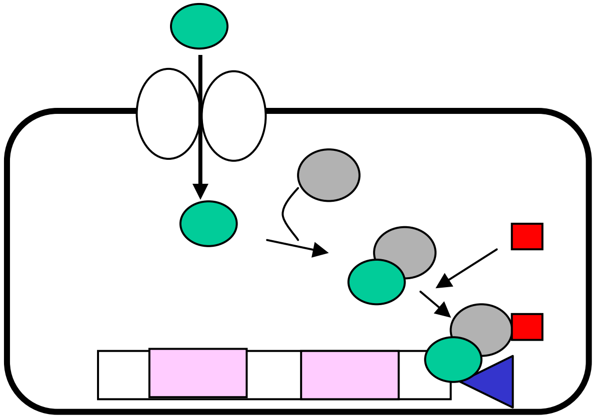
Adaptive response of unicellular organisms to environmental change

For frequently occurring environmental changes

Signal transduction machineries were employed, which

1) **Work fast in a highly specific manner.**
2) **Have evolved in experiencing the similar environmental changes that occurred many time in the past.**



For rarely occurring, but many kinds of environmental chang

Cells may not necessarily have evolved signal transduction machineries for all of them.

Question

How can cells adapt their gene expression patterns to rarely occurring environmental changes for which no signal transduction machineries are available?

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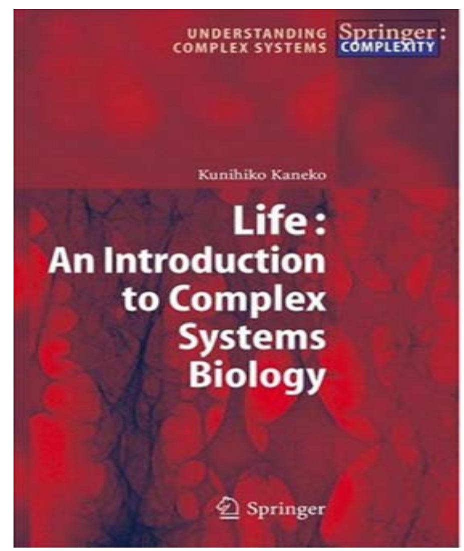
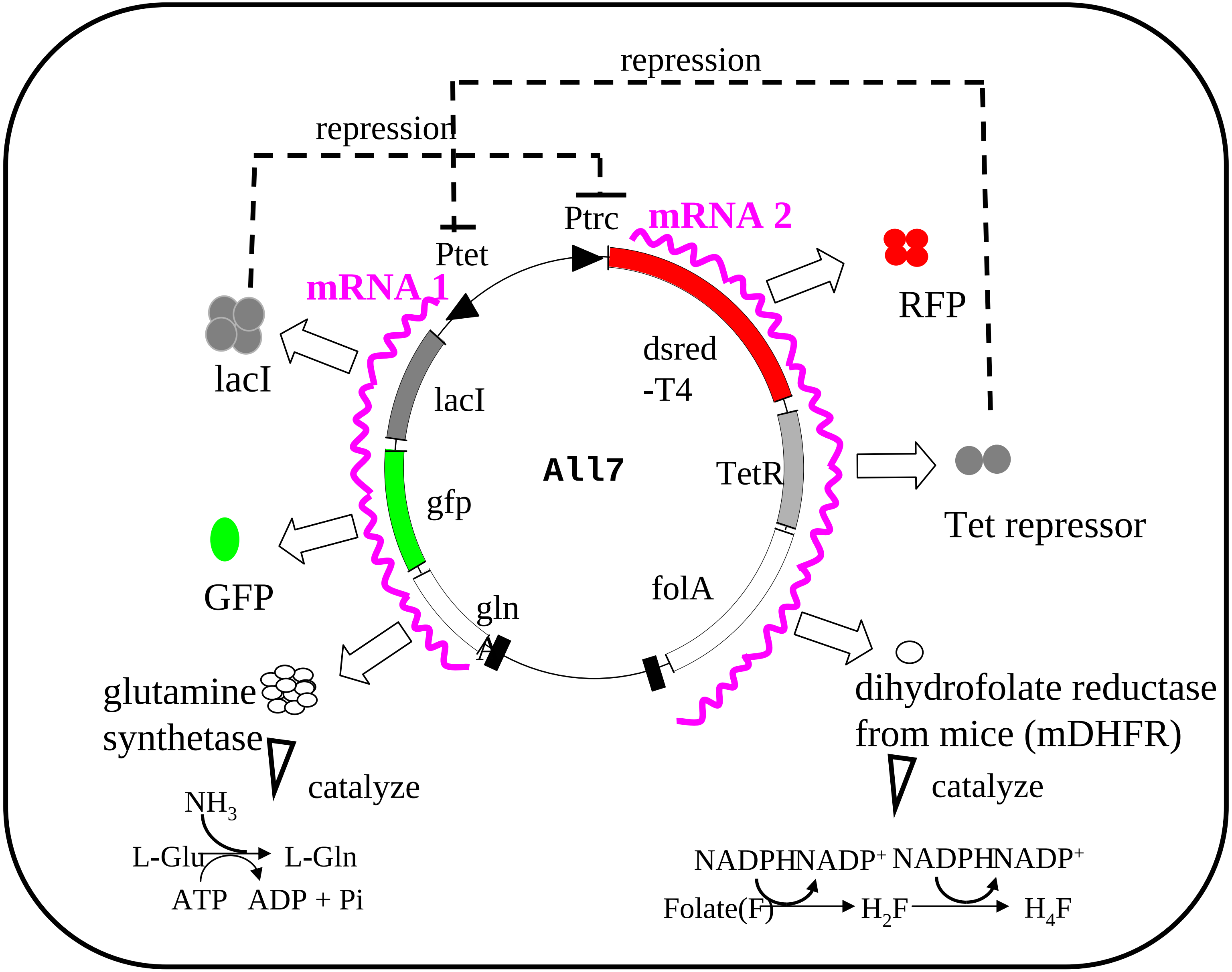
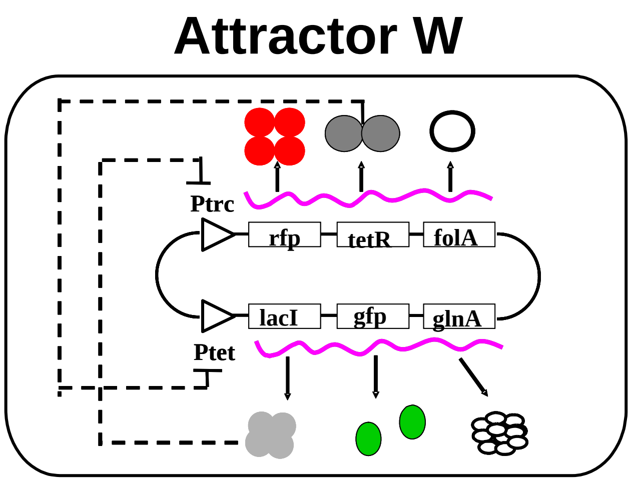
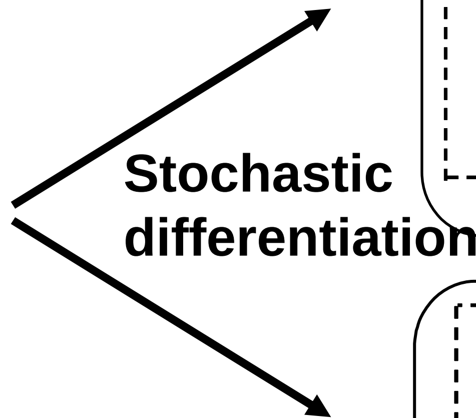


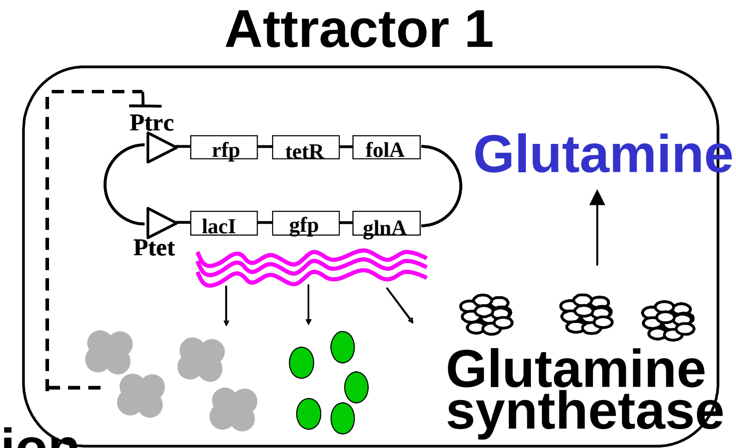


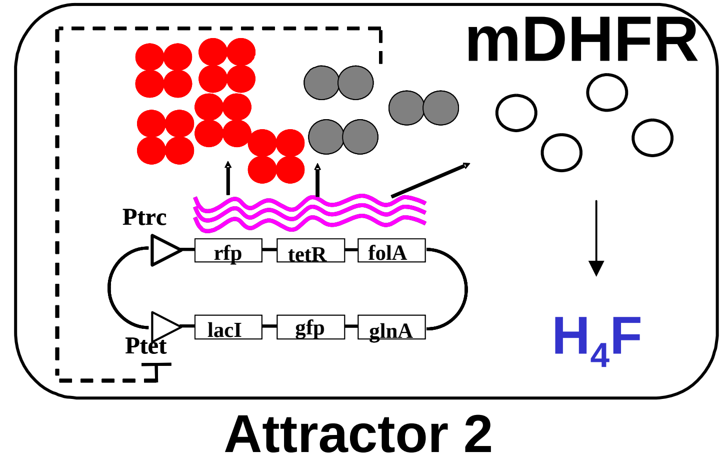
Gardner, T. S., Cantor, C. R. & Collins, J. J. (2000). *Nature* **403**, 339-42

Elowitz MB, Leibler S (2000). Nature **403**: 335-338.

