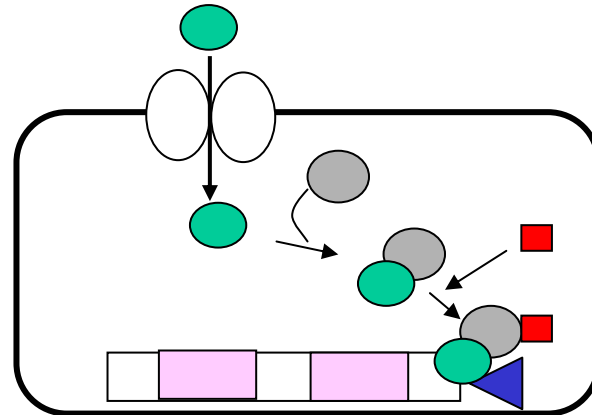


Adaptive response of unicellular organisms to environmental change

## 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 changes

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?



**Akiko Kashiwagi**



**Itaru Urabe**



**Kunihiro Kaneko  
(Univ. Tokyo)**

## **Acknowledgement**

Barry L. Wanner (Purdue Univ.)

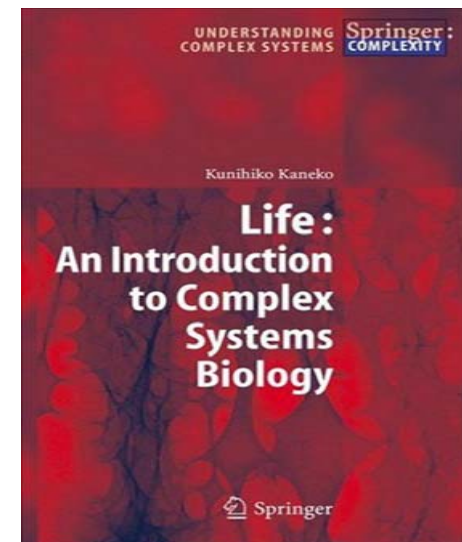
Nancy Kleckner (Harvard Univ.)

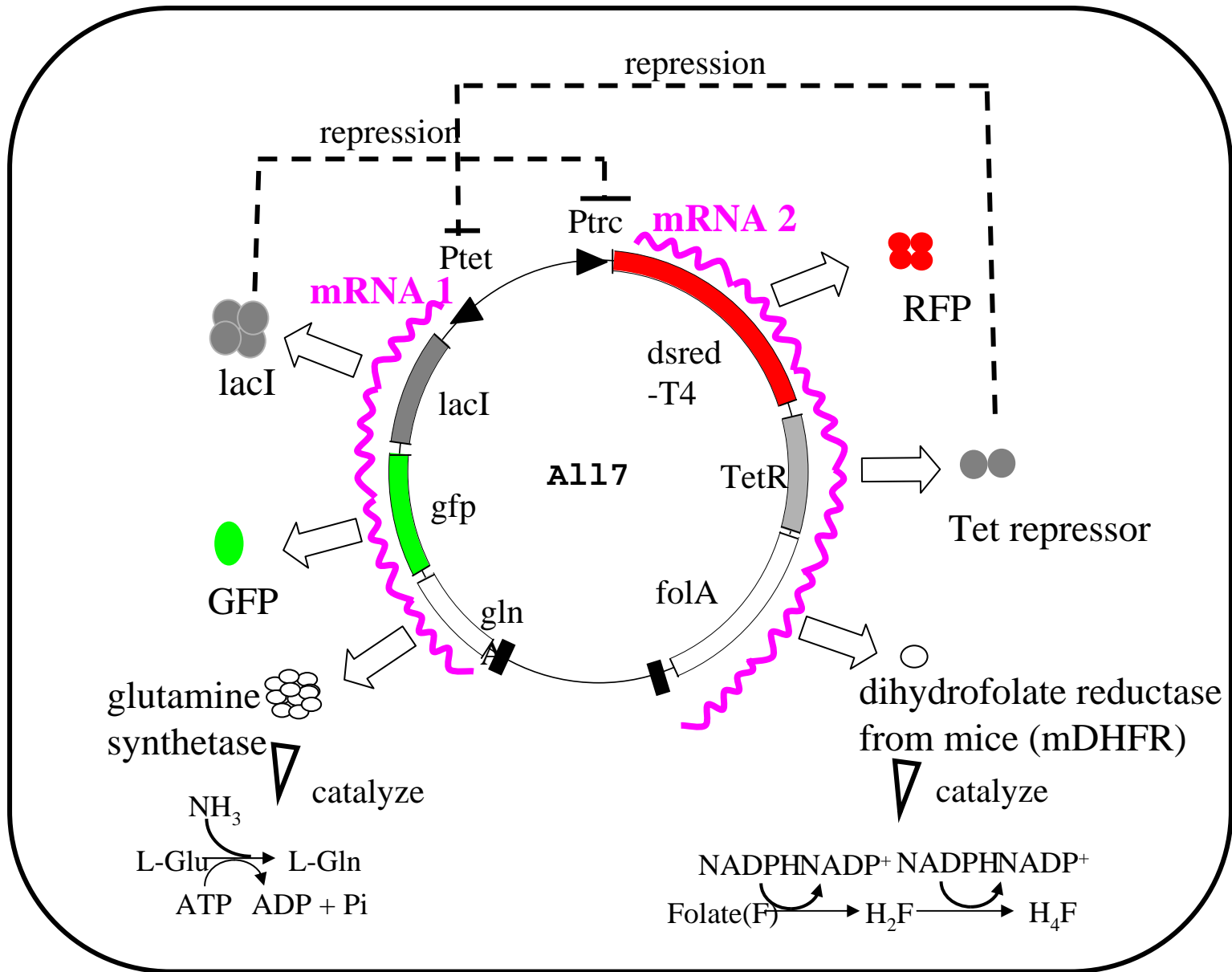
Chikara Furusawa (Osaka Univ.)

