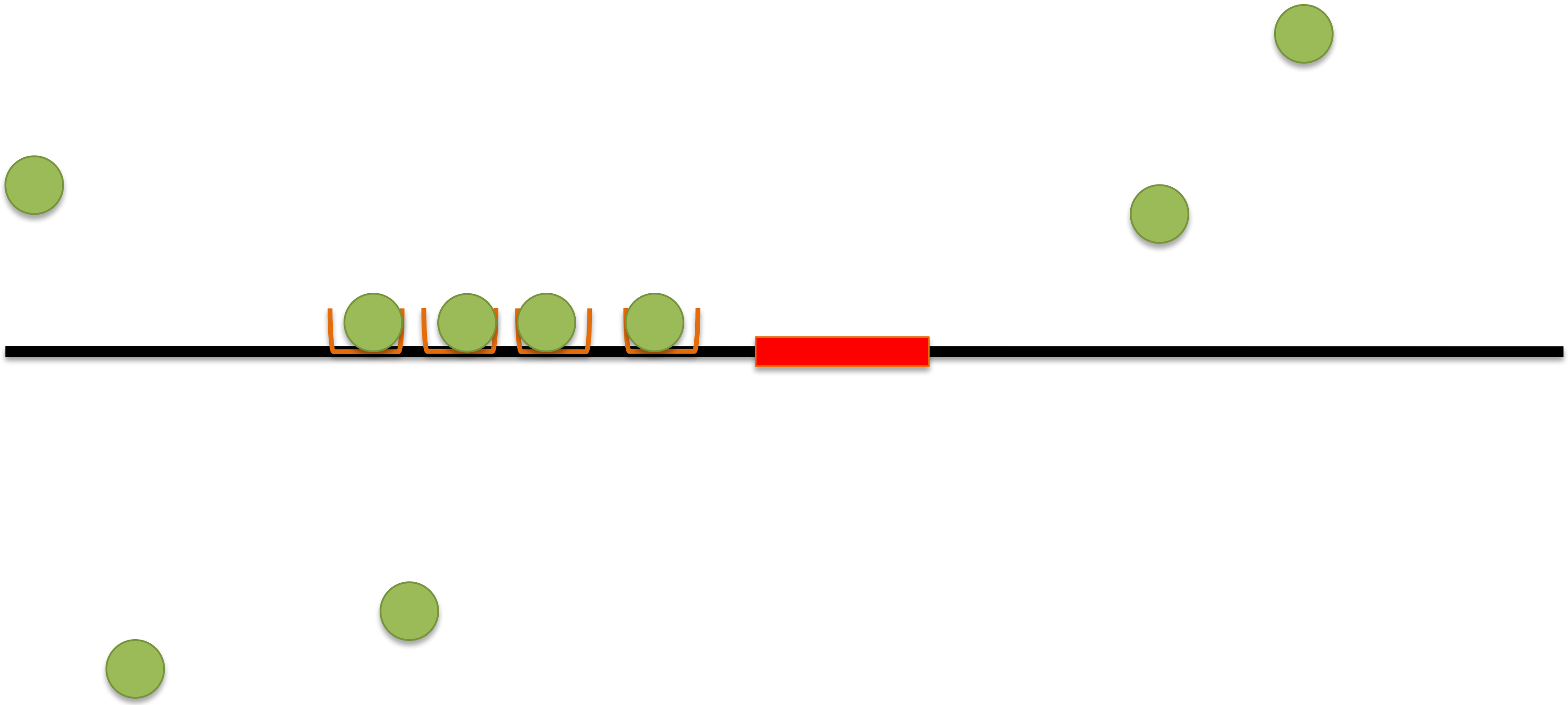
The system



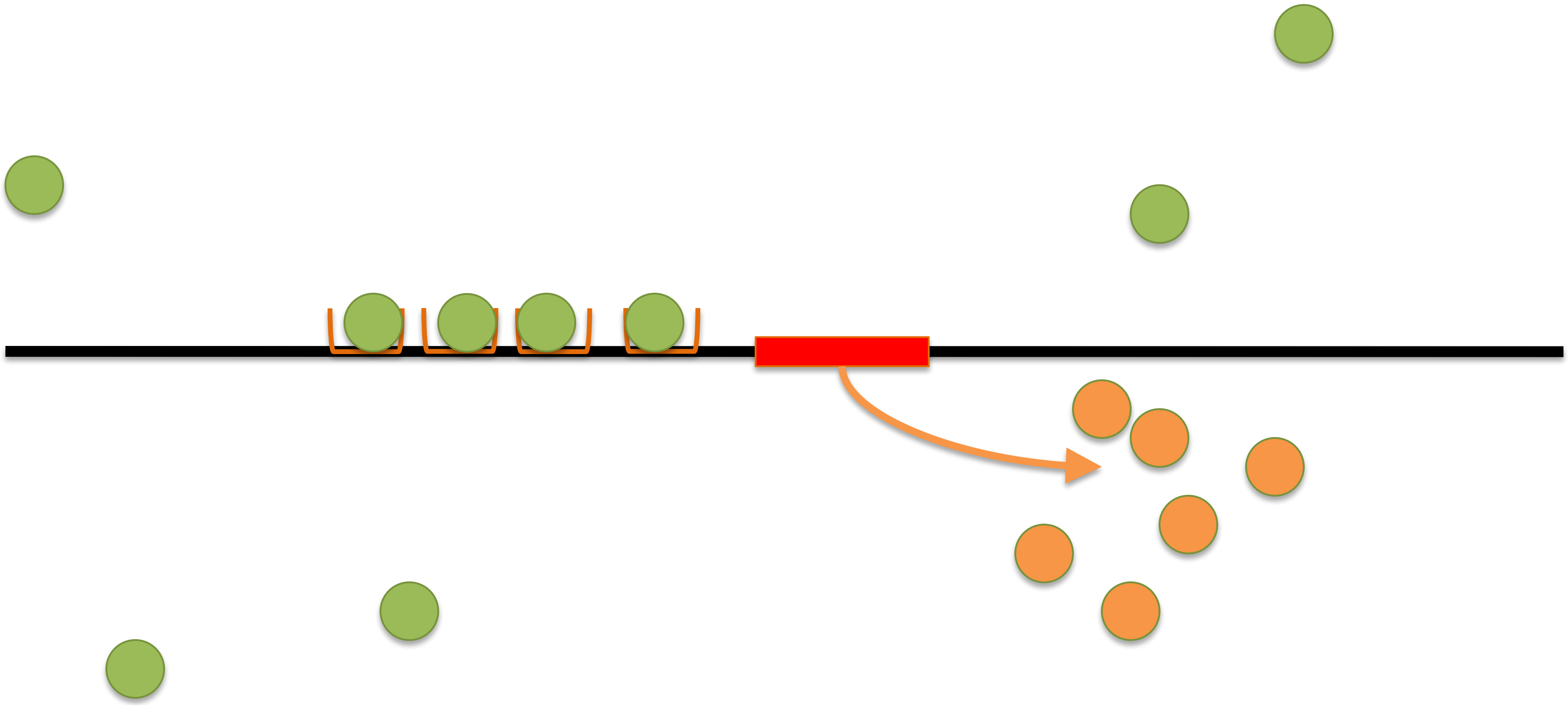
The system



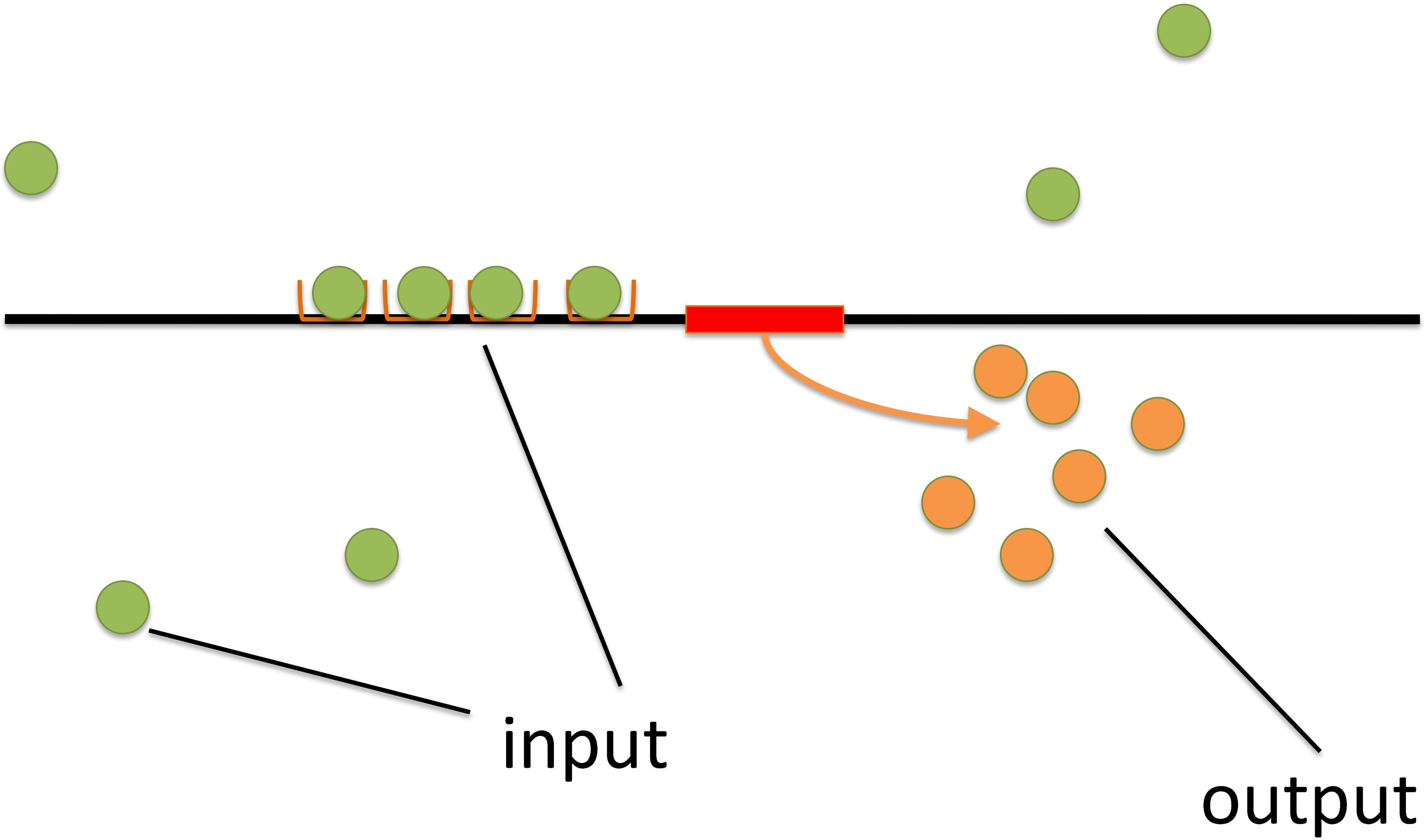
The system



The system



The system



Mathematical description

$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$

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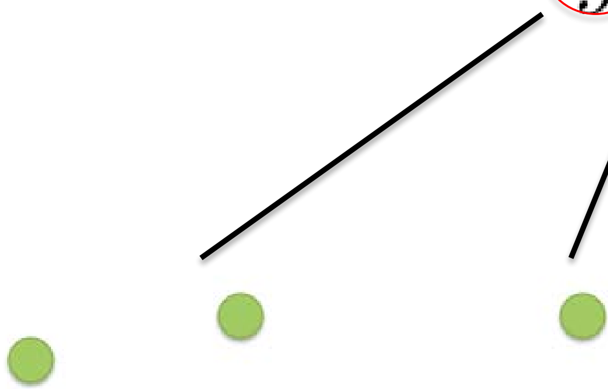
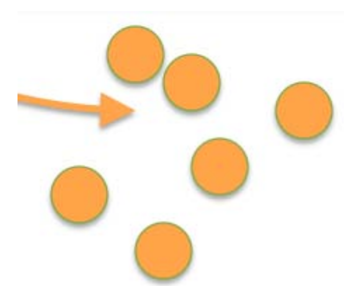
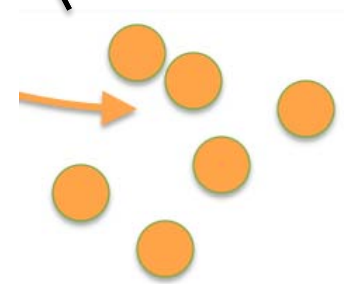


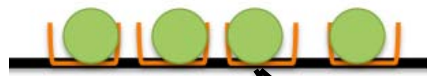


Mathematical description