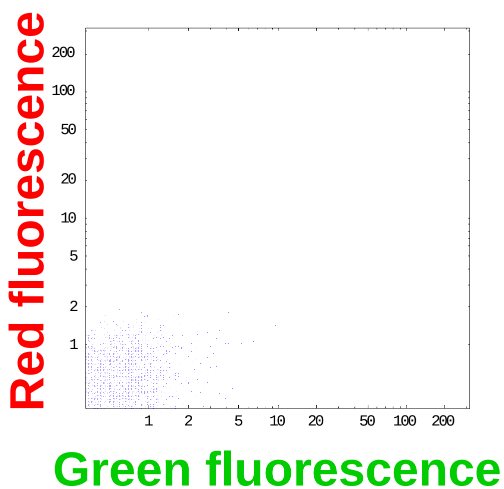




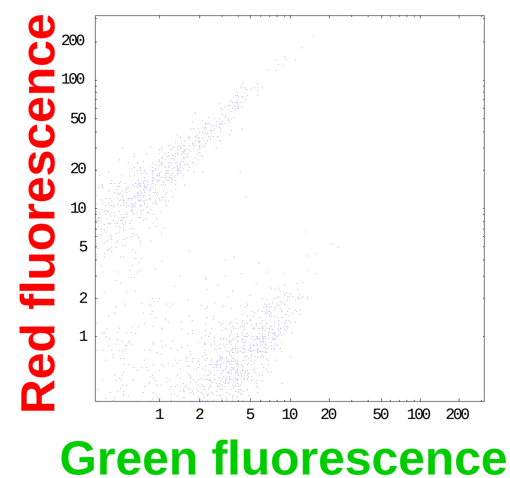




Three stable gene expression patterns (attractors) in two different environments



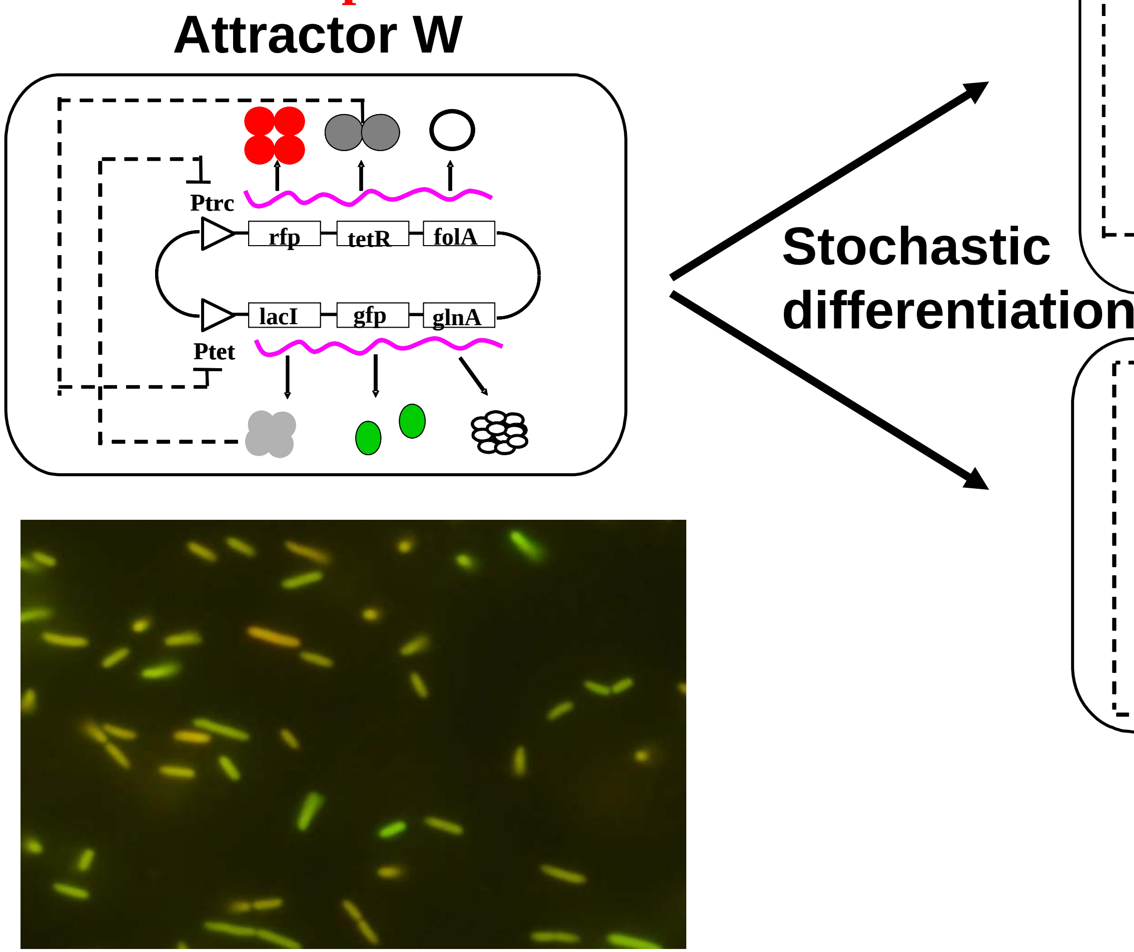
By increasing the total concentration of both repressors

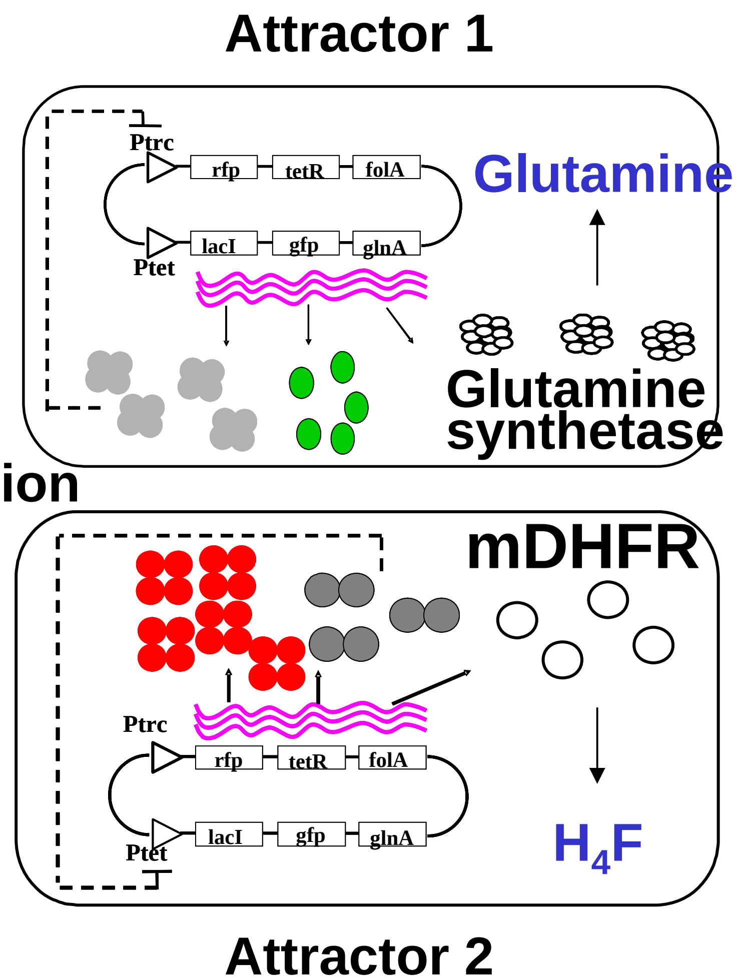


The stochastic differentiation is a property designed in the mutually inhibitory network.

Question:

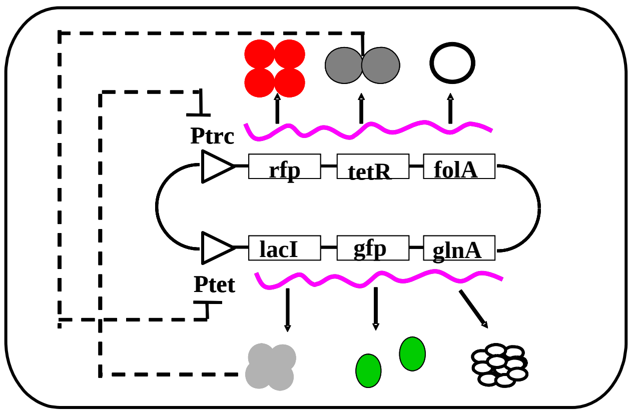
Against the stochastic nature, do the cells, when imposed to selective environments, choose the adaptive attractor?