Satoshi Sawai (Osaka Univ.)

Katsuhiko Sato (Univ. Tokyo)

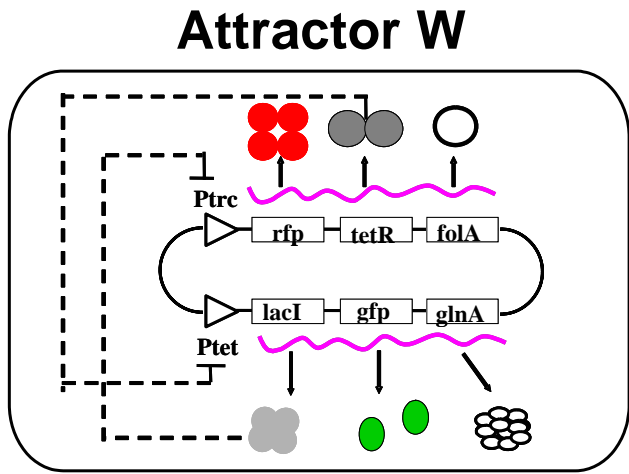
Tsuyoshi Chawanya (Osaka Univ.)



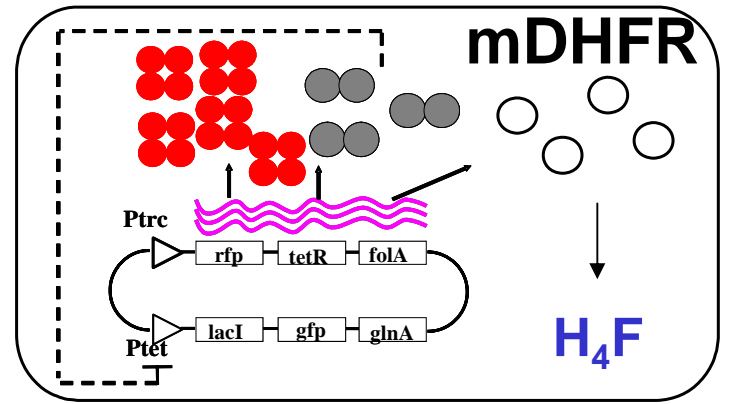
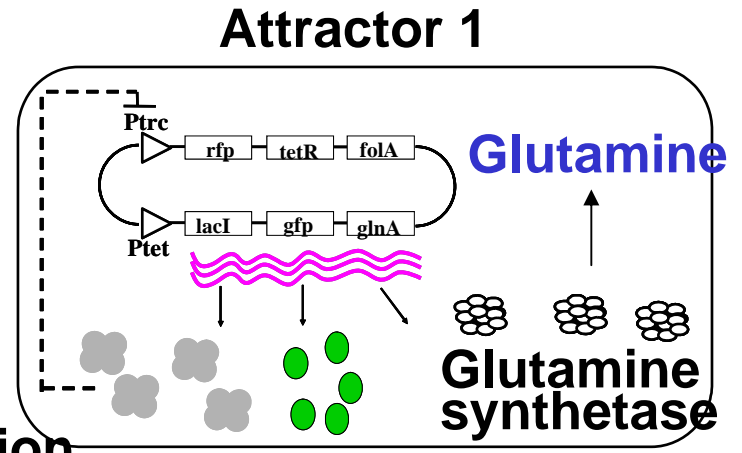


Gardner, T. S., Cantor, C. R. & Collins, J. J. (2000). *Nature* **403**, 339-42  
 Elowitz MB, Leibler S (2000). *Nature* **403**: 335-338.