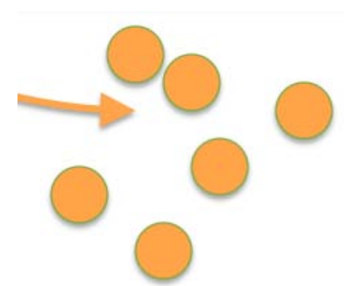
$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$



Mathematical description



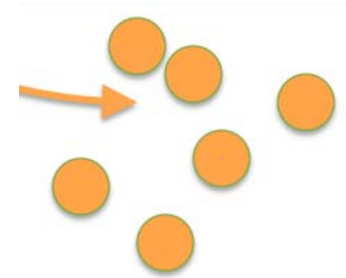
$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$

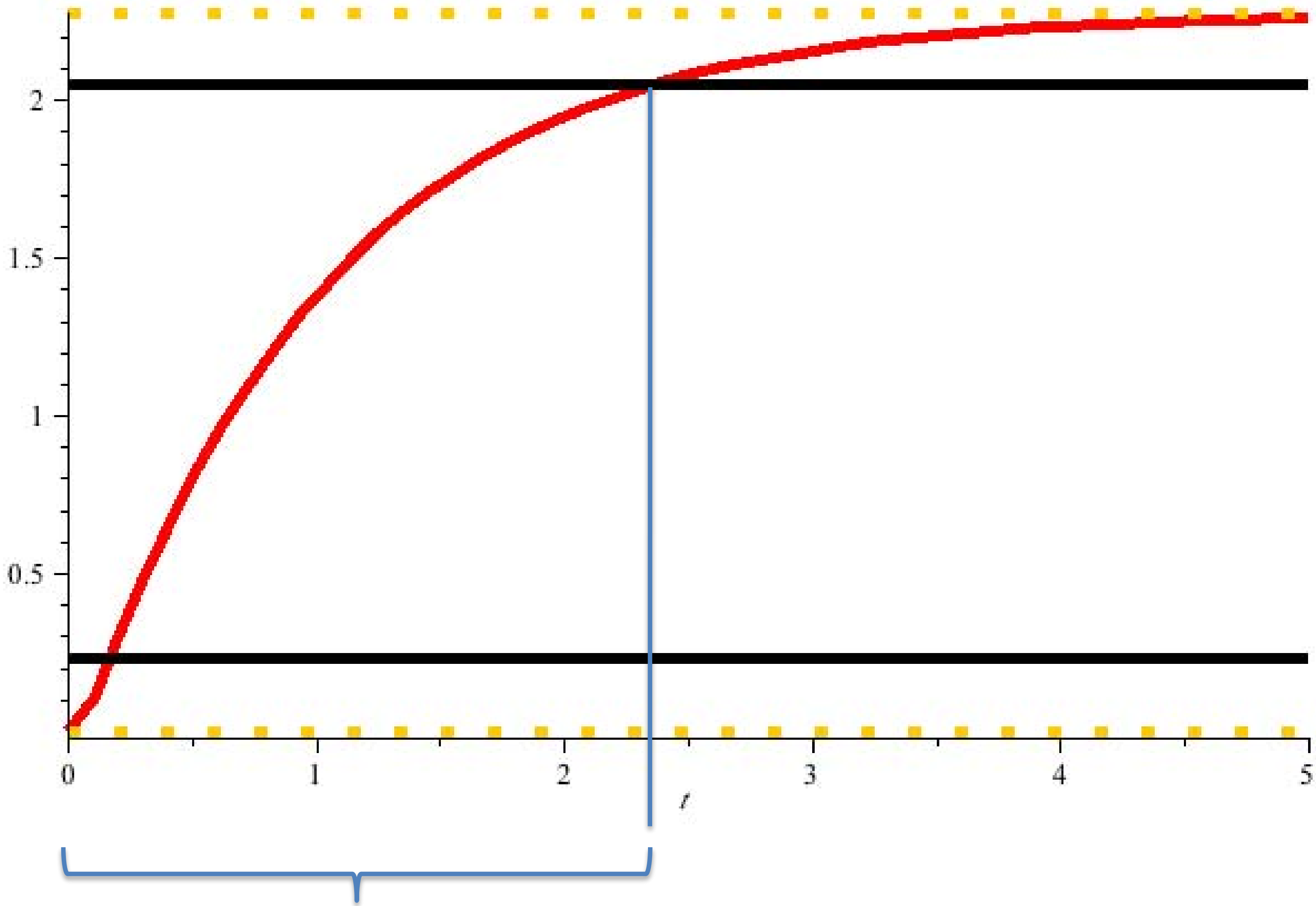


Mathematical description

$$\beta \frac{K^h}{K^h + K^h} = \frac{1}{2}\beta$$

$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$





Time to switch on

Time to switch

$$T(\theta) = \frac{1}{\mu} \ln\left(\frac{1}{1-\theta}\right)$$

We observe:

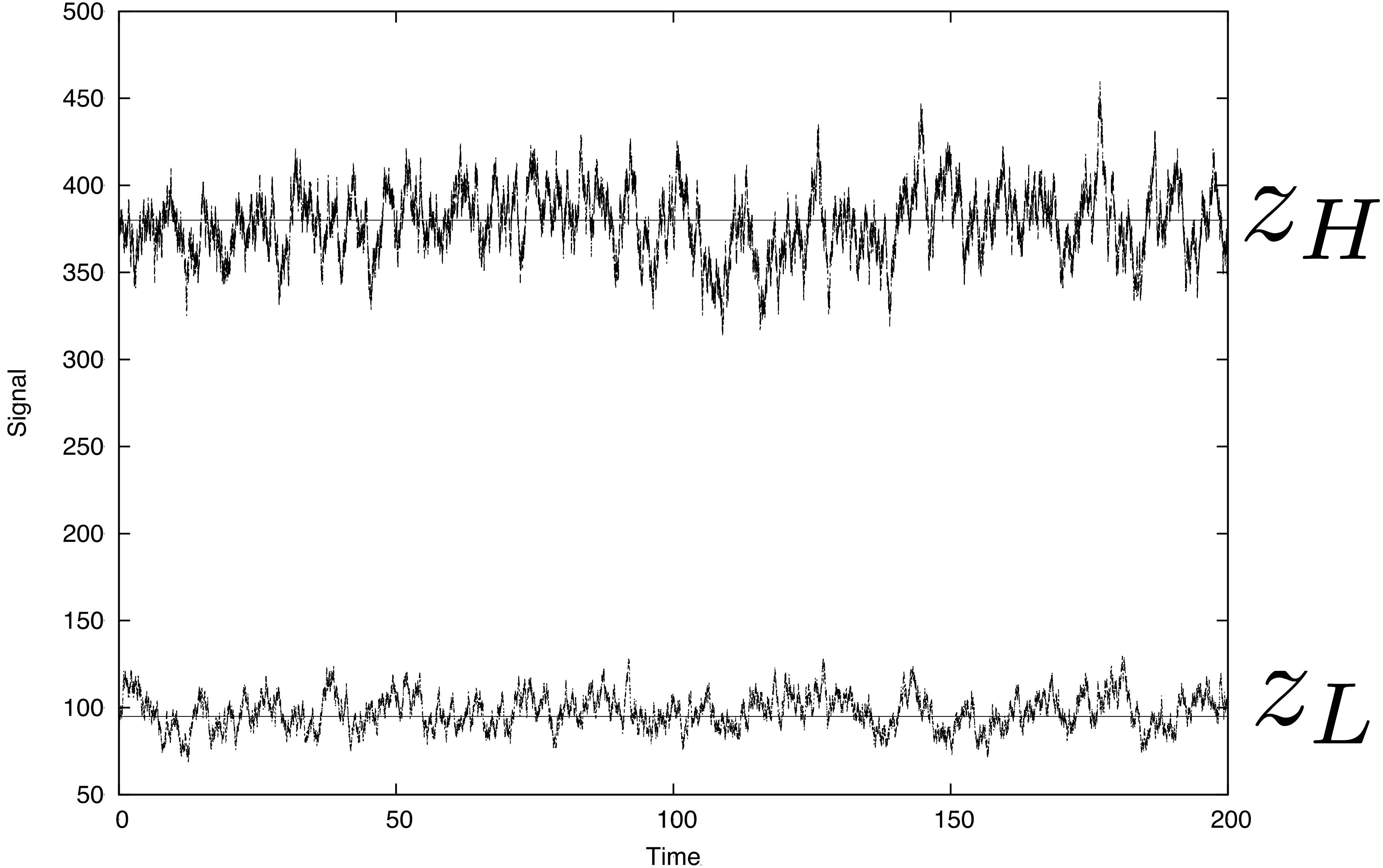
$$\lim_{\mu \to \infty} T(\theta) = 0$$

Time to switch

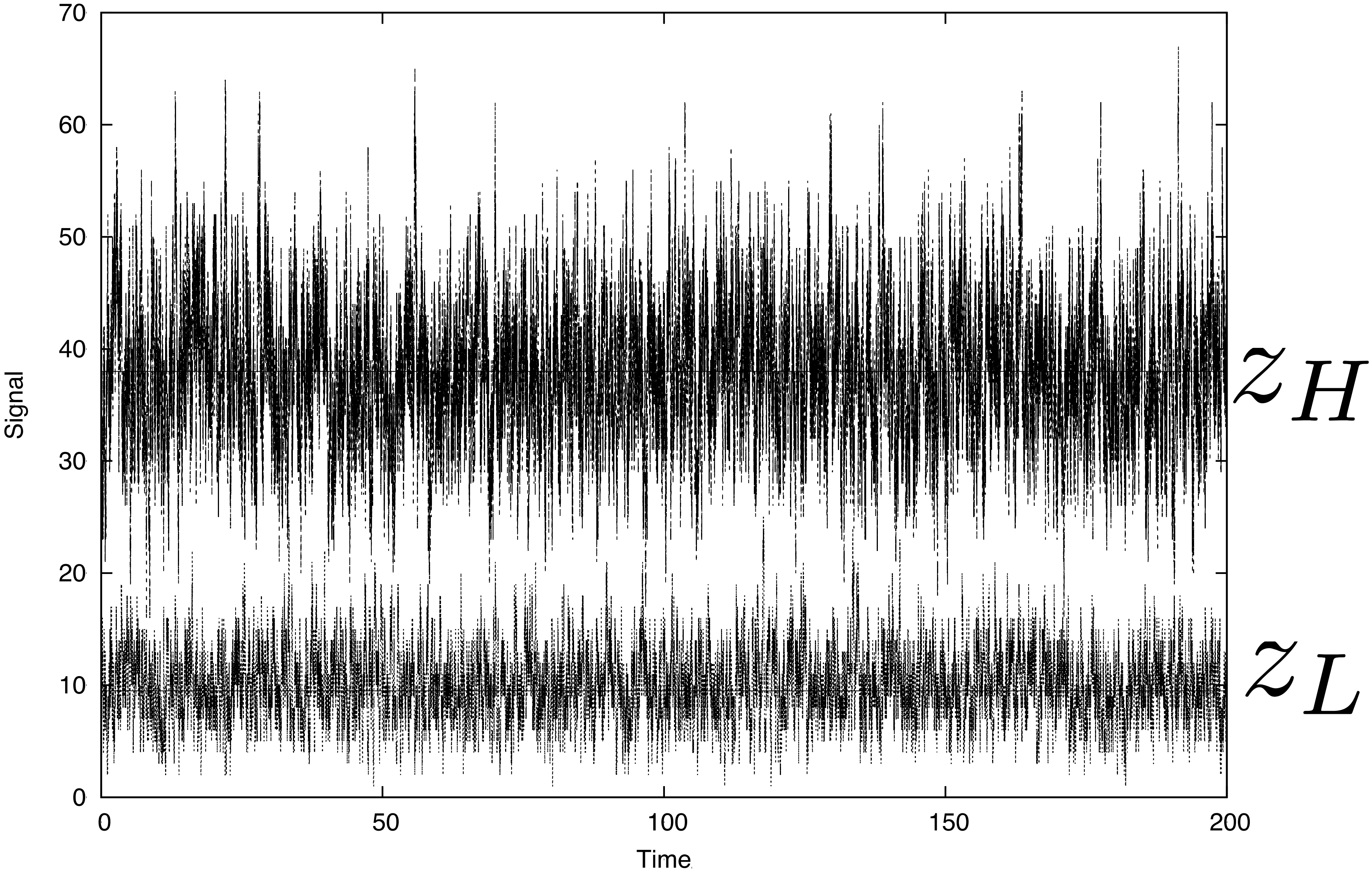
$$\lim_{\mu \to \infty} \underbrace{(z_H - z_L)}_{\text{“Signal strength”}} = 0$$

$$\lim_{\mu \to \infty} T(\theta) = 0$$

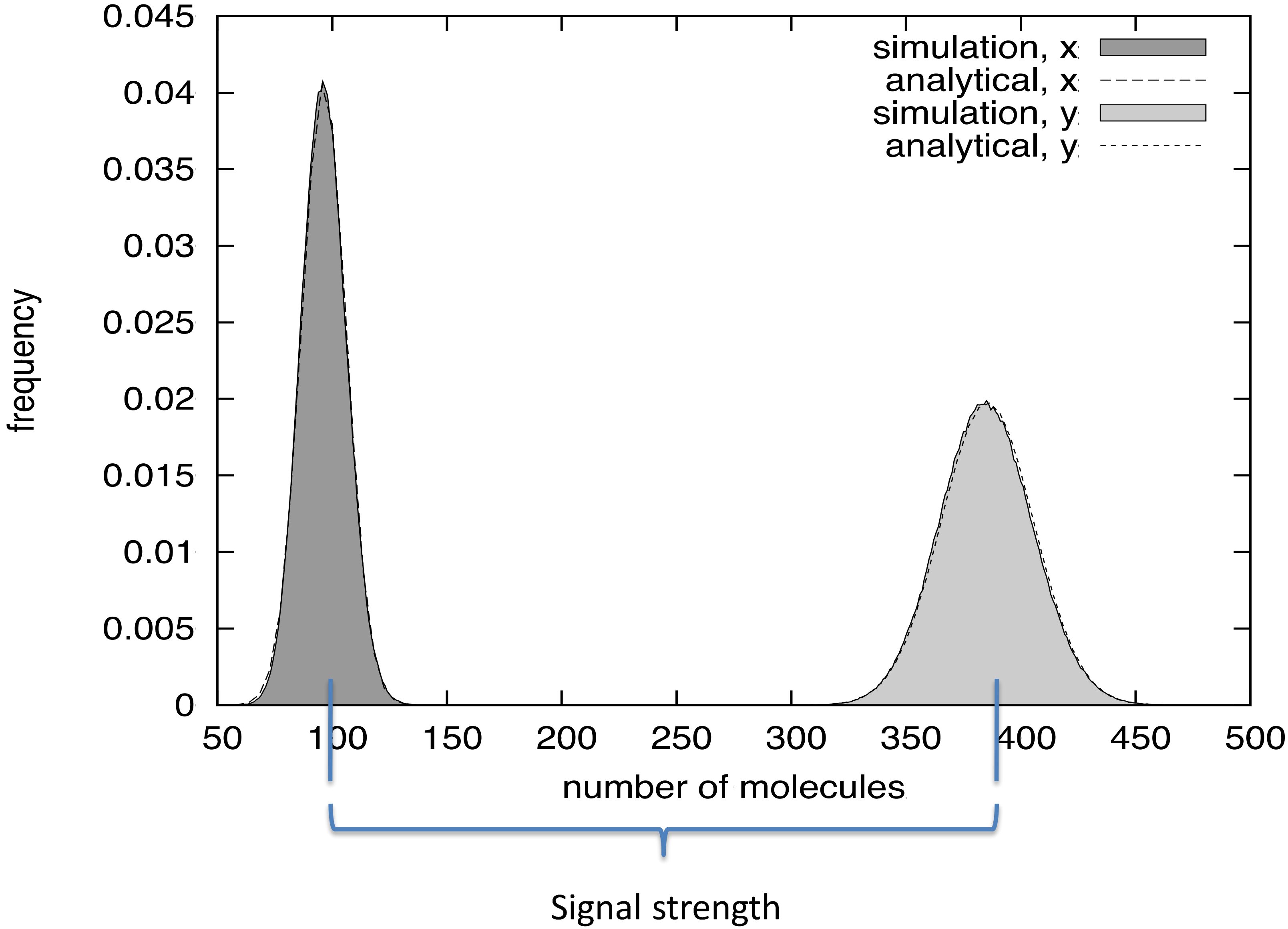
Steady state $\mu = 1$



Steady state $\mu = 10$



Noise/stochastic fluctuations



Noise

$$\text{Noise} = \frac{\sigma_y^2}{(\text{signal strength})^2}$$

Linear noise approximation

$$\text{Noise} = \frac{\sigma_y^2}{(\text{signal strength})^2}$$

$$\mathcal{N} = \underbrace{\frac{z_H}{(z_H - z_L)^2}}_{\text{intrinsic}} + \underbrace{\underbrace{\left[\frac{\beta f'_H}{z_H - z_L}\right]^2}_{\text{regulation factor}} \underbrace{\frac{\tau_y}{\tau_z^2 \tau_y + \tau_z}}_{\text{time factor}} \sigma_y^2}_{\text{extrinsic}}$$

Noise-time trade-off

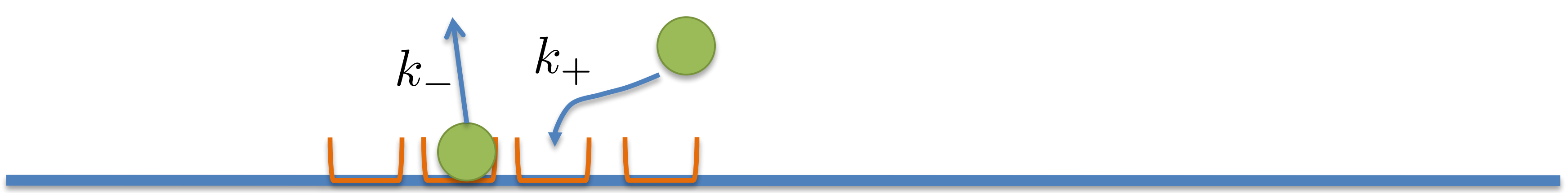
A)

As in the 1 gene case:

$$T \sim \frac{1}{\mu} \qquad \mathcal{N} \sim \mu$$

B)