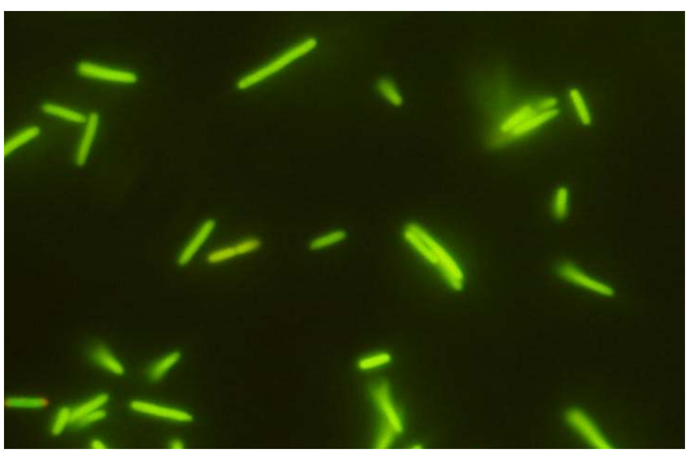


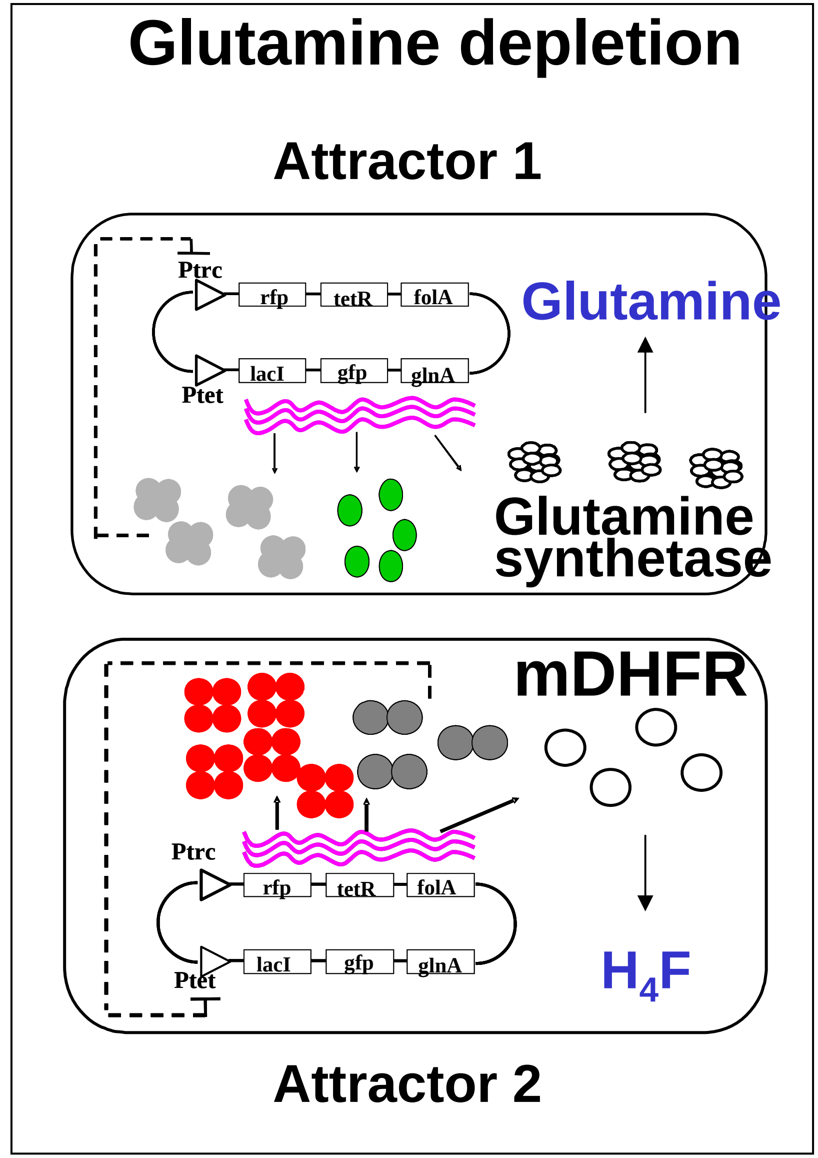
Question:
When we impose glutamine depletion, do they choose Attractor 1 where glutamine synthetase is expressed to compensate for the depletion?

Attractor W



Fitness-induced selection

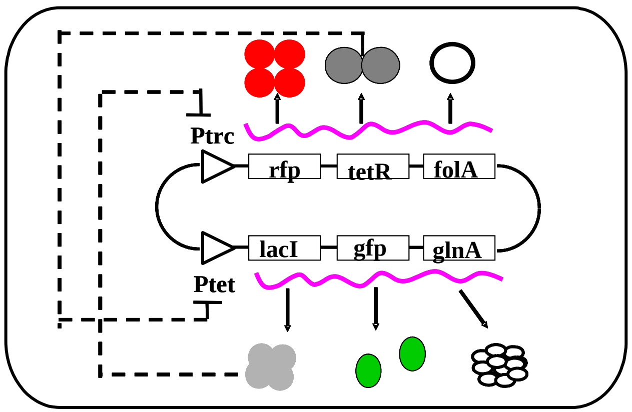


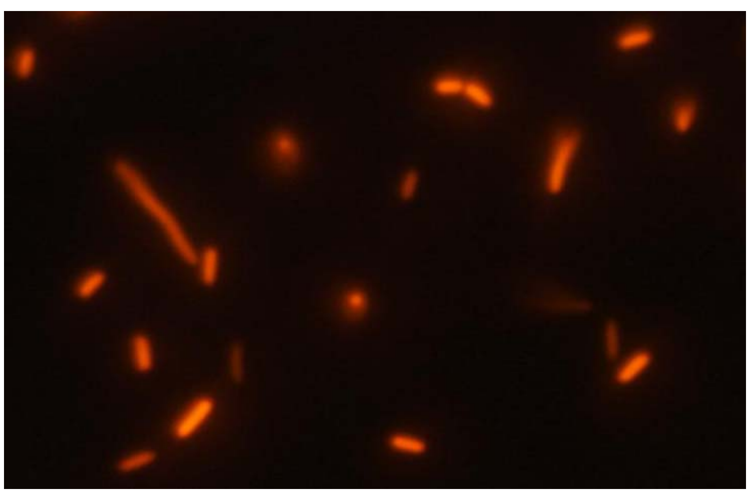


Question:

When we impose tetrahydrofolate depletion, do they choose Attractor 2 where mDHFR is expressed to compensate for the depletion?

Attractor W

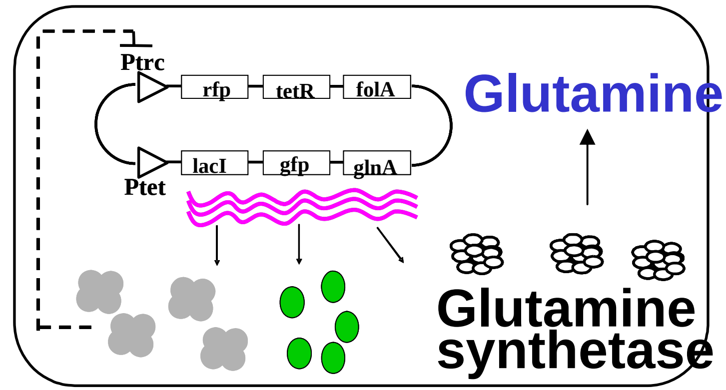


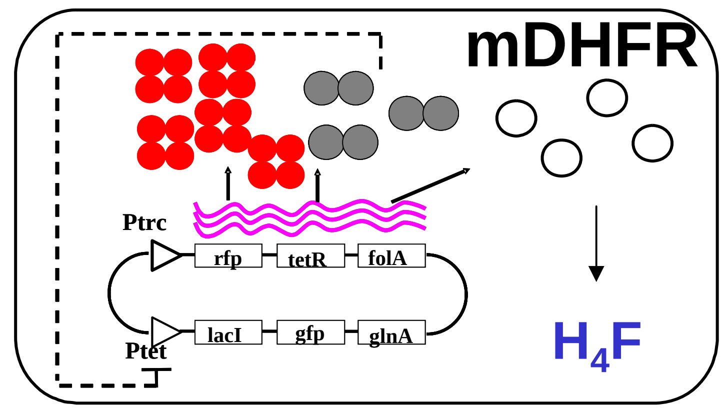


Fitness-induced selection

Tetrahydrofolate (H_4F) depletion

Attractor 1

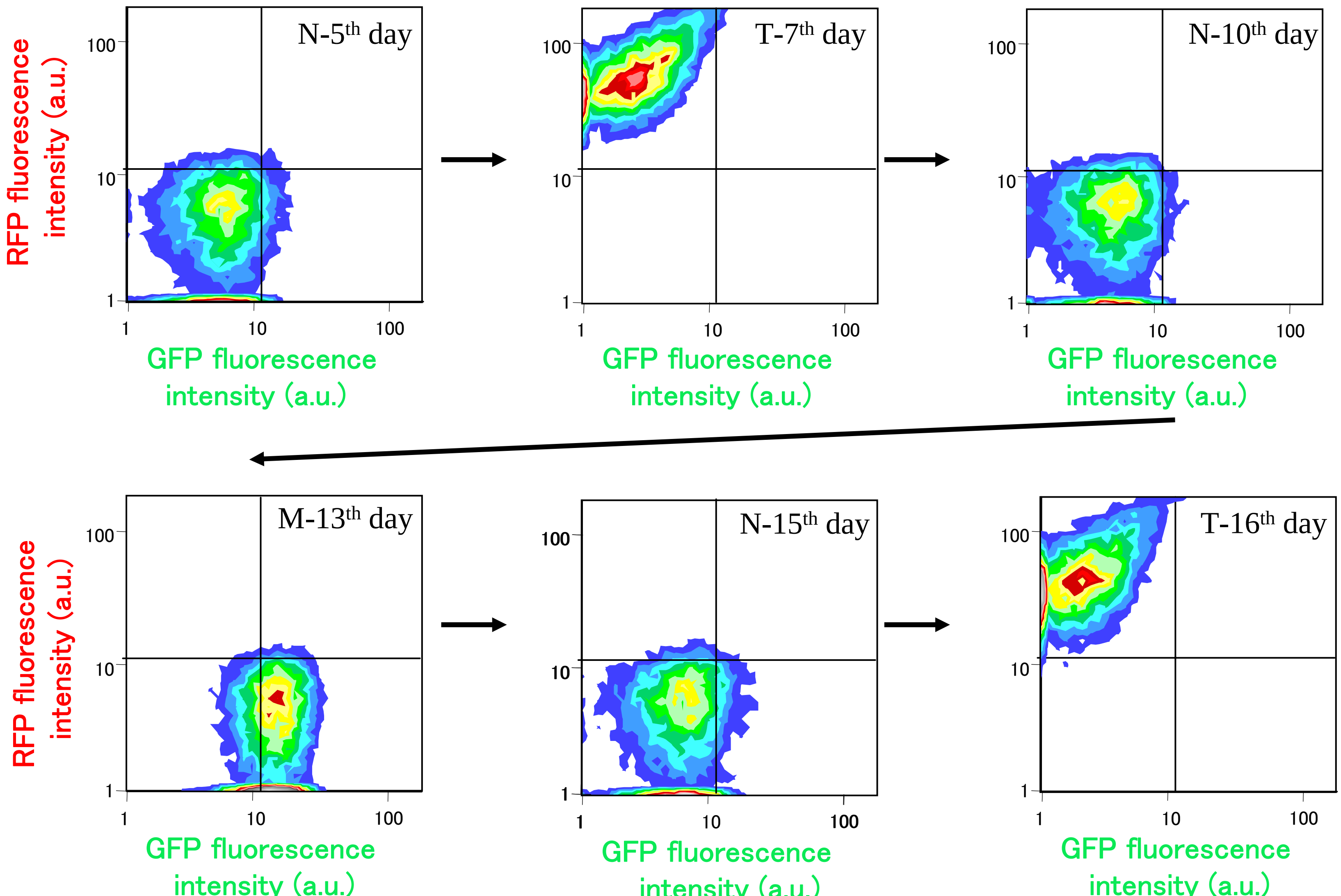




Attractor 2

Adaptive response in a changing environment

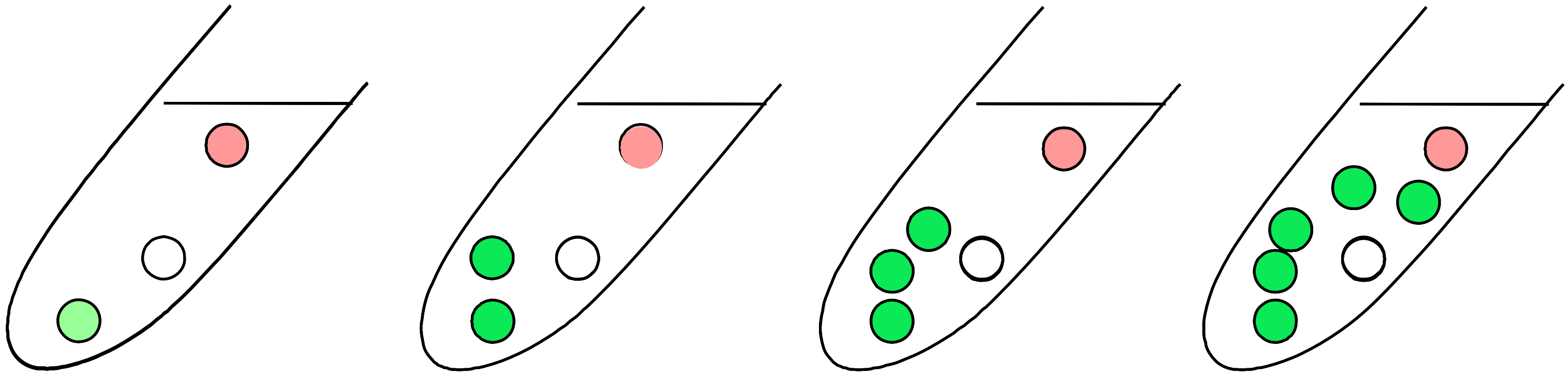
Medium N →Medium T →Medium N →Medium M→Medium N → Medium T