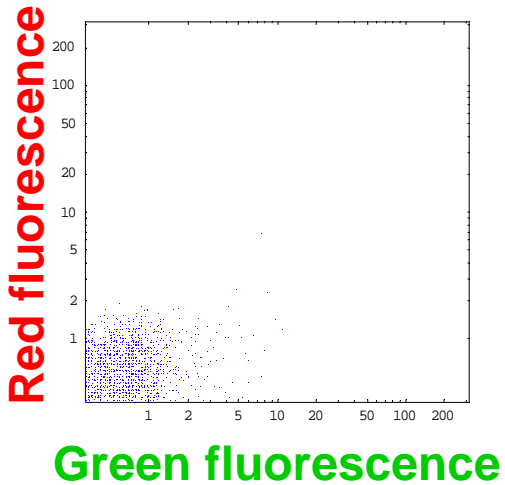




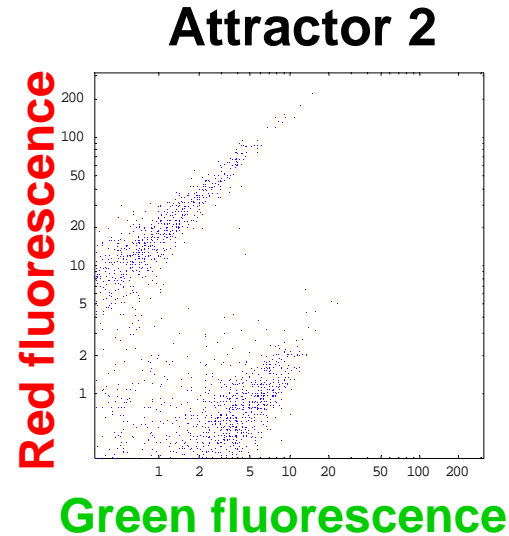
Stochastic differentiation



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



By increasing the total concentration of both repressors

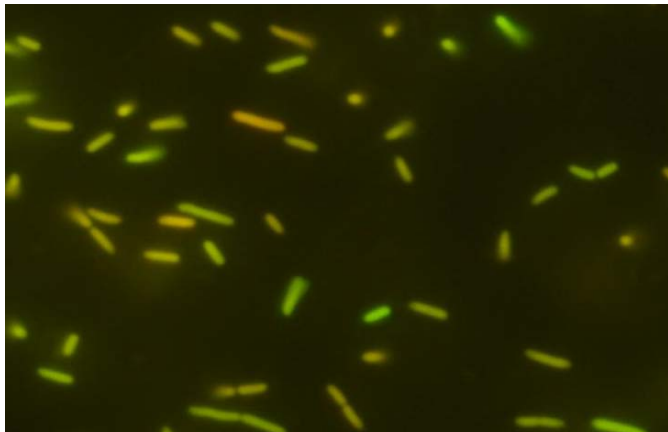
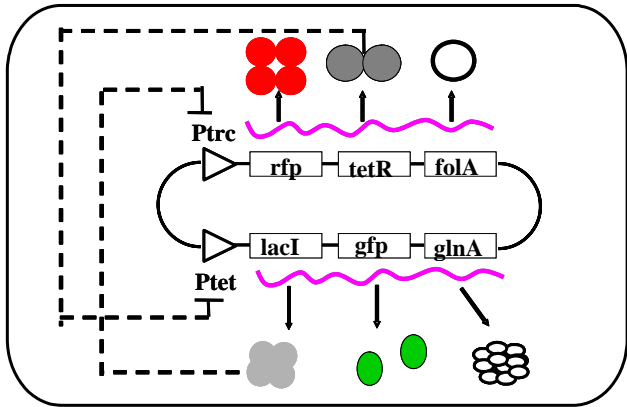


The stochastic differentiation is a property designed in the mutually inhibitory network.

**Question:**

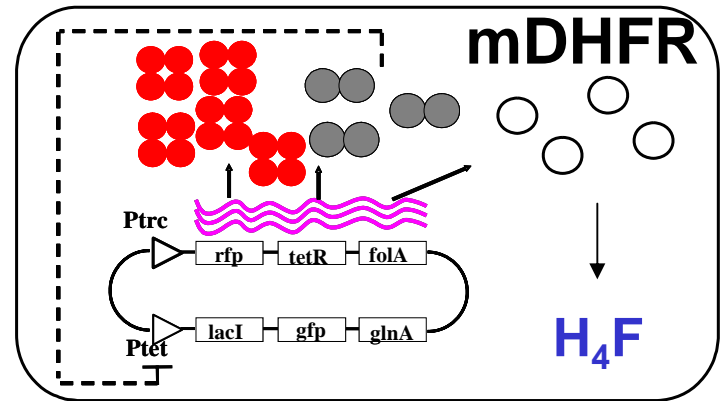
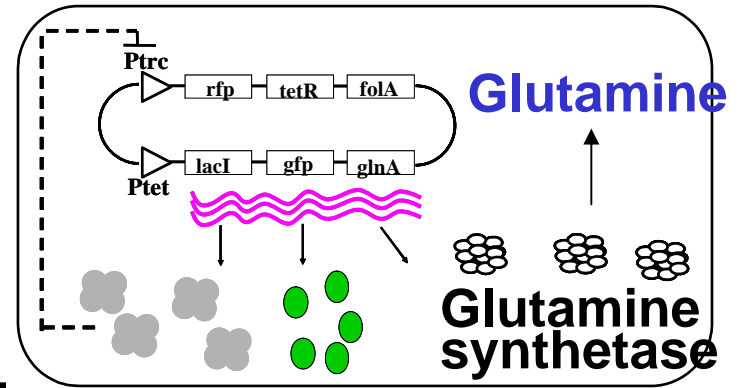
**Against the stochastic nature, do the cells, when imposed to selective environments, choose the adaptive attractor?**

**Attractor W**



**Stochastic differentiation**

**Attractor 1**

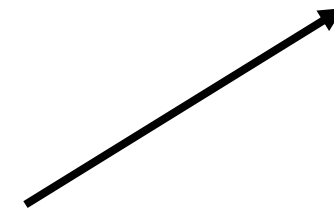
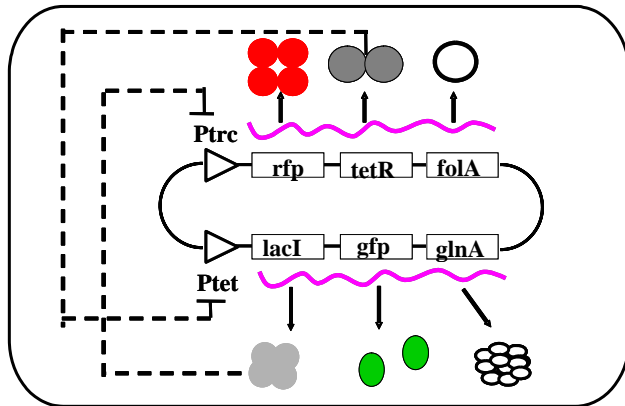