There is an optimal $\frac{k_-}{k_+}$ for time and noise respectively

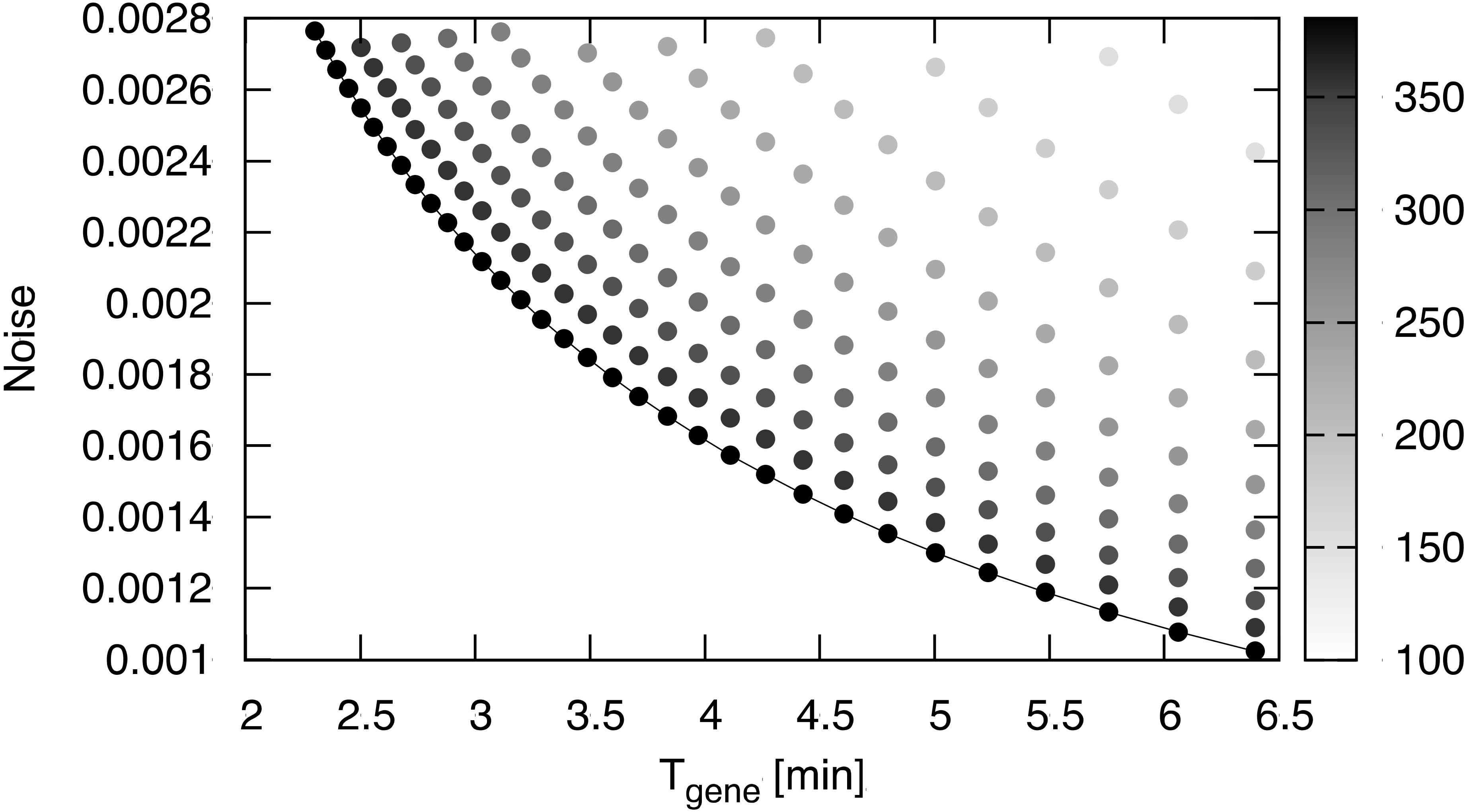


Can we do any better than this?

$$\mathcal{N}: \quad \beta \nearrow \quad \Longrightarrow (z_H - z_L) \nearrow$$

$$\text{Cost: } \zeta \doteq \alpha + \beta f_H$$

Noise-time-cost trade-off

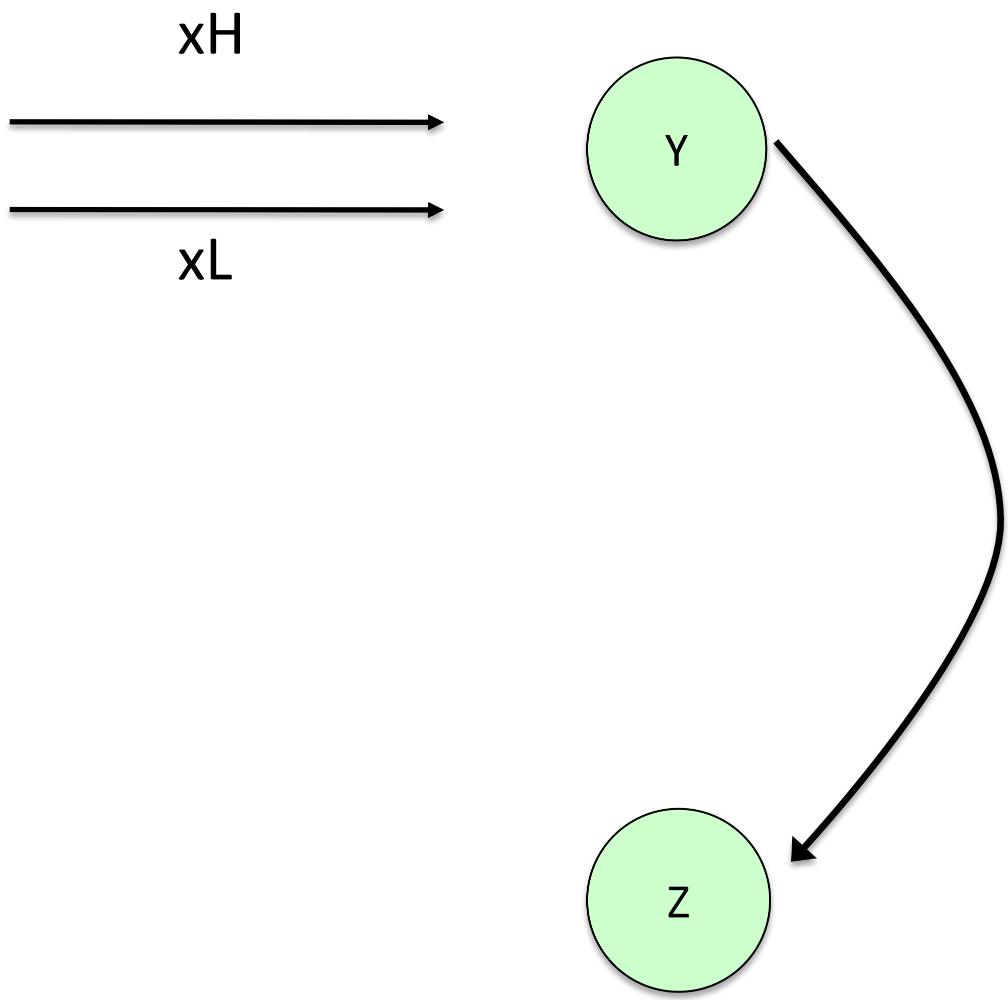


Summary 1

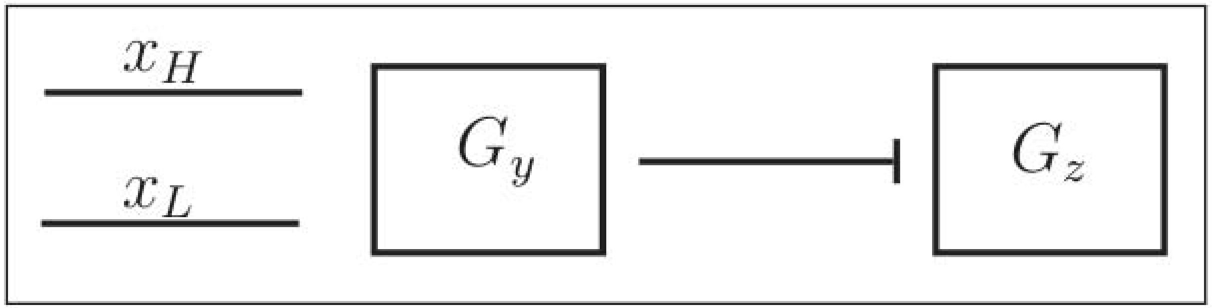
- There is a trade-off between the accuracy and speed.
- The trade-off curve can be improved by higher rate of synthesis (i.e. cost).
- There are optimal values for other parameters

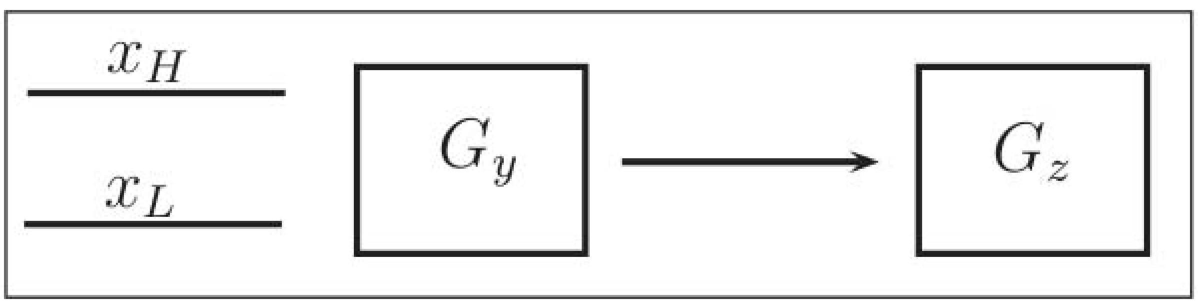
$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$