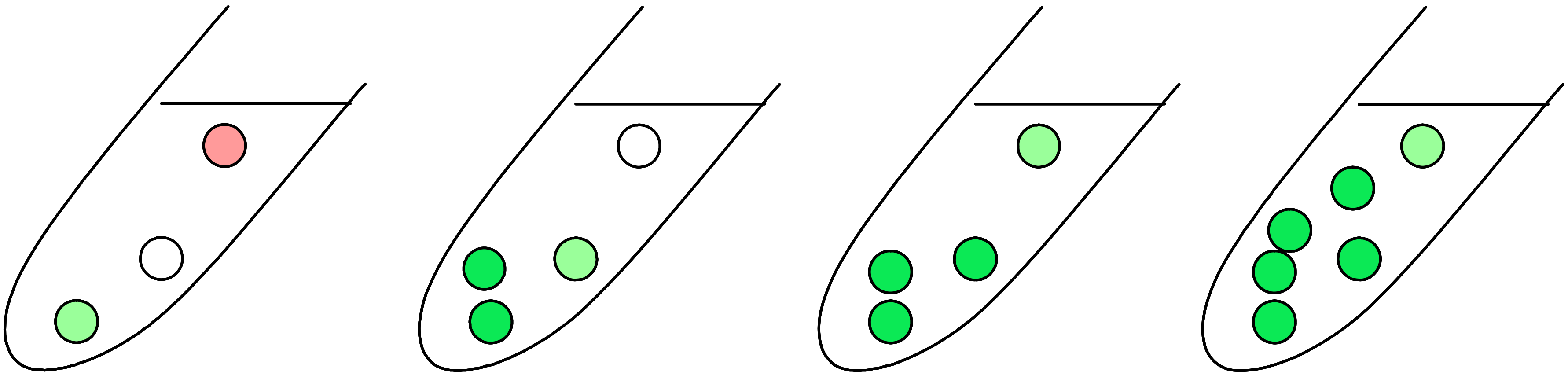
The cells responded adaptively to the changing environment without signal transduction machineries.

Two possible scenarios for the adaptive response of the cell po

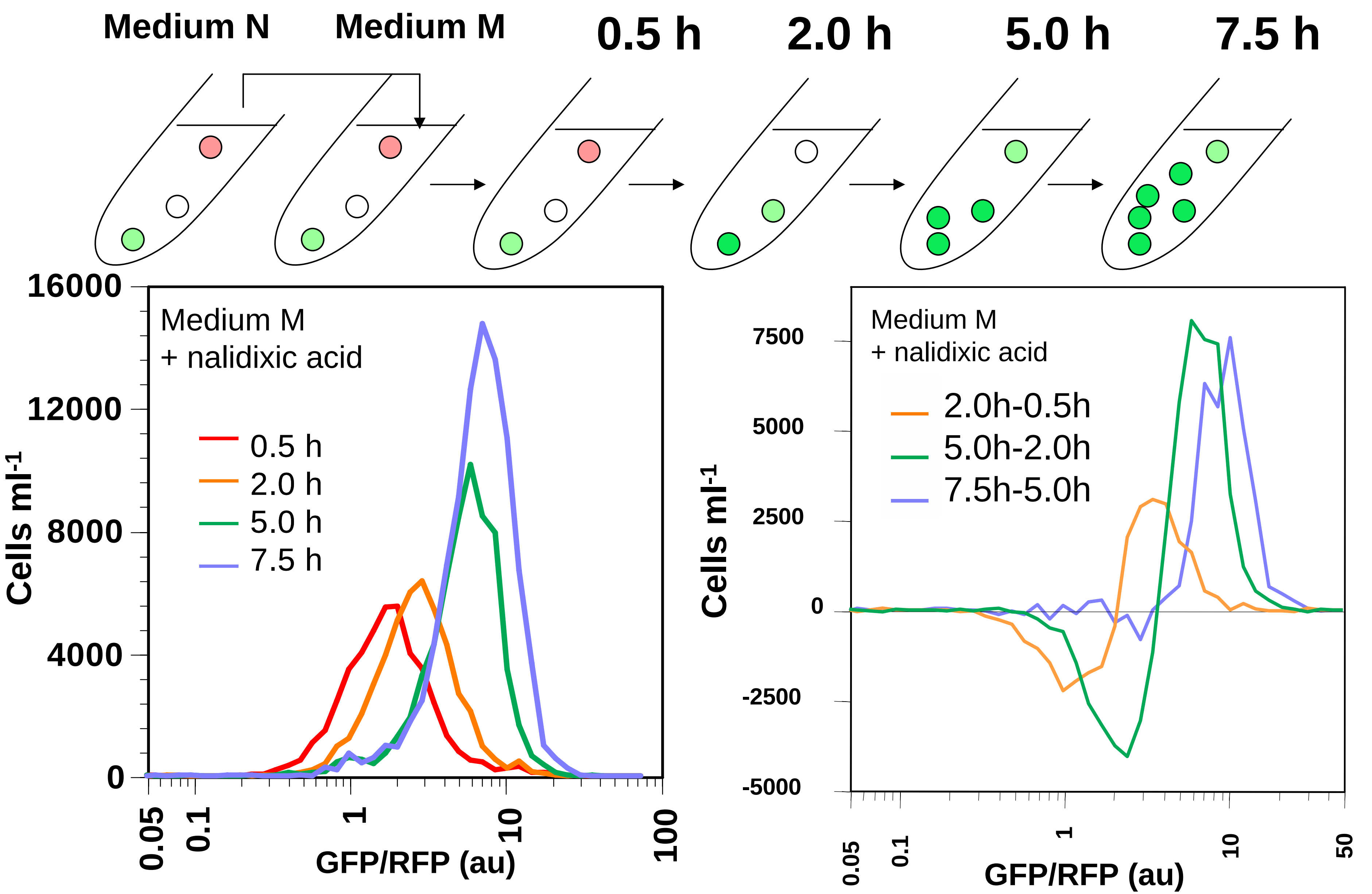
Scenario 1: the propagation of a few cells that happened to ex the fitter phenotype



Scenario 2: the adaptive change in gene expression of each cell before its growing



Temporal change of gene expression in response to glutamine depletion



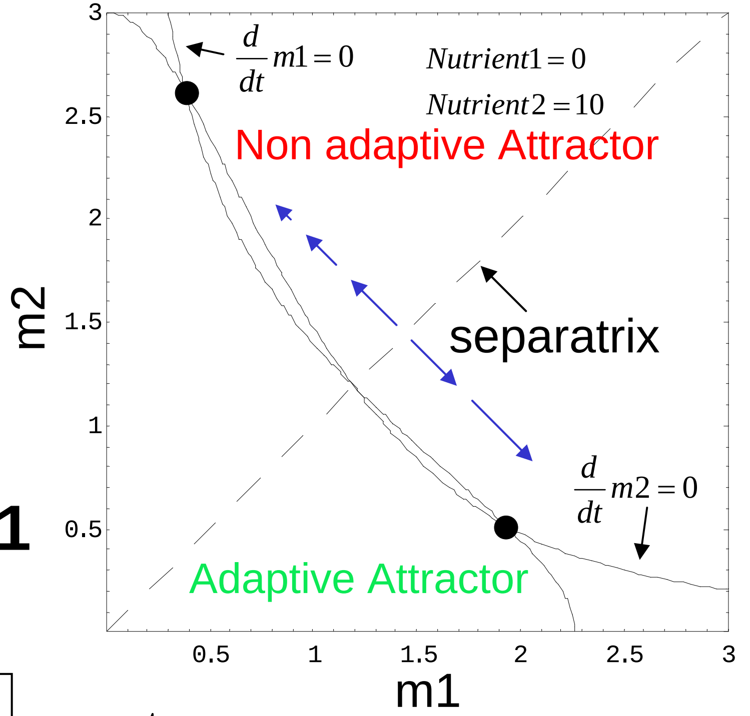
Attractor 2 ← **AttractorW** → **Attractor 1**

Mechanism of the fitness-induced attractor selection

$$\frac{d}{dt}m1 = \frac{S(act)}{1+m2^2} - D(act)\times m1 + \eta_1$$

$$\frac{d}{dt}m2 = \frac{S(act)}{1+m1^2} - D(act)\times m2 + \eta_2$$

$$\frac{d}{dt}act = \frac{pro}{\left(\left(\frac{Nut\_thread_1}{m1+Nutrient1}\right)^{n_1}+1\right)\times\left(\left(\frac{Nut\_thread_2}{m2+Nutrient2}\right)^{n_2}+1\right)} - cons\times act$$