**Attractor 2**

# Question:

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

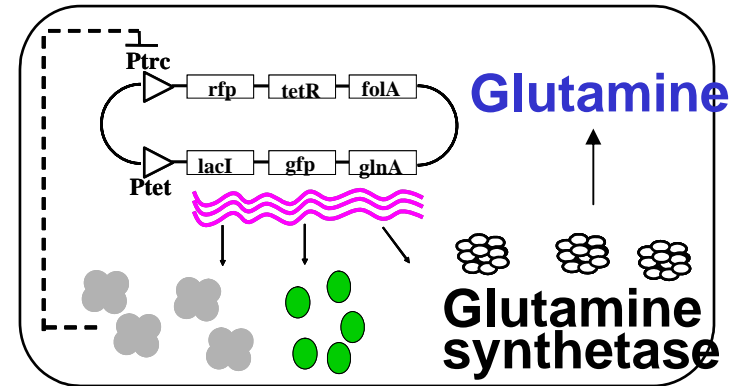
### Attractor W



Fitness-induced selection

## Glutamine depletion

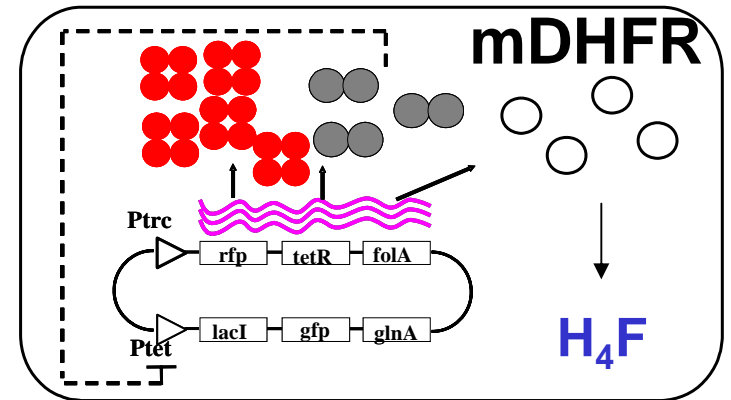
### Attractor 1



Glutamine

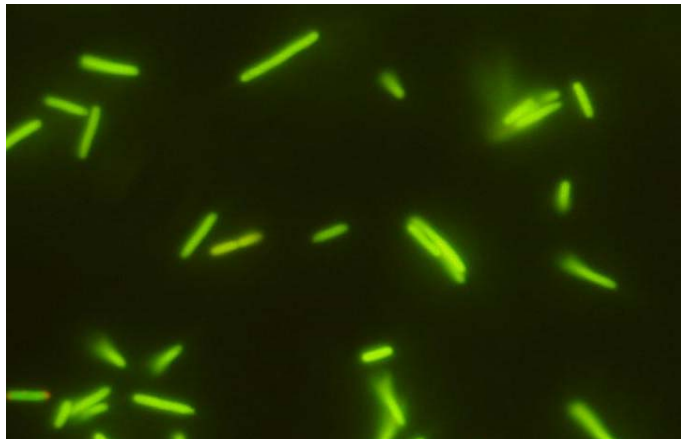
Glutamine synthetase

### mDHFR

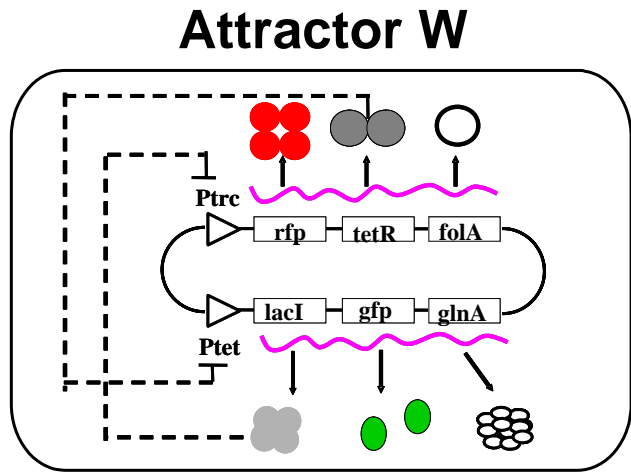


H<sub>4</sub>F

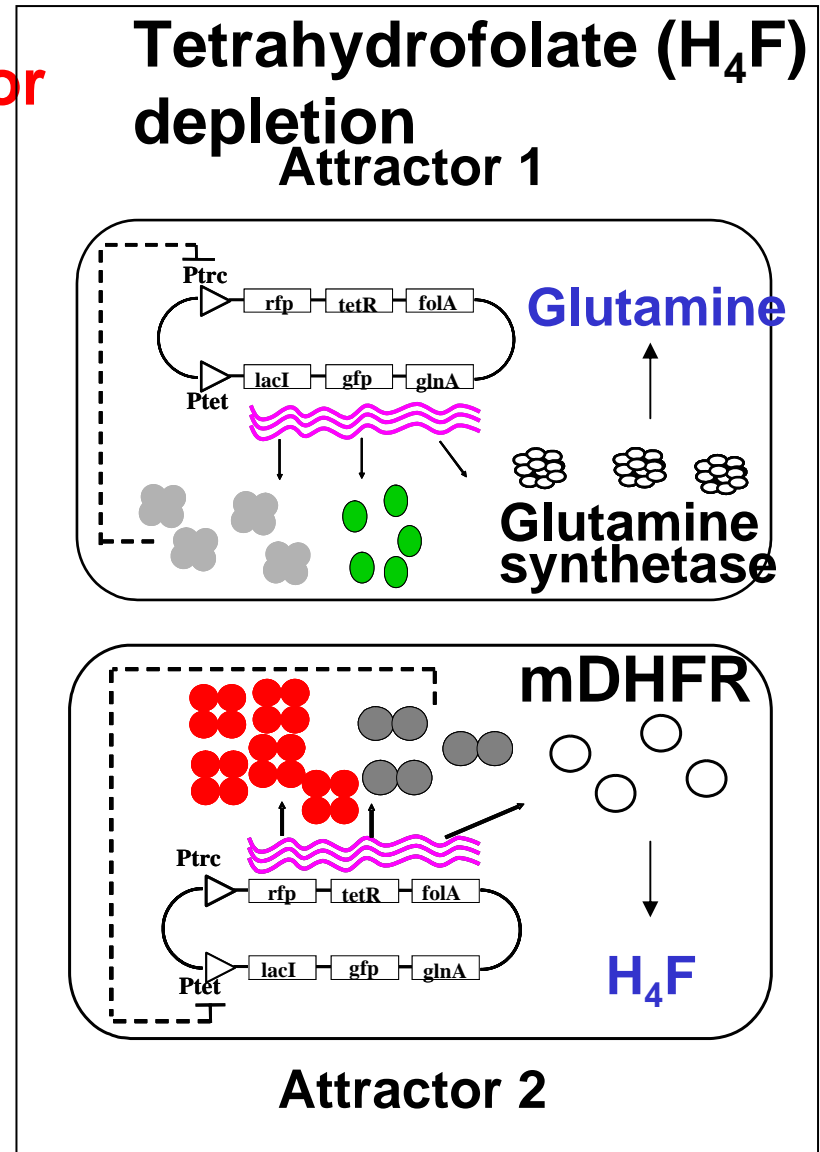
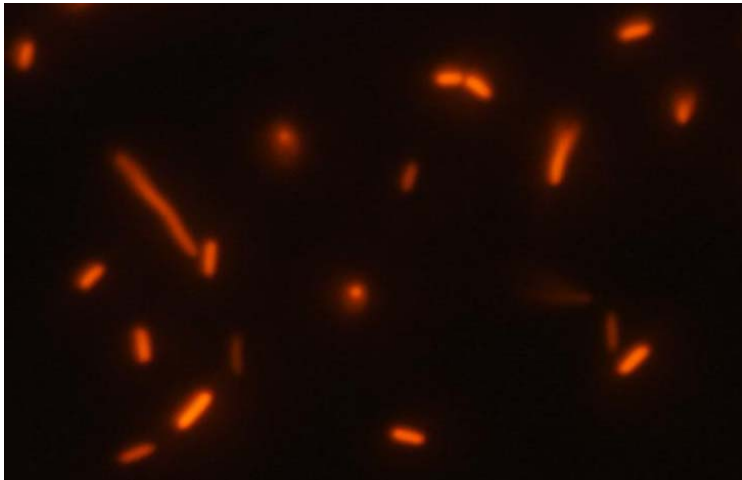
### Attractor 2