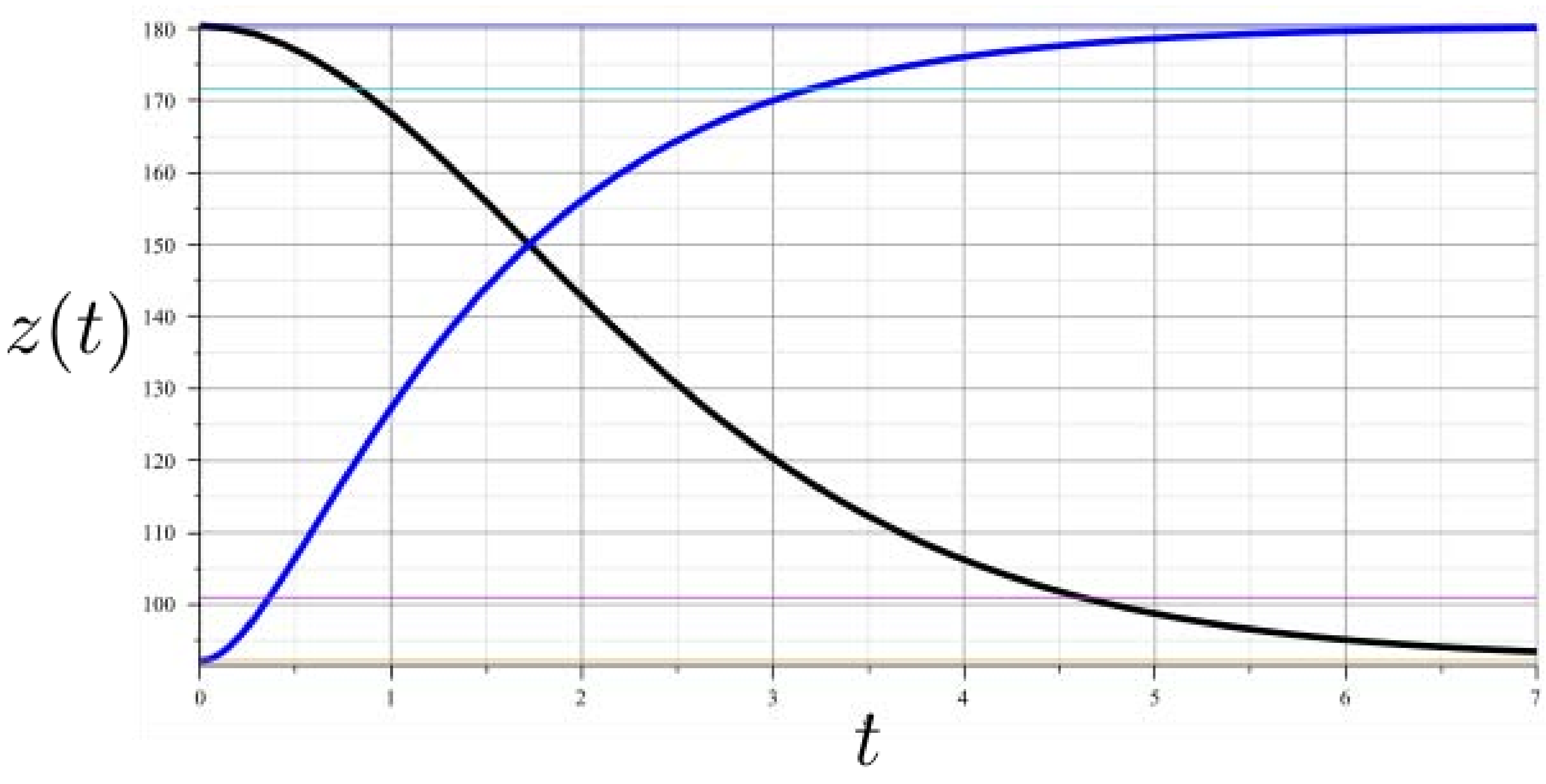
3 genes

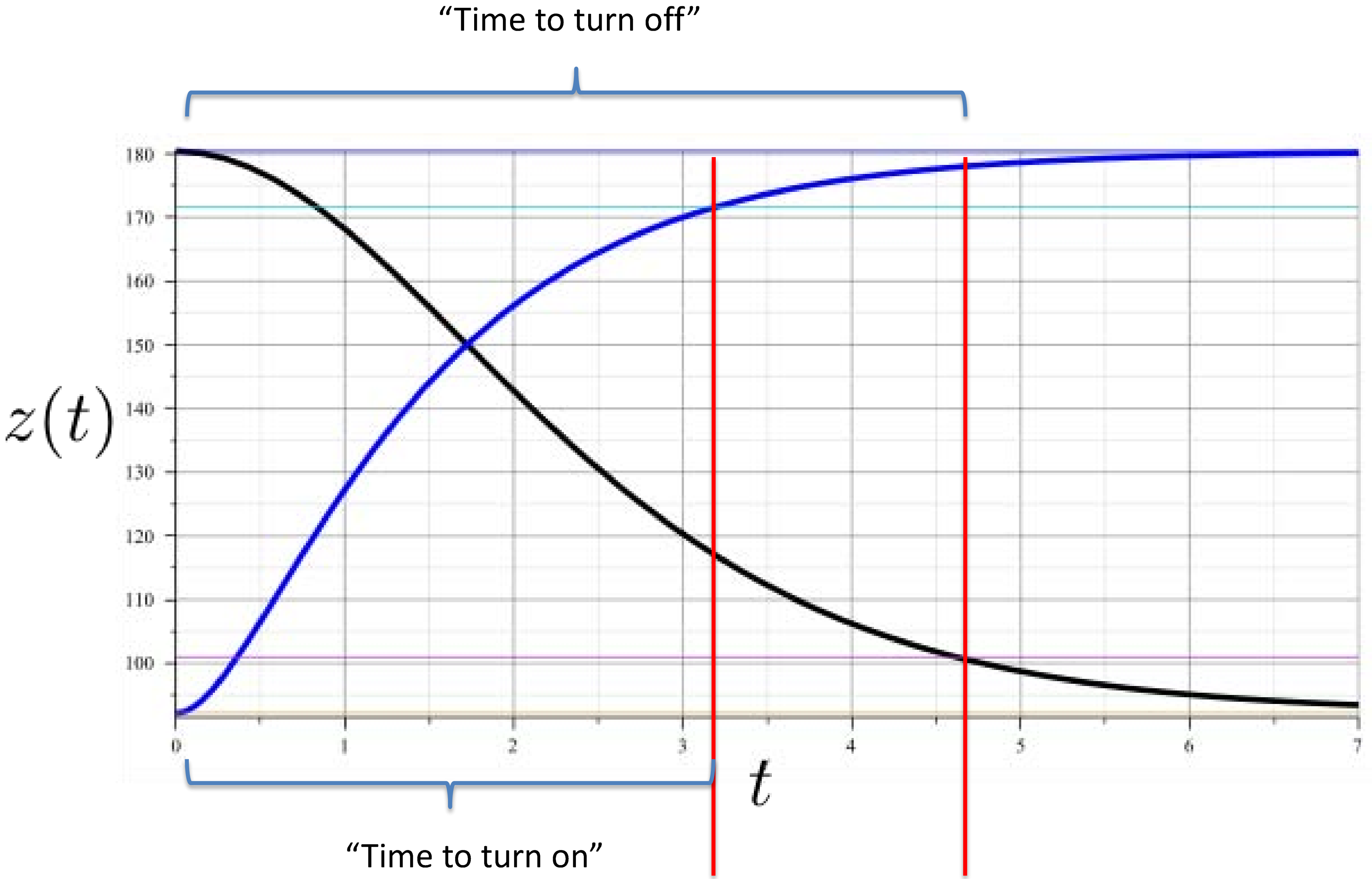


Standard system






$z(t)$
180
170
160
150
140
130
120
110
100
0
1
2
3
4
5
6
7
t


"Time to turn off"
180
170
160
150
140
130
120
110
100
z(t)
0
1
2
3
4
5
6
7
t
"Time to turn on"

Noise-Time Trade-off

A)

There is an optimal K for time and noise.

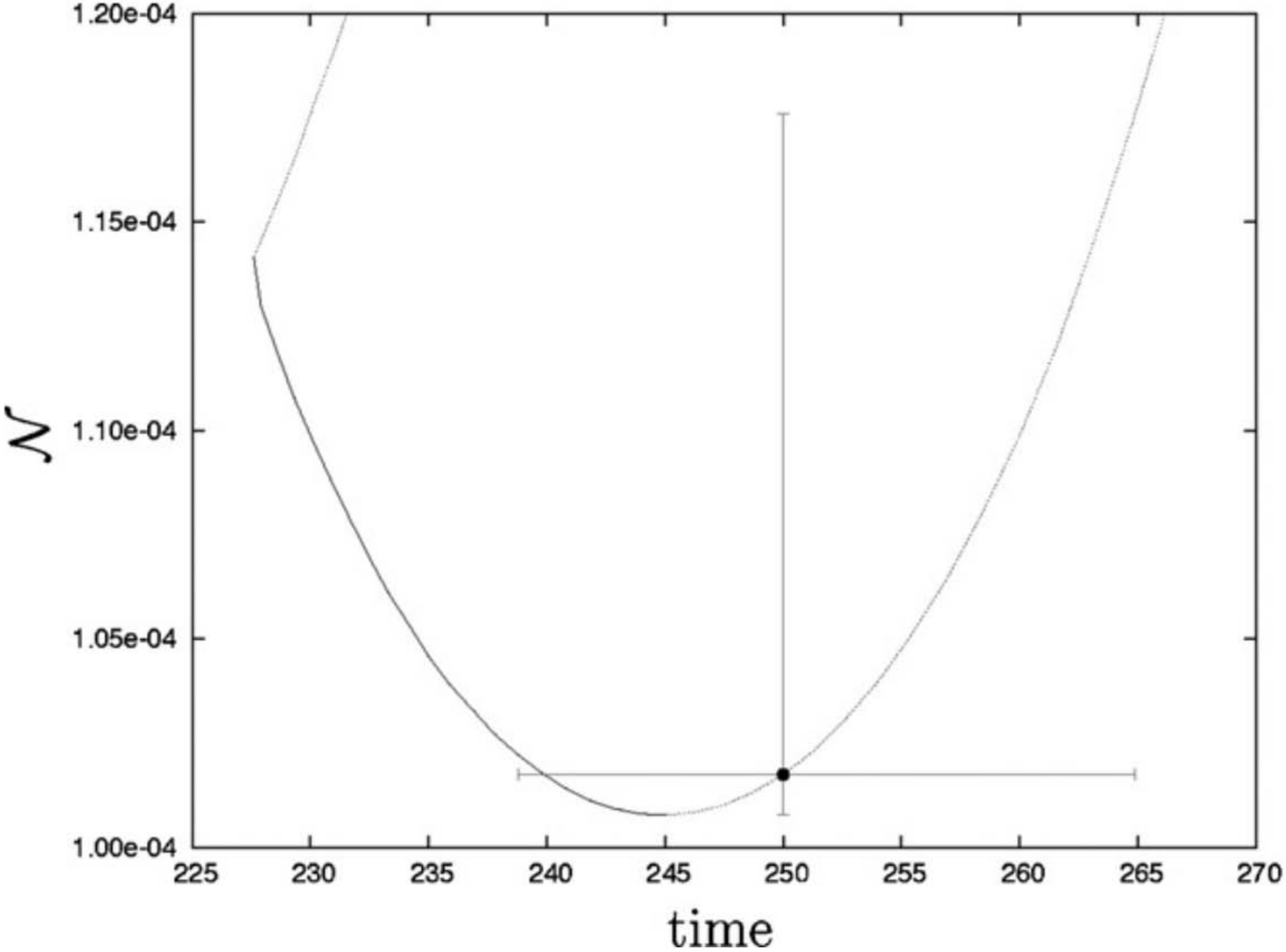
$$\dot{z} = \alpha + \beta \frac{y^h}{y^h + K^h} - \mu_z z$$

B)