Adaptive attractor with a lager m1

Unstable steady state with m1=m2

Non adaptive attractor with a smaller m1

Decrease in cellular activity

Decrease in deterministic control

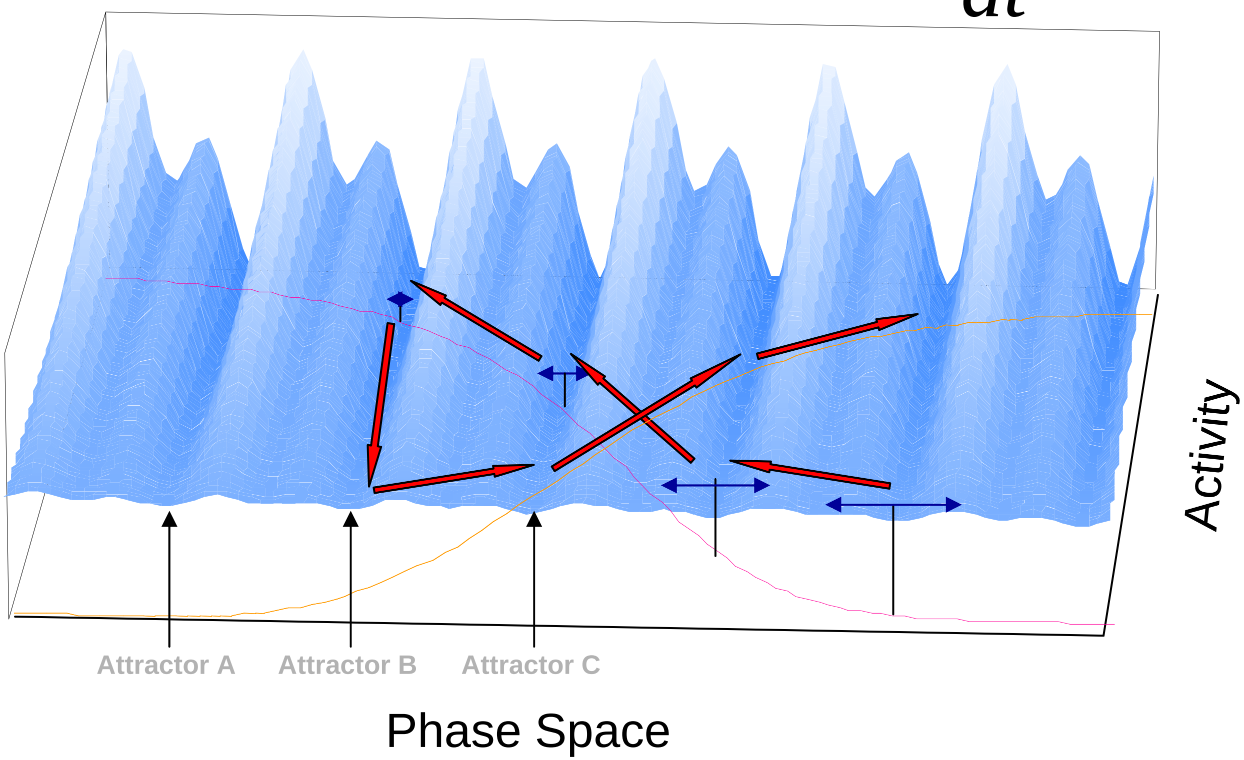
Domination of noise

Large fluctuation

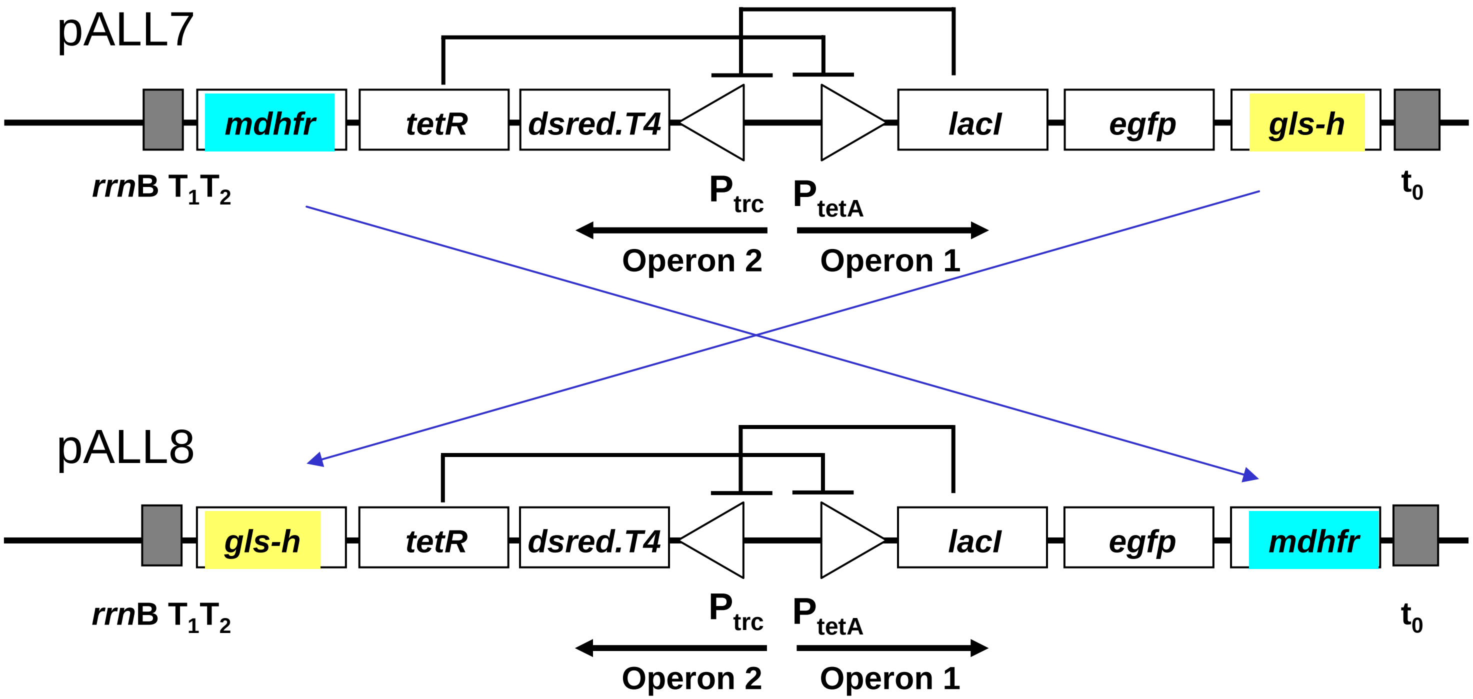
Summary

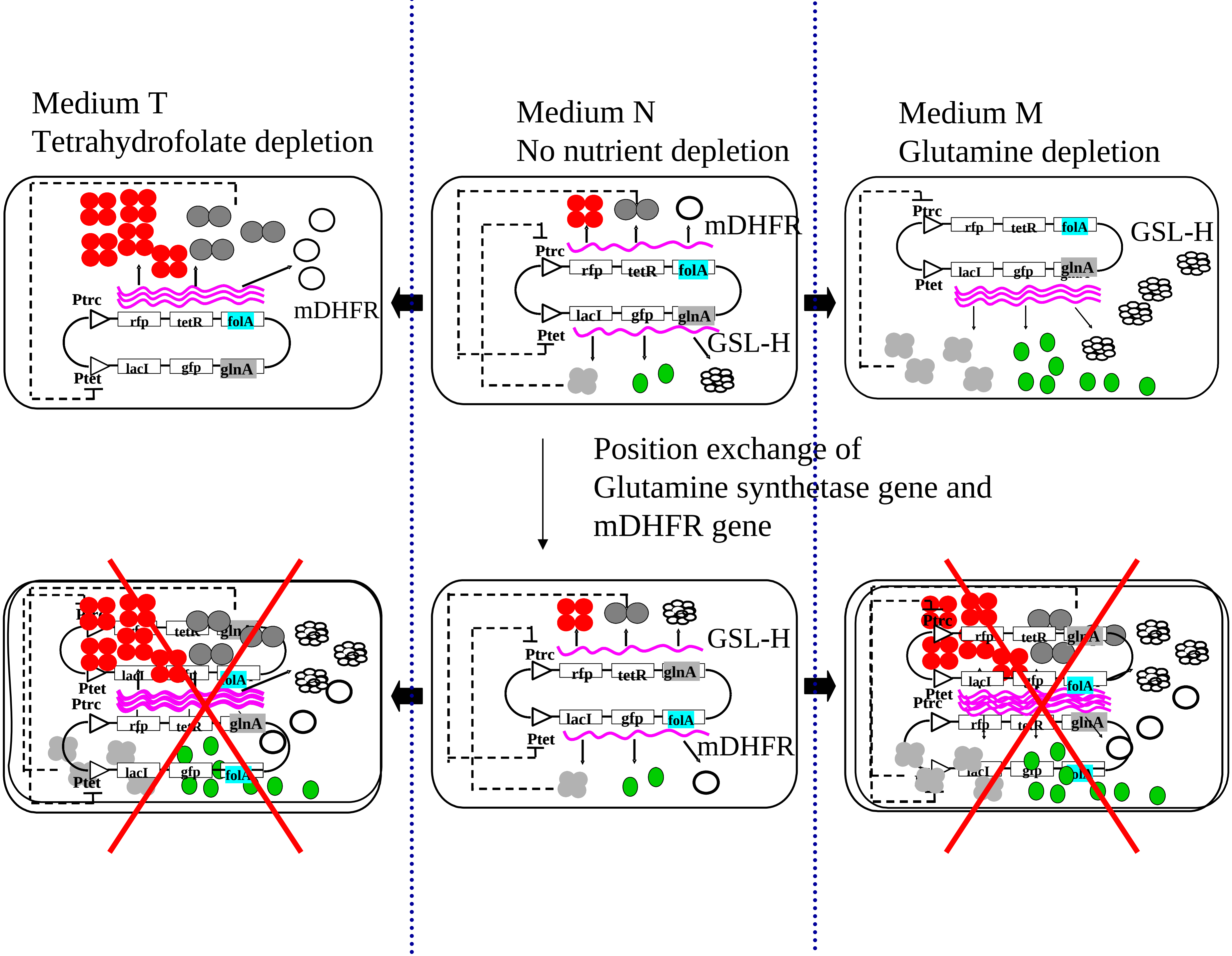
Fitness-induced attractor selection can work for adaptive response to environmental changes for which no signal transduction machineries are available. Because of its noise-driven manner, it may be not very efficient.

$$\frac{d}{dt}\vec{x} = \vec{f}(\vec{x}) \times activity + \vec{\eta}$$



Did unknown signal transduction machineries, which could be encoded on *E.coli* genome, transfer the information of the nutrient depletion to the promoter regions in the mutually inhibitory operons?