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

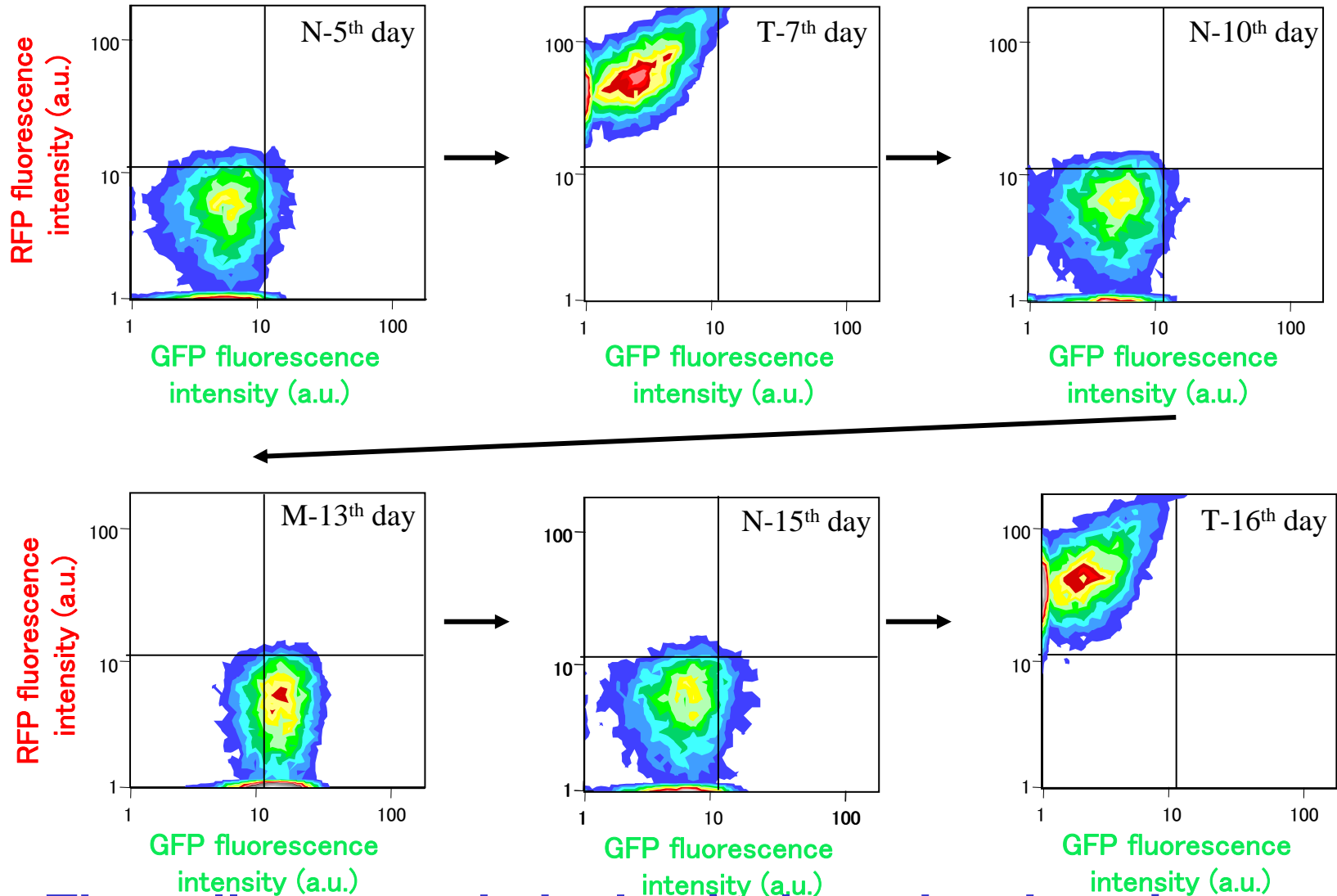


**Fitness-  
induced  
selection**



## Adaptive response in a changing environment

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

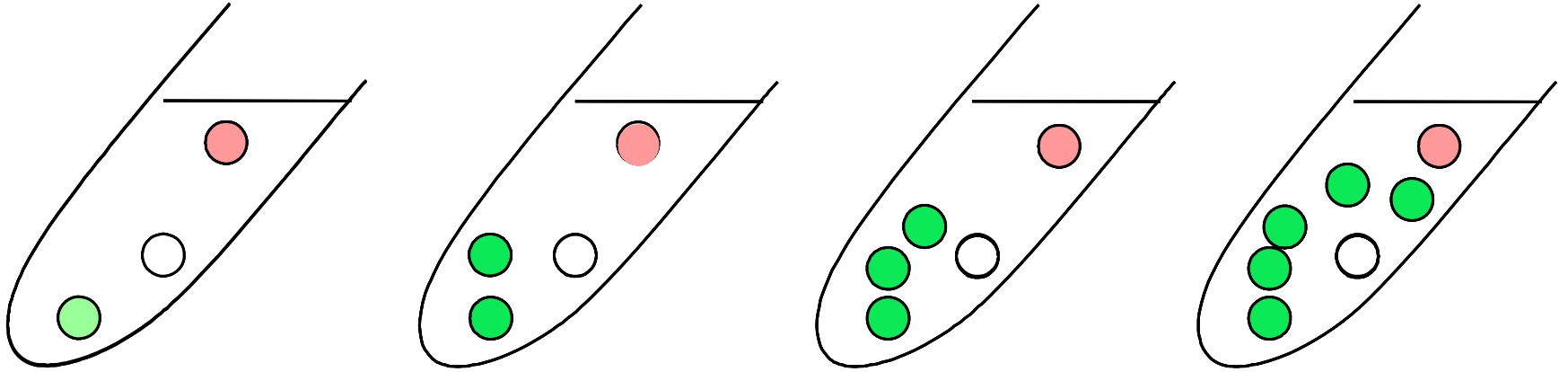


The cells responded adaptively to the changing environment without signal transduction machineries.