As in the 1 gene case:

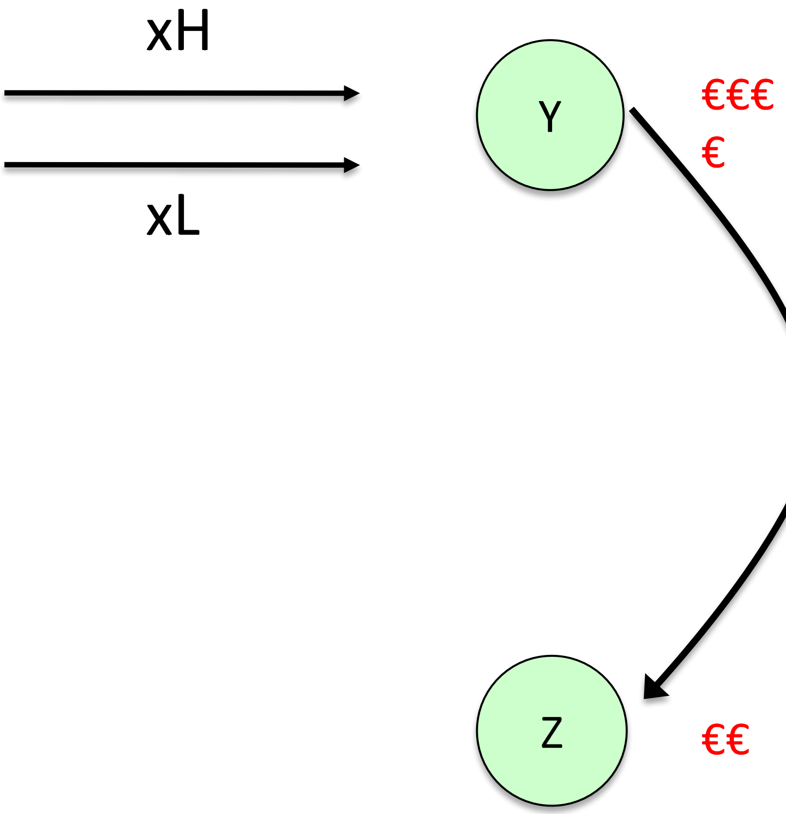
$$T \sim \frac{1}{\mu} \qquad \mathcal{N} \sim \mu$$

K-mediated trade-off



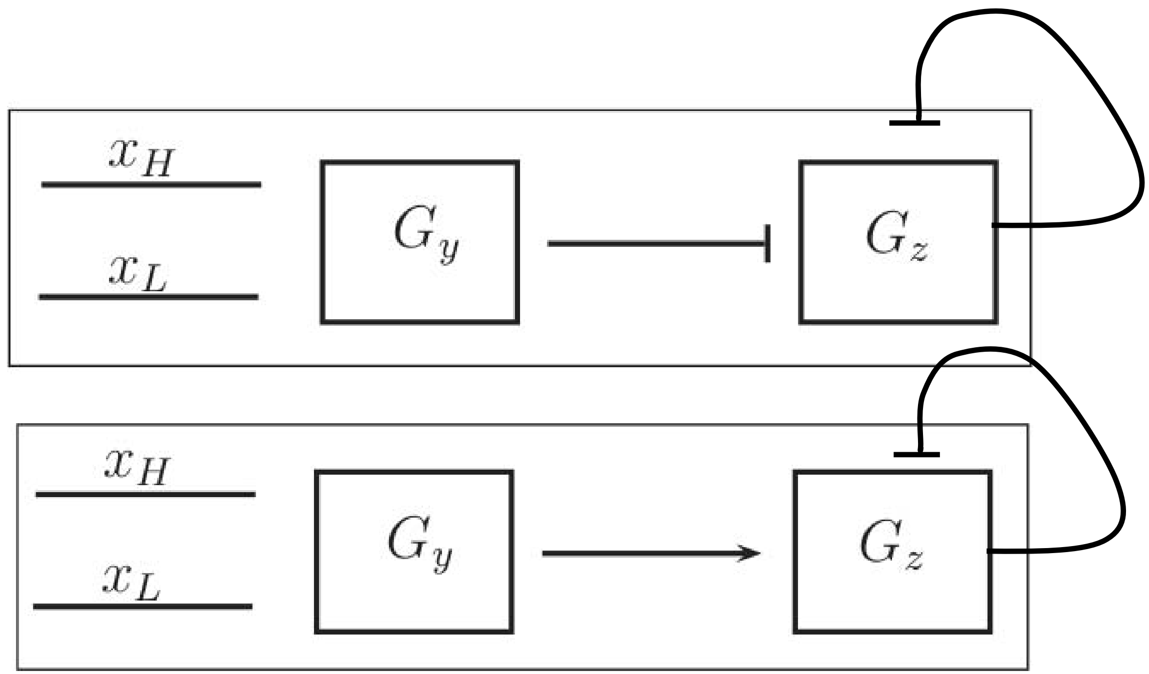
Cost allocation

$$\zeta \doteq \beta_z f_z(y_H) + \beta_y f_y(x_H)$$



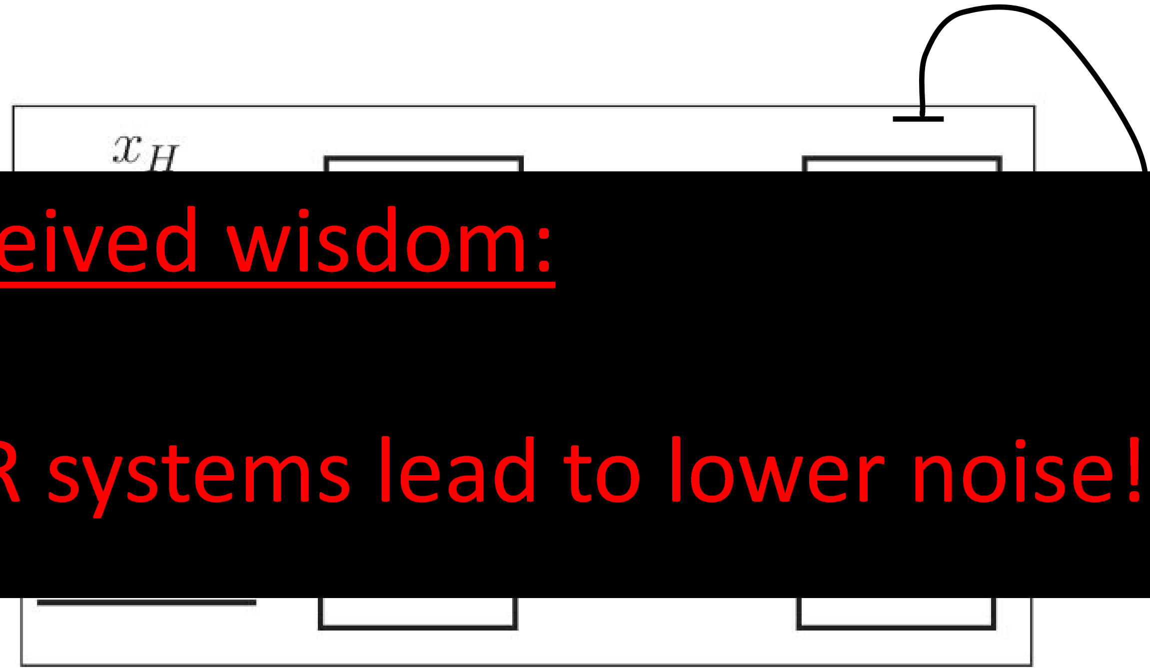
- For time does not matter!
- For noise there is an optimum.

Can we do any better than this? Adding auto-repression



$$\dot{z} = \frac{\bar{K}^{\bar{h}}}{\bar{K}^{\bar{h}} + z^{\bar{h}}} \cdot \frac{\bar{K}^{\bar{h}} + z_H^{\bar{h}}}{\bar{K}^{\bar{h}}} \beta f - \mu z$$

Can we do any better than this?
Adding auto-repression

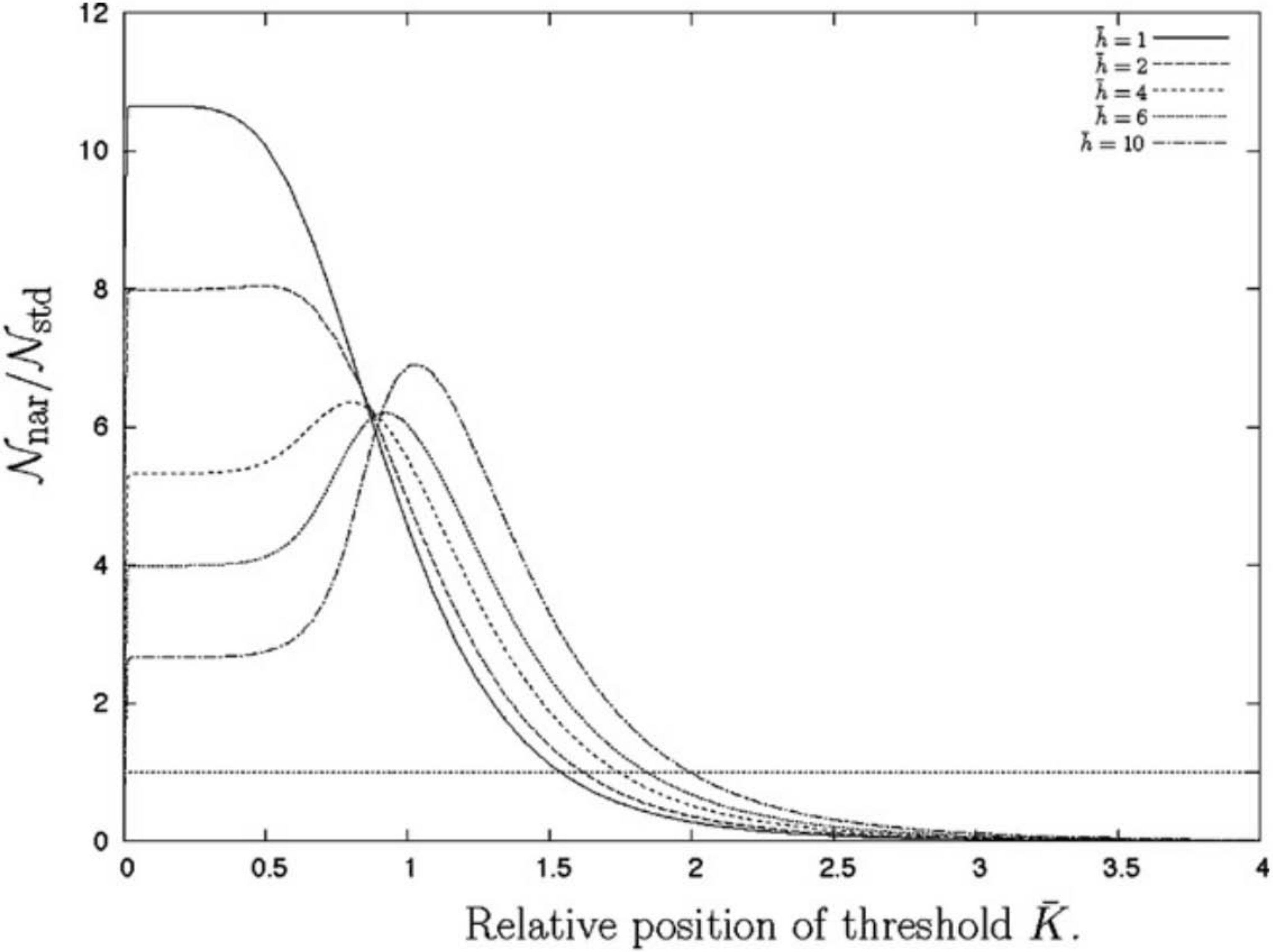


Received wisdom:

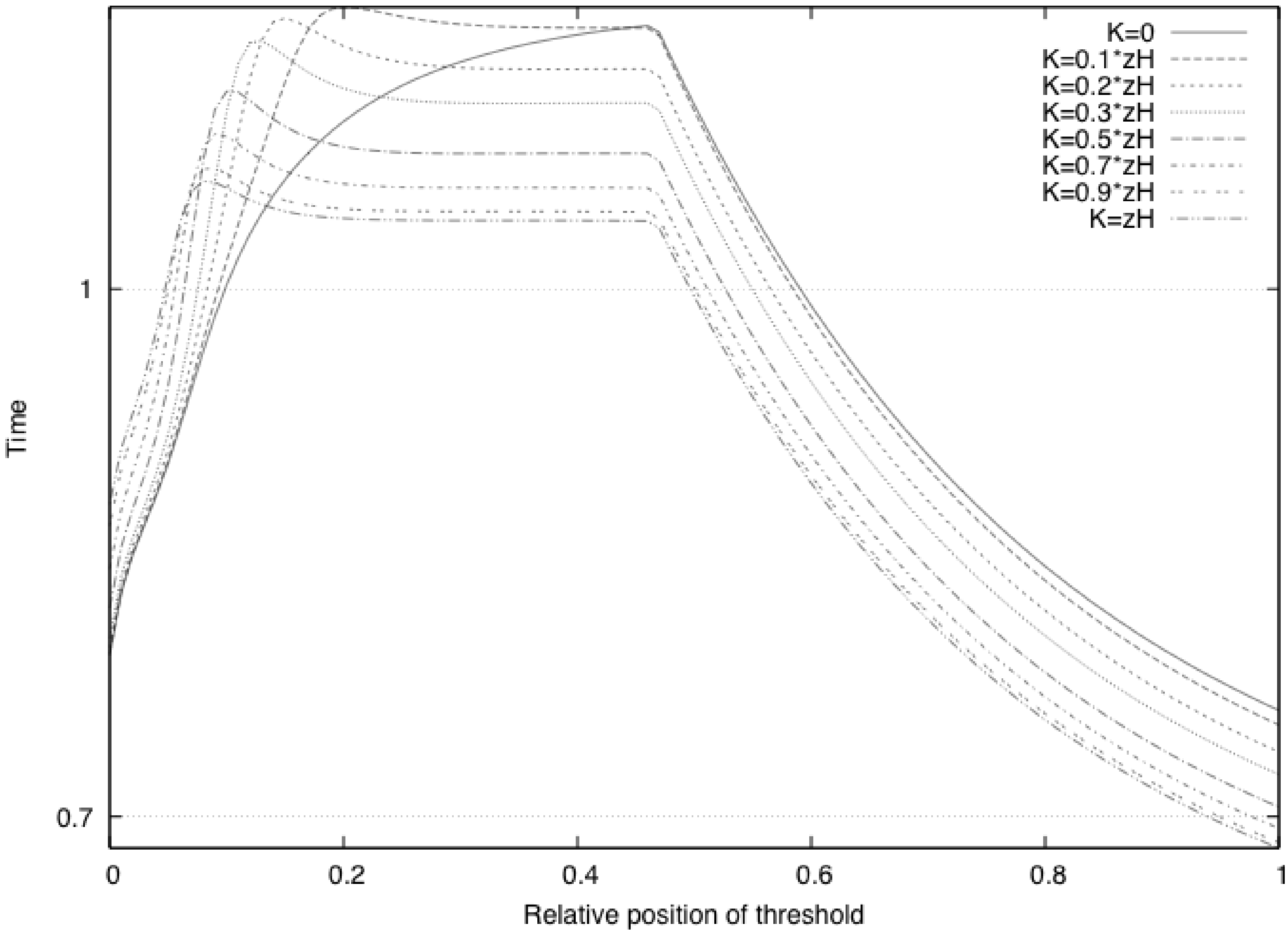
NAR systems lead to lower noise!

$$\dot{z} = \frac{\bar{K}^{\bar{h}}}{\bar{K}^{\bar{h}} + z^{\bar{h}}} \cdot \frac{\bar{K}^{\bar{h}} + z_H^{\bar{h}}}{\bar{K}^{\bar{h}}} \beta f - \mu z$$

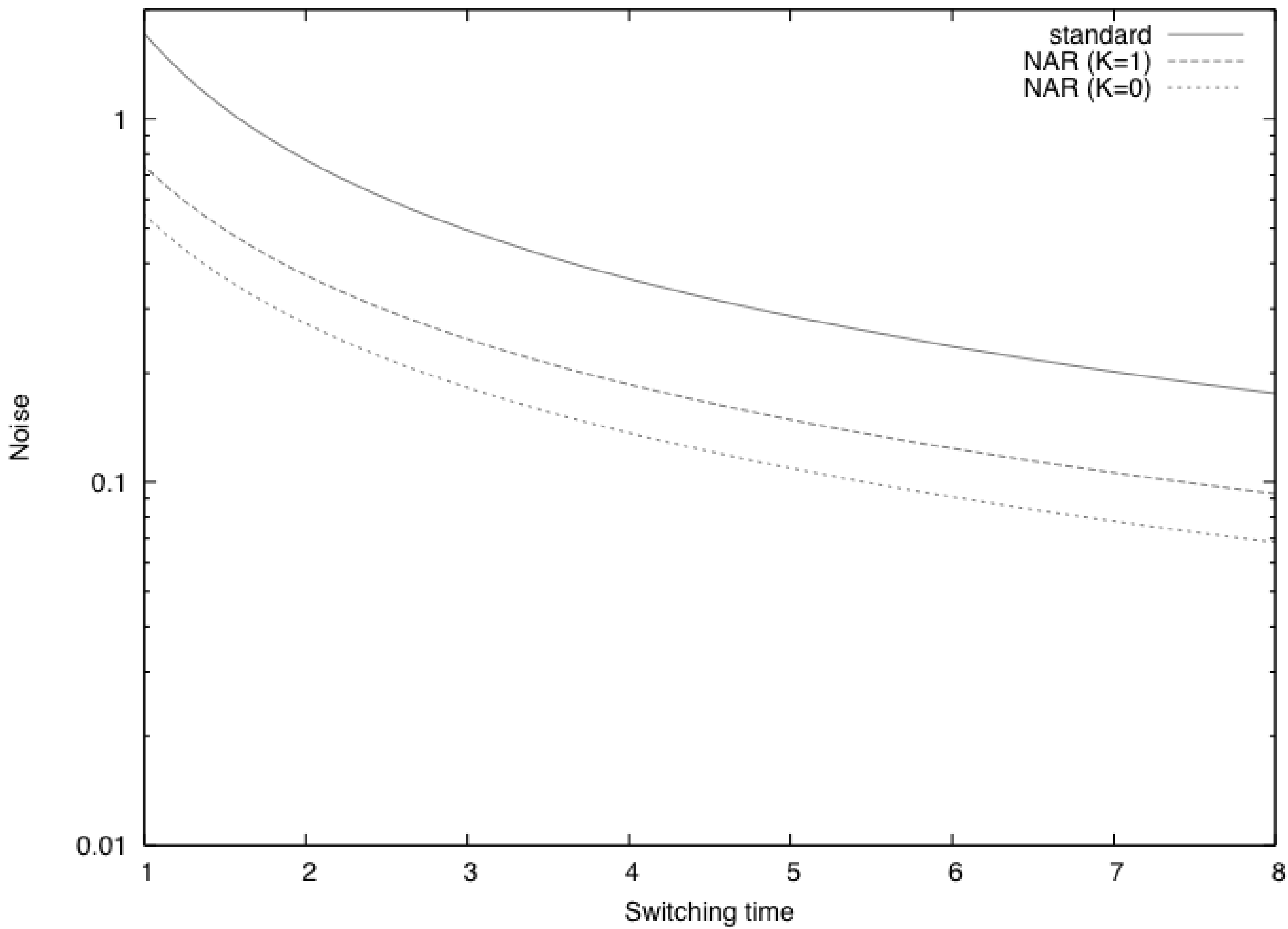
NAR is sometimes noisier



NAR is sometimes faster.



NAR has always a better trade-off



Summary 2

- For gene networks there is an optimal K, h, and cost allocation.
- Instead of a single trade-off, there are 2 trade-offs between time and noise.
- The nar system is more efficient than the standard system.
- (The par system is not suitable due to bi-stability.)

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Optimal parameter settings for information processing in gene regulatory networks

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ABSTRACT

Gene networks can often be interpreted as computational circuits. This article investigates the computational properties of gene regulatory networks defined in terms of the speed and the accuracy of the output of a gene network. It will be shown that there is no single optimal set of parameters, but instead, there is a trade-off between speed and accuracy. Using the trade-off it will also be shown how systems with various parameters can be ranked with respect to their computational efficiency. Numerical analysis suggests that the trade-off can be improved when the output gene is repressing itself, even though the accuracy or the speed of the auto-regulated system may be worse than the unregulated system.