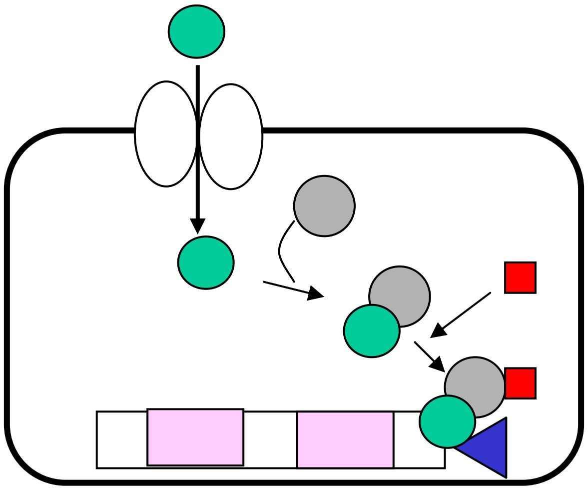




Medium T
Tetrahydrofolate depletion
Medium N
No nutrient depletion
Medium M
Glutamine depletion
mDHFR
GSL-H
Ptrc
Ptet
rfp
tetR
folA
lacI
gfp
glnA
Position exchange of
Glutamine synthetase gene and
mDHFR gene

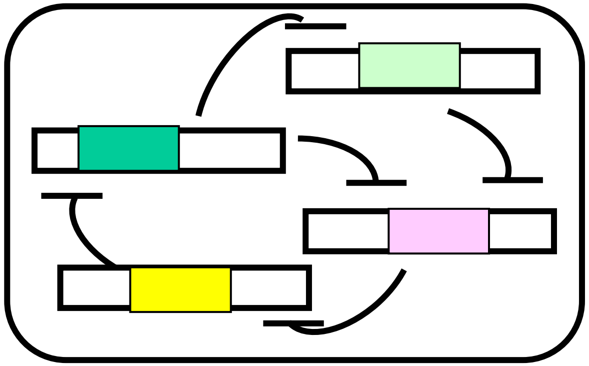
Two complimentary mechanisms for adaptive response to environmental changes

Signal transduction from environment to promoters



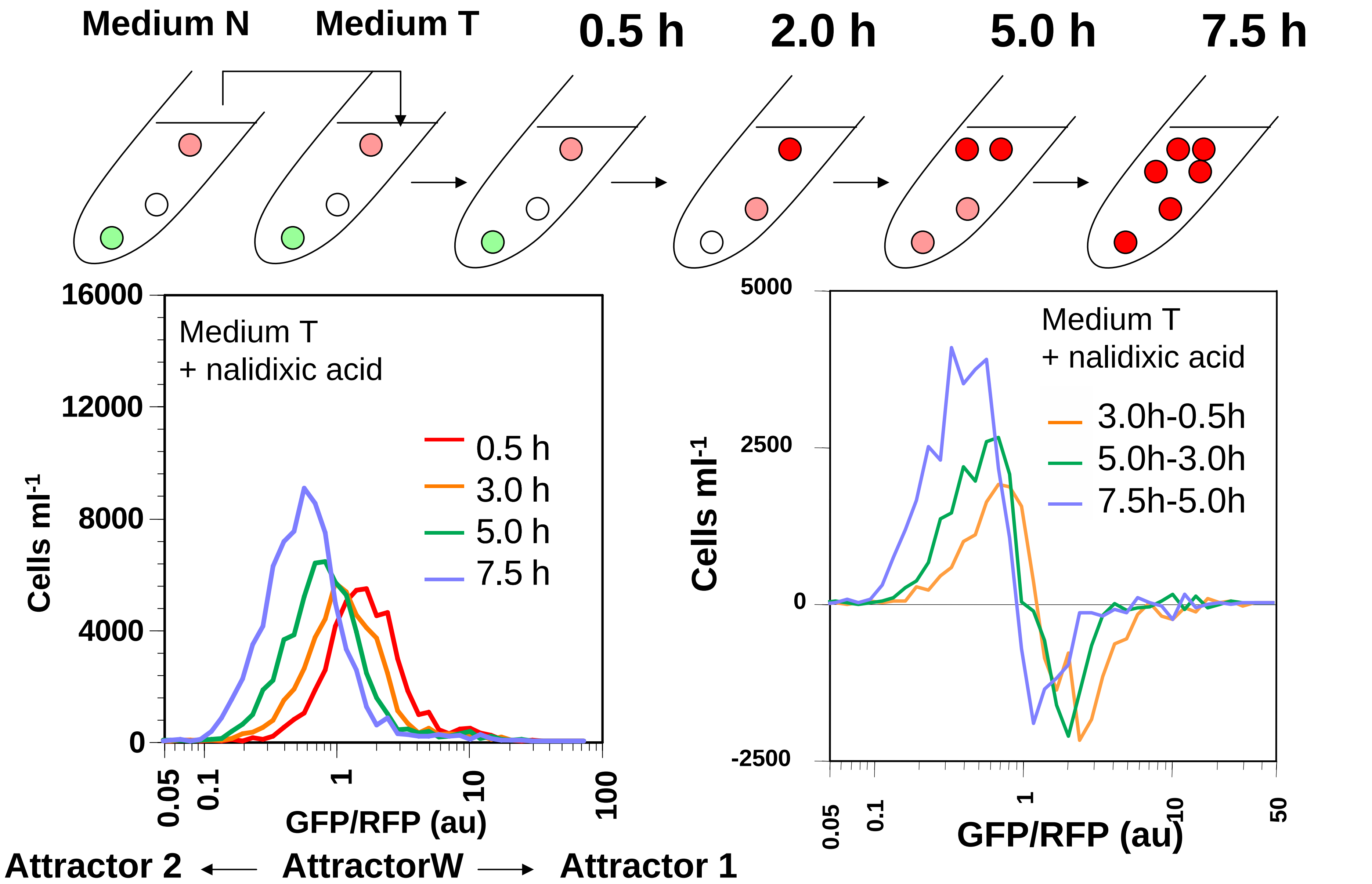
1) Requires molecular devices, which the organisms have evolved in experiencing the similar environmental changes in the past.
2) Works by a chain reaction of molecular chips, each of which works in an if-then-else protocol with a certain threshold.