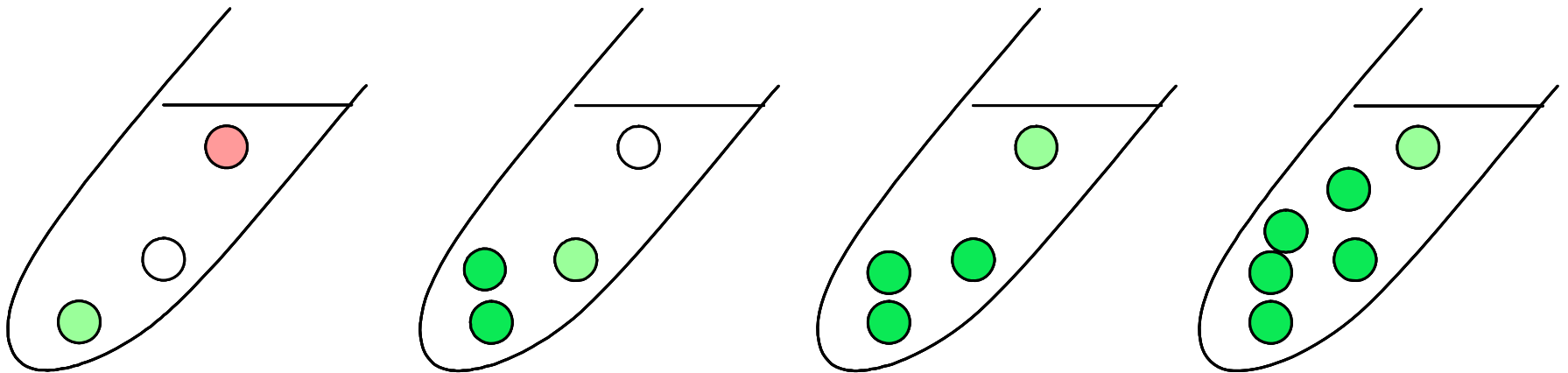


# Two possible scenarios for the adaptive response of the cell population

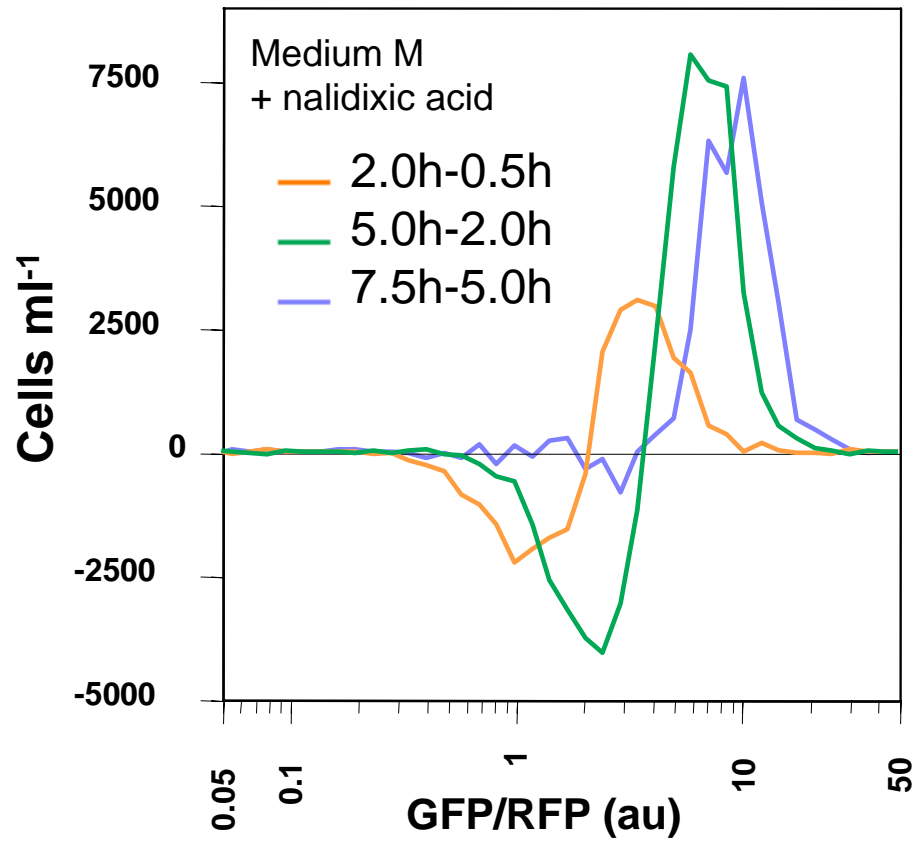