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Computational limits to binary genes

Nicolae Radu Zabet and Dominique F. Chu

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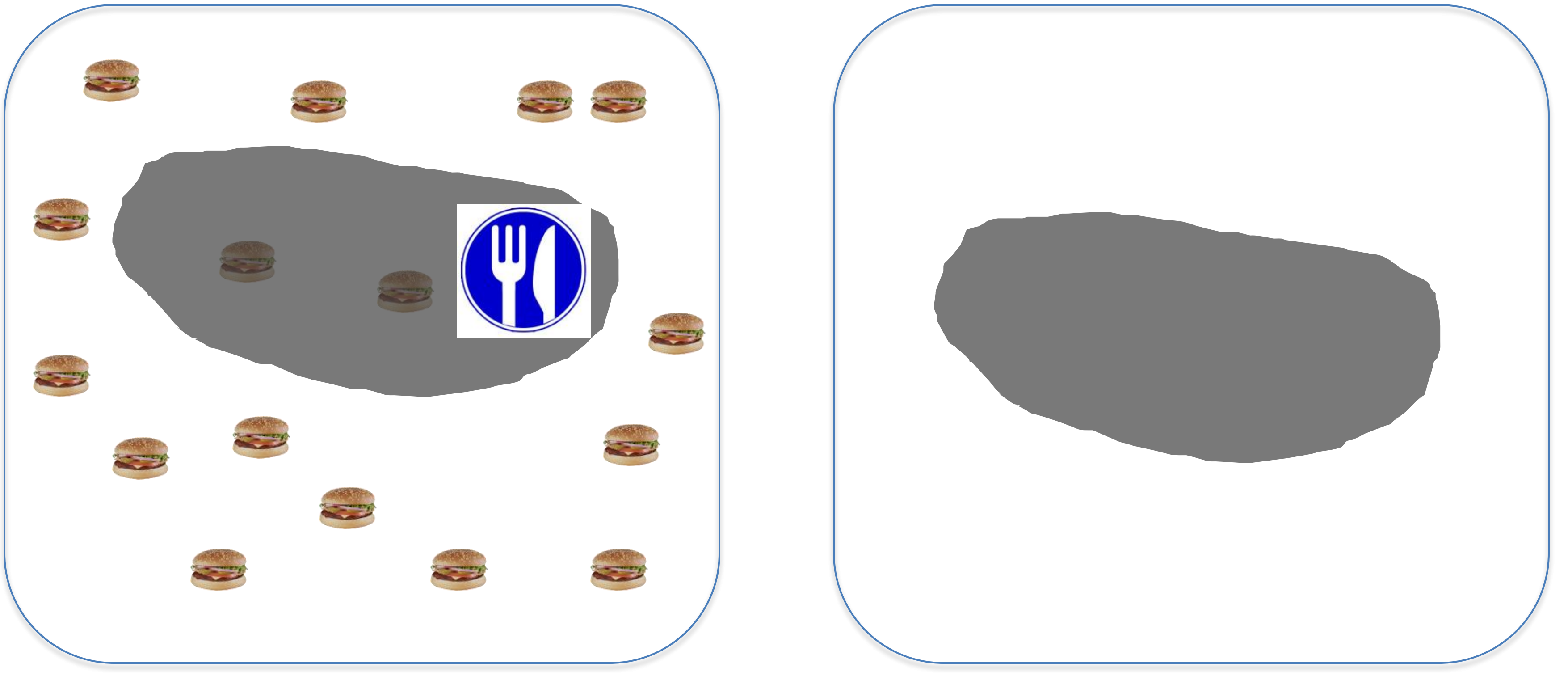
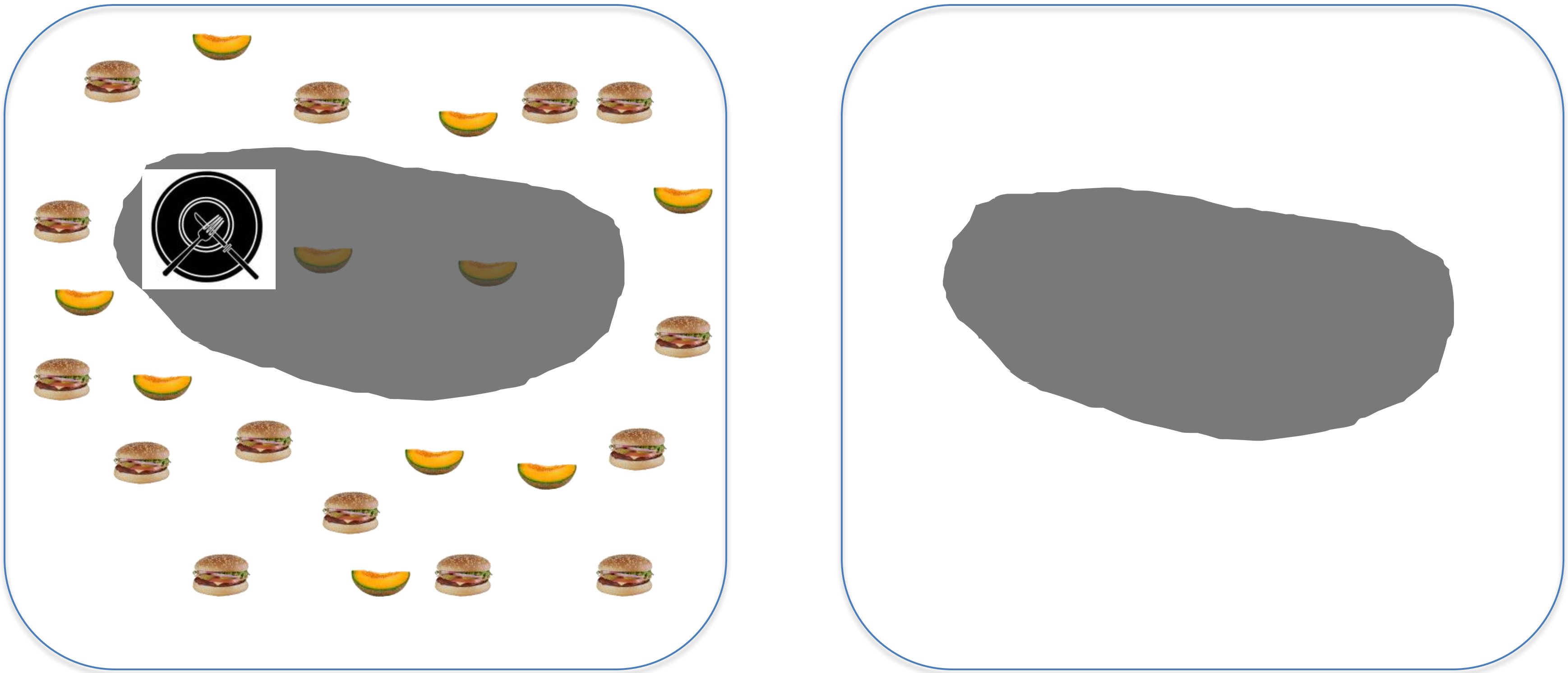
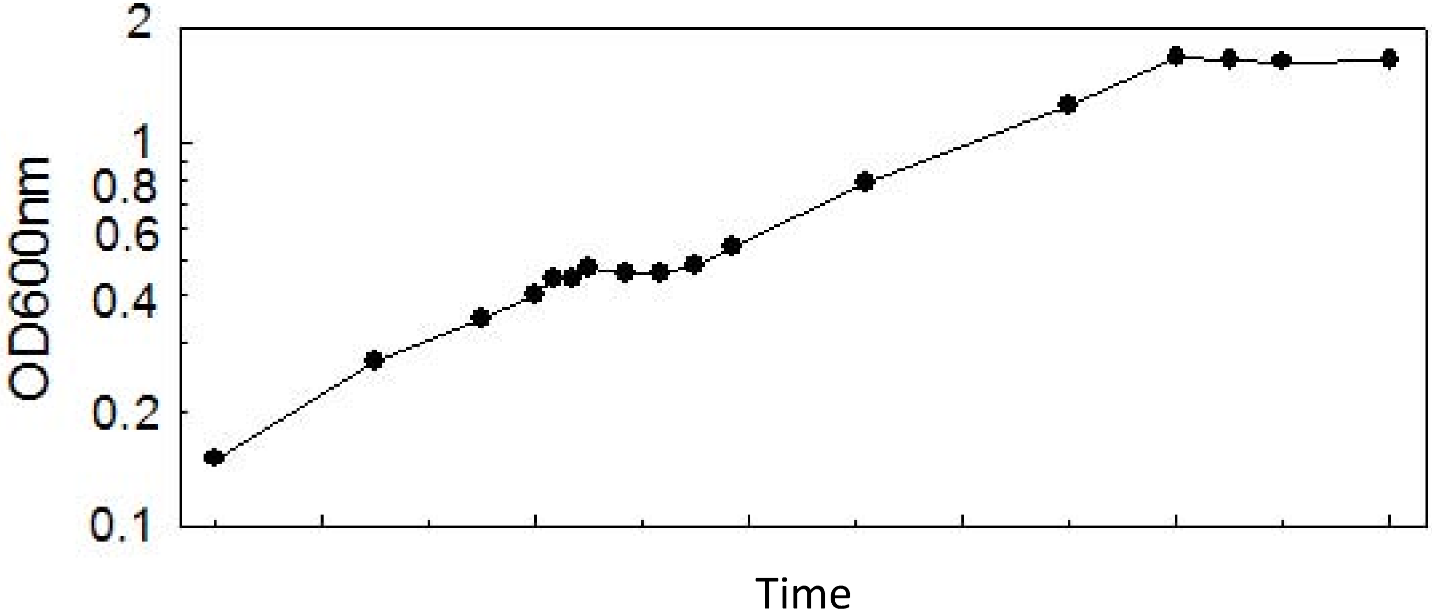
Simple if-then



Simple if-then





http://www.ou.edu/microarray/oumcf/diauxicgrowth.gif

Noise

$$\mathcal{N} = \underbrace{\frac{z_H}{(z_H - z_L)^2}}_{\text{intrinsic}} + \underbrace{\underbrace{\left[\frac{\beta f'_H}{z_H - z_L}\right]^2}_{\text{regulation factor}} \underbrace{\frac{\tau_z^2 \tau_y}{\tau_y + \tau_z}}_{\text{time factor}} \sigma_y^2}_{\text{extrinsic}}$$

- Higher Hill coef, then lower noise.
- Higher signal strength, then lower noise.

Comes from the shape of the regulation. Vanishes as h becomes large

Noise

$$\tau = \frac{1}{\mu}$$

$$\mathcal{N} = \underbrace{\frac{z_H}{(z_H - z_L)^2}}_{\text{intrinsic}} + \underbrace{\underbrace{\left[\frac{\beta f'_H}{z_H - z_L}\right]^2}_{\text{regulation factor}} \underbrace{\frac{\tau_z^2 \tau_y}{\tau_y + \tau_z}}_{\text{time factor}} \sigma_y^2}_{\text{extrinsic}}$$

- Slower "computing," less noise.

Corresponds to computing time. Averages out the variance from input.