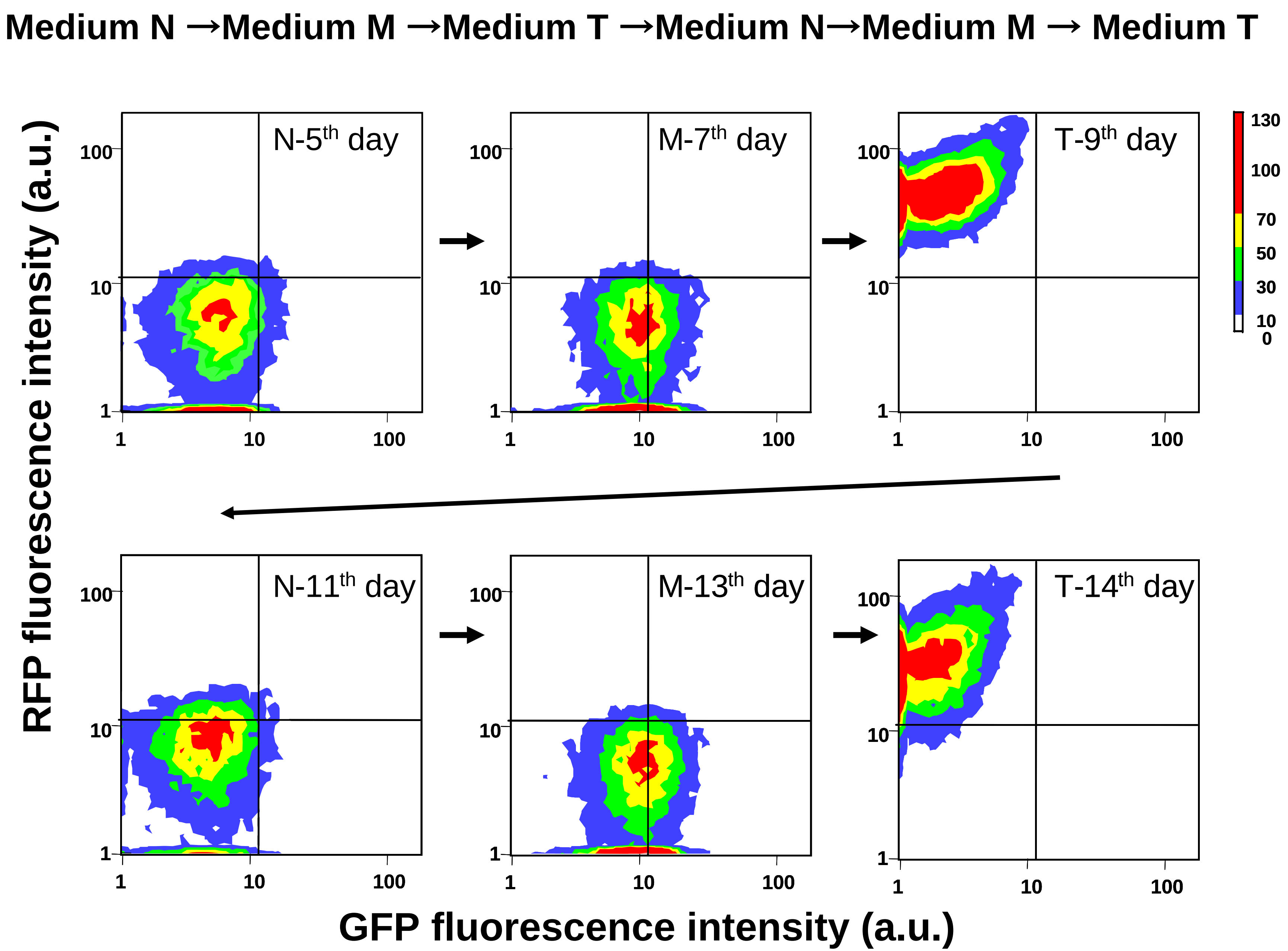
Fitness-induced Attractor selection



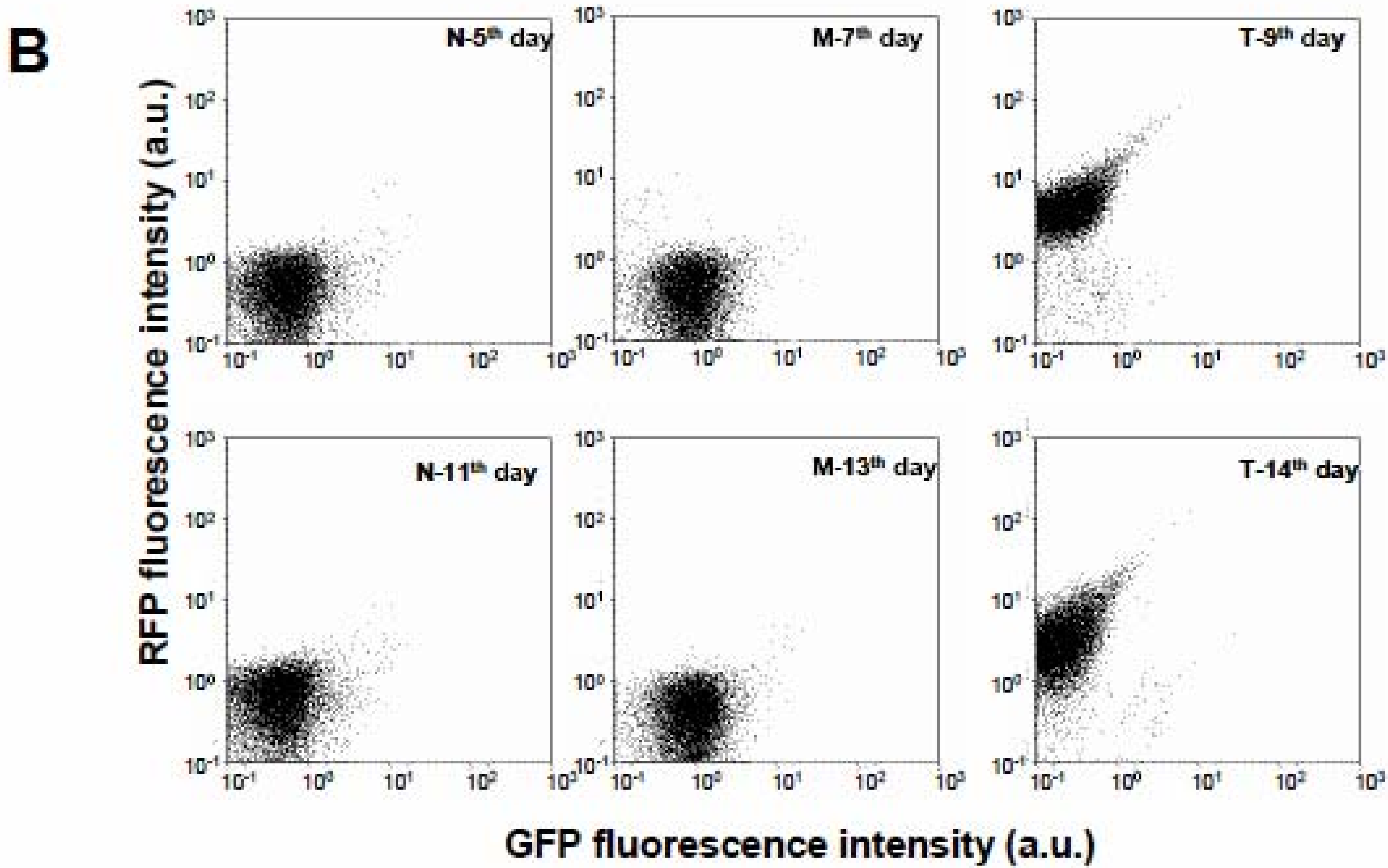
1) Requires regulatory loops that are inherently embedded in the genomic complex network.
2) Works in a noise-tolerant even noise-induced manner.

Temporal change of gene expression in response to Medium T





Medium N →Medium M →Medium T →Medium N→Medium M → Medium T
N-5th day
M-7th day
T-9th day
N-11th day
M-13th day
T-14th day
130
100
70
50
30
10
0
1
10
100
RFP fluorescence intensity (a.u.)
GFP fluorescence intensity (a.u.)


B
N-5th day
M-7th day
T-9th day
N-11th day
M-13th day
T-14th day
RFP fluorescence intensity (a.u.)
GFP fluorescence intensity (a.u.)

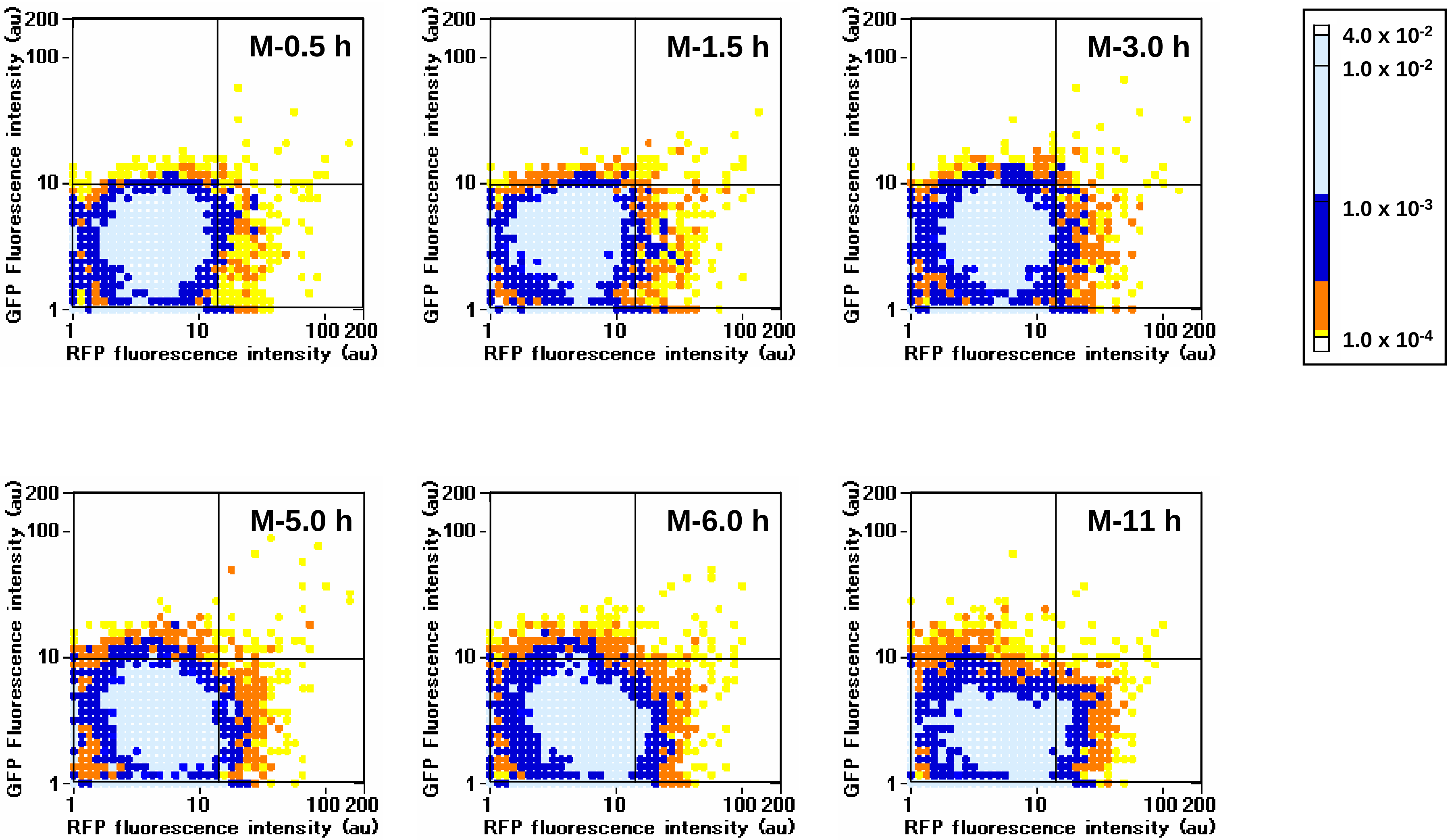


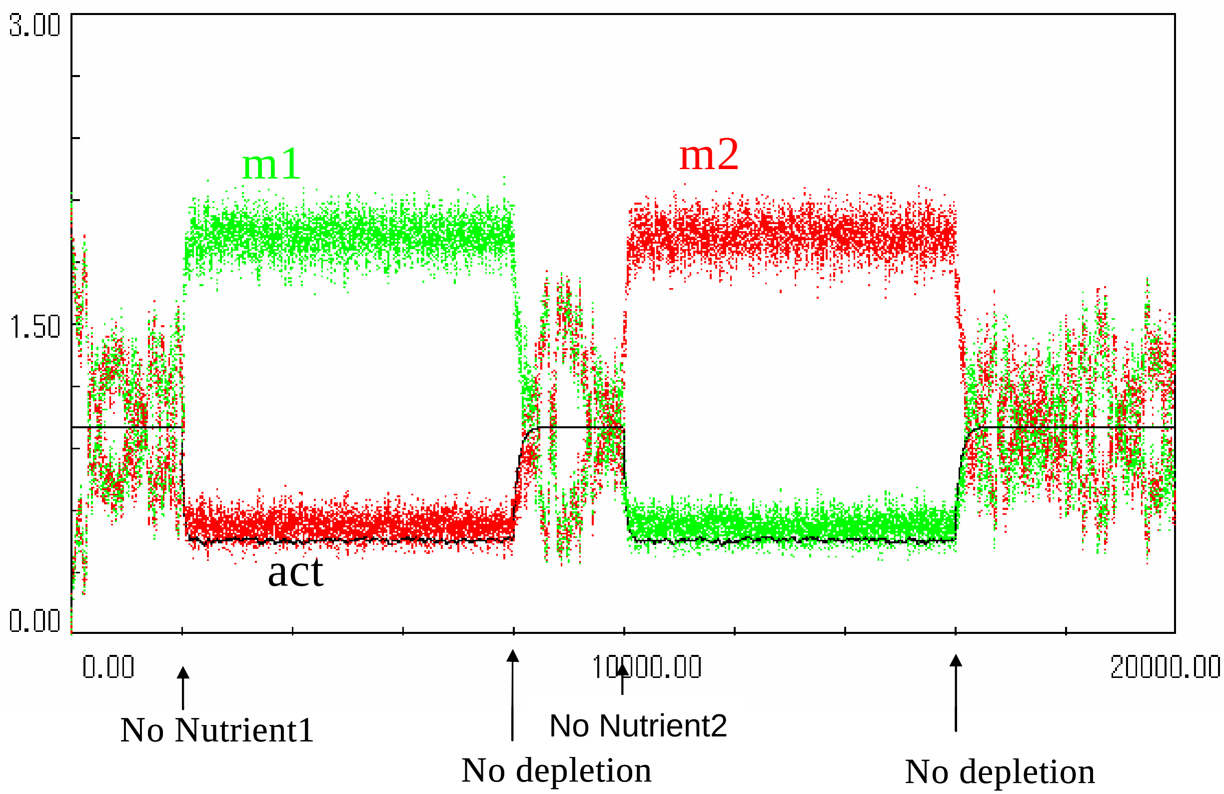
Fig. R1-2-1 The temporal change of the cell population inoculated from Medium N to Medium M.
The density is presented by the ratio of the number of dots at each window to the total dots observed