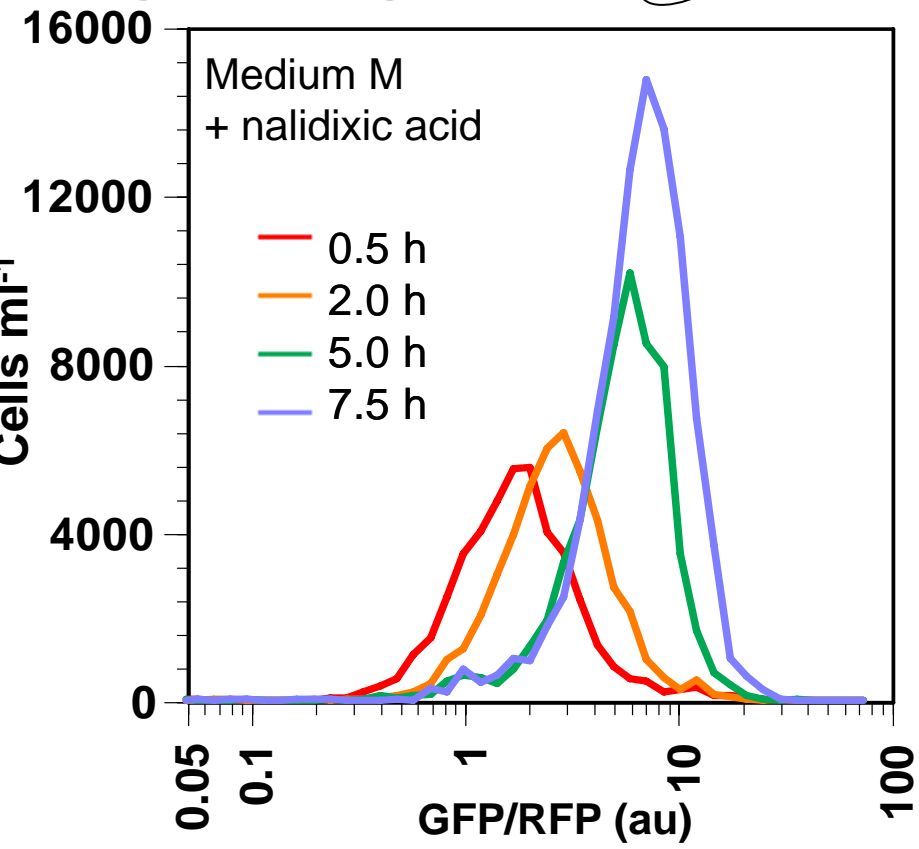
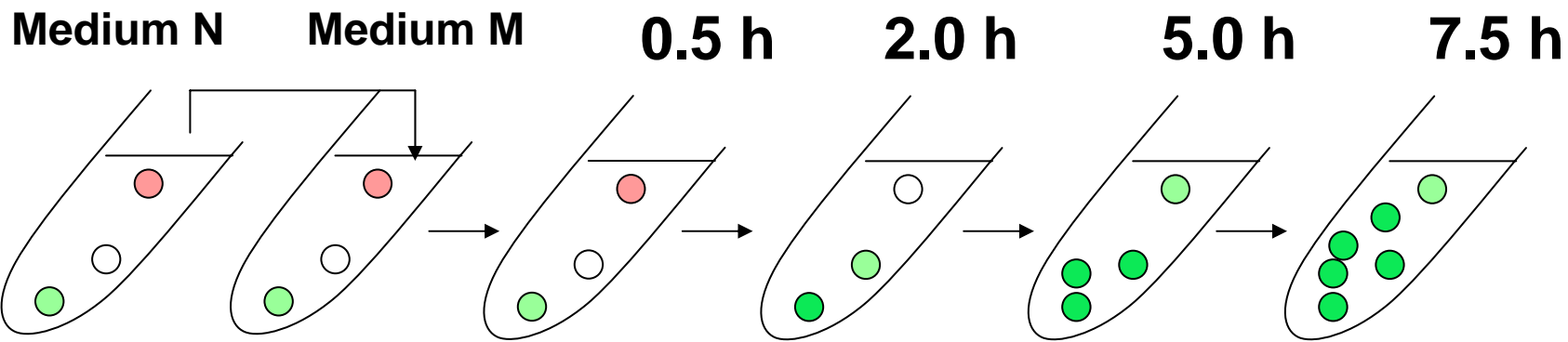
**Scenario 1:** the propagation of a few cells that happened to express the fitter phenotype