$$\frac{d}{dt}m1 = \underbrace{\frac{syn(act)}{1+m2^2}}_{\text{Synthesis rate}} - \underbrace{\deg(act)\times m1}_{\text{Degradation rate}} + \underbrace{\eta_1}_{\text{noise}}$$

$$syn(act) = \frac{6act}{2+act};\ \deg(act) = act;$$

$$\frac{d}{dt}m2 = \frac{syn(act)}{1+m1^2} - \deg(act)\times m2 + \eta_2$$

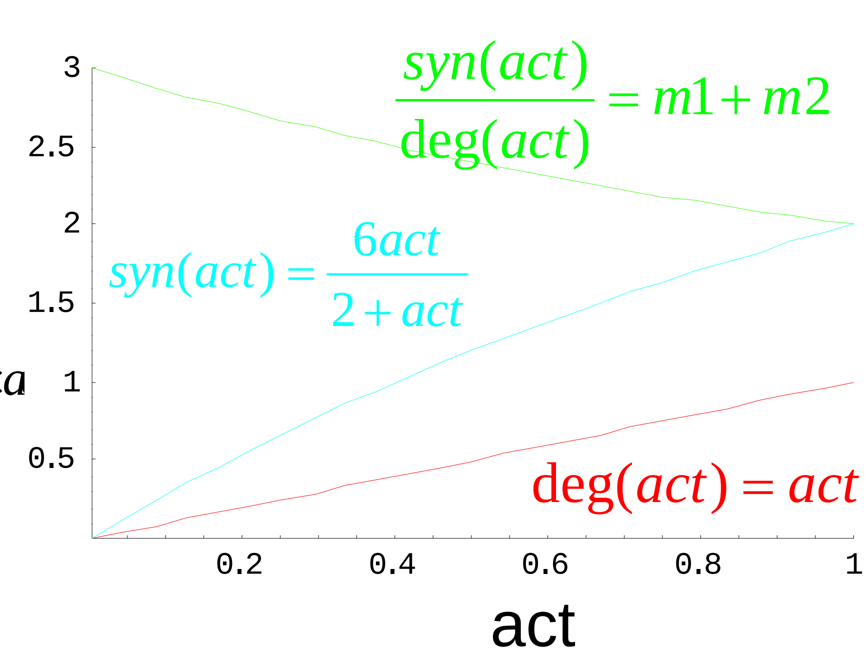
$$\frac{d}{dt}act = \frac{pro}{\left(\left(\frac{Nut\_thread_1}{m1+Nutrient1}\right)^{n_1}+1\right)\times\left(\left(\frac{Nut\_thread_2}{m2+Nutrient2}\right)^{n_2}+1\right)} - cons\times act$$

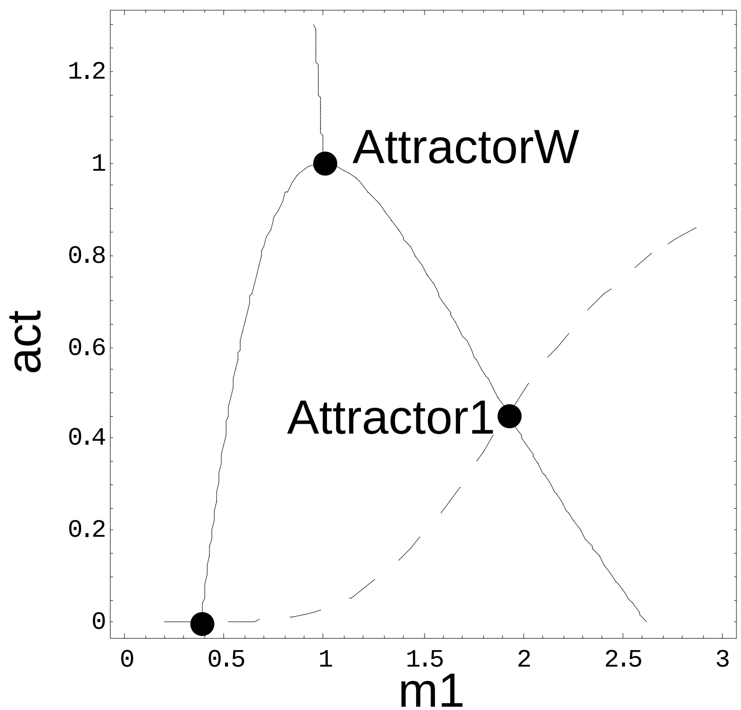


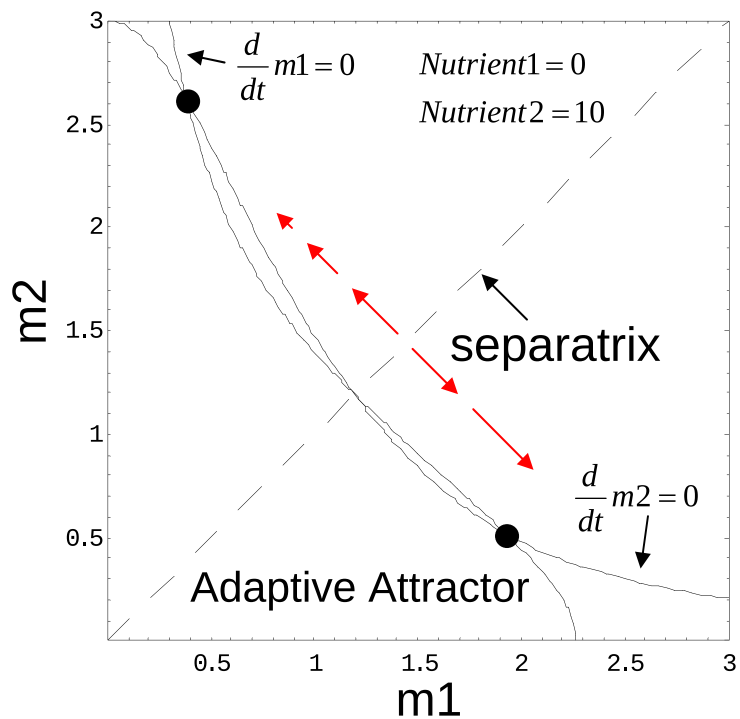
$$\frac{d}{dt}m1 = \frac{syn(act)}{1+m2^2} - \deg(act)\times m1 + \eta_1$$

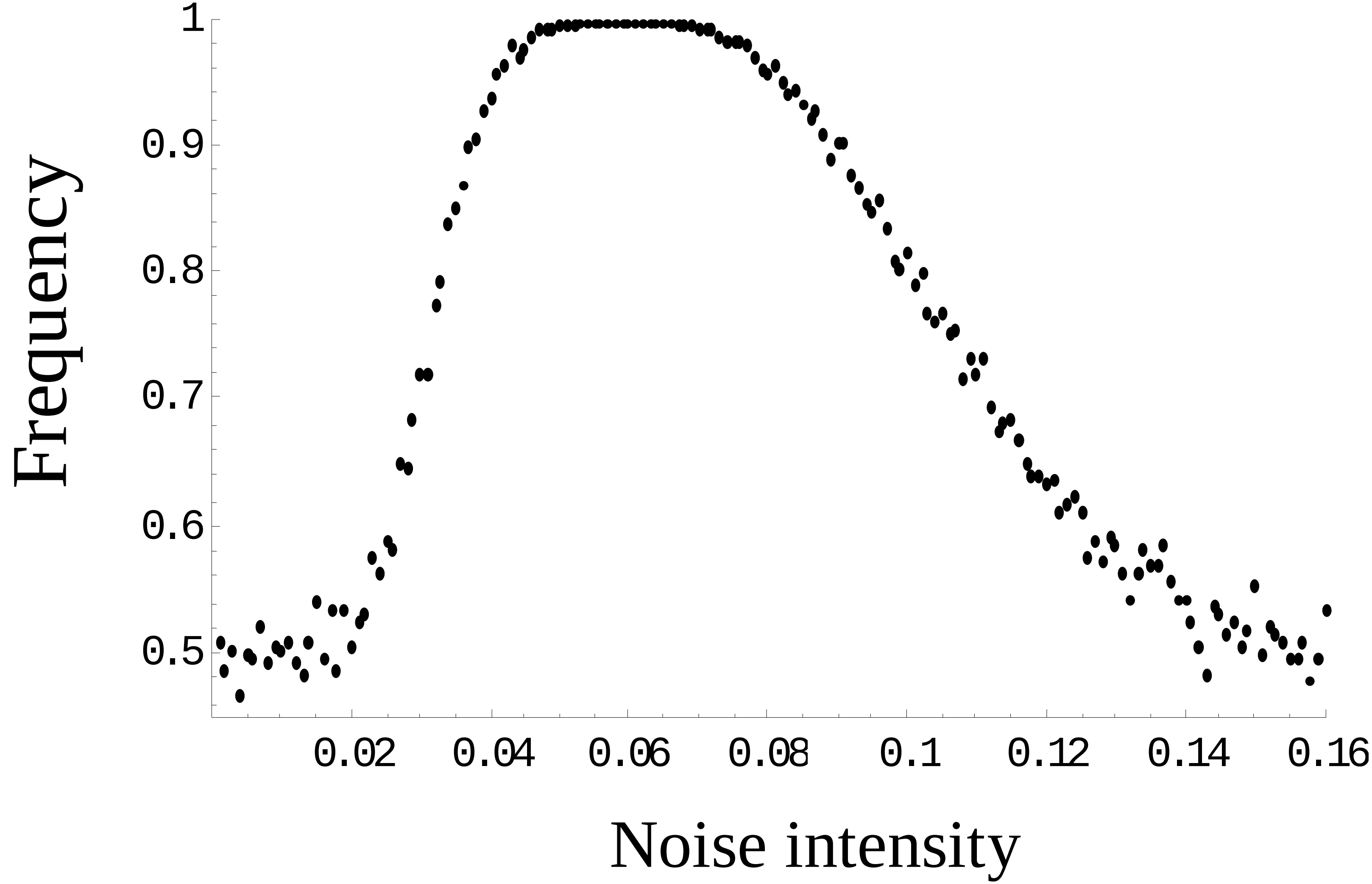
$$\frac{d}{dt}m2 = \frac{syn(act)}{1+m1^2} - \deg(act)\times m2 + \eta_2$$

$$\frac{d}{dt}act = \frac{pro}{\left(\left(\frac{Nut\_thread_1}{m1+Nutrient1}\right)^{n_1}+1\right)\times\left(\left(\frac{Nut\_thread_2}{m2+Nutrient2}\right)^{n_2}+1\right)} - cons\times a$$









Noise dependence of attractor selection