**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

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

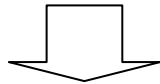
$$\frac{d}{dt} m2 = \frac{S(act)}{1+m1^2} - D(act) \times m2 + \eta_2$$

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

**Adaptive attractor with a larger m1**



**Unstable steady state with m1=m2**



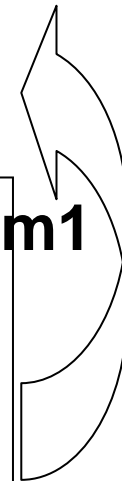
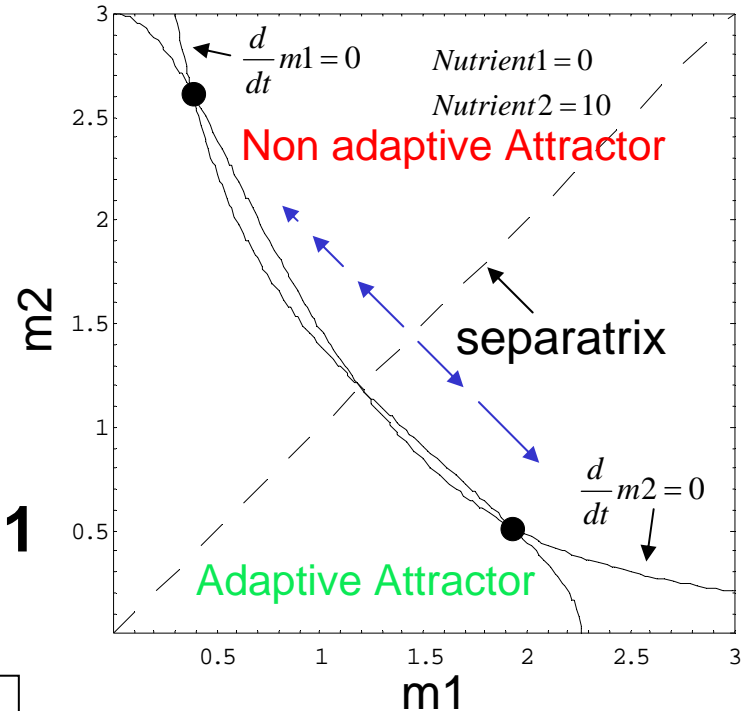
**Non adaptive attractor with a smaller m1**

**Decrease in cellular activity**

**Decrease in deterministic control**

**Domination of noise**

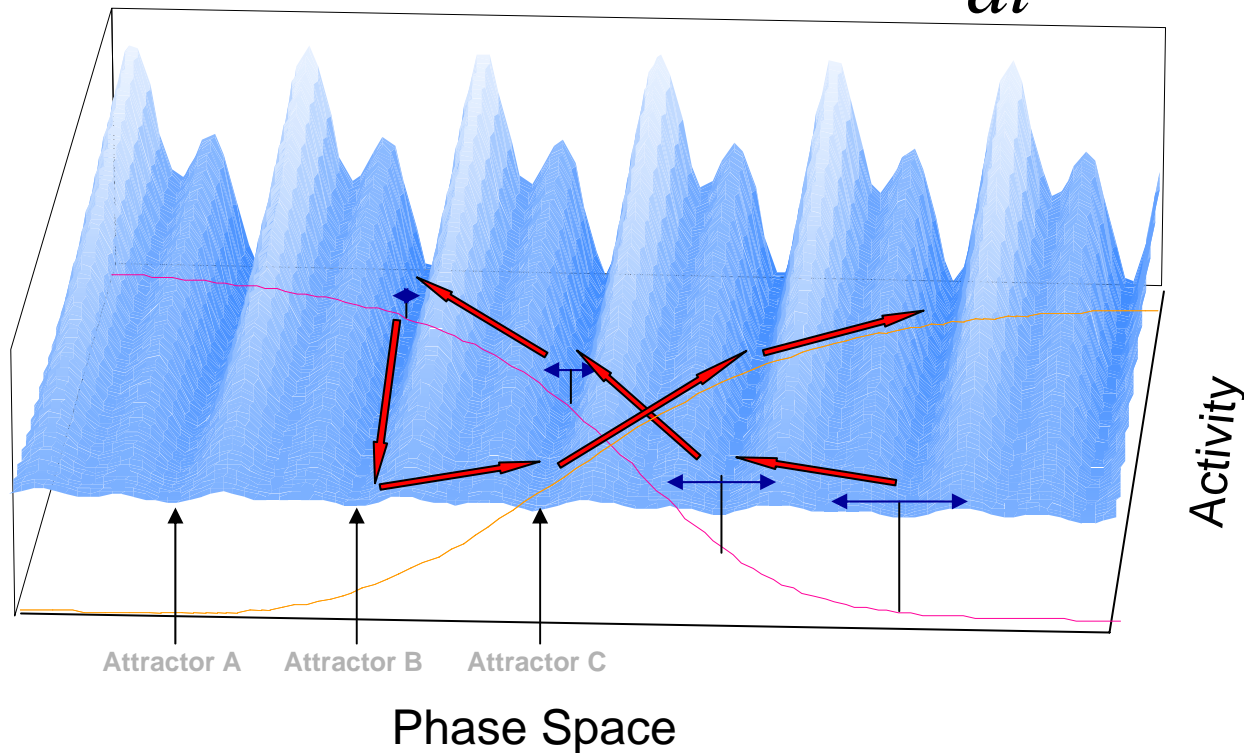
**Large fluctuation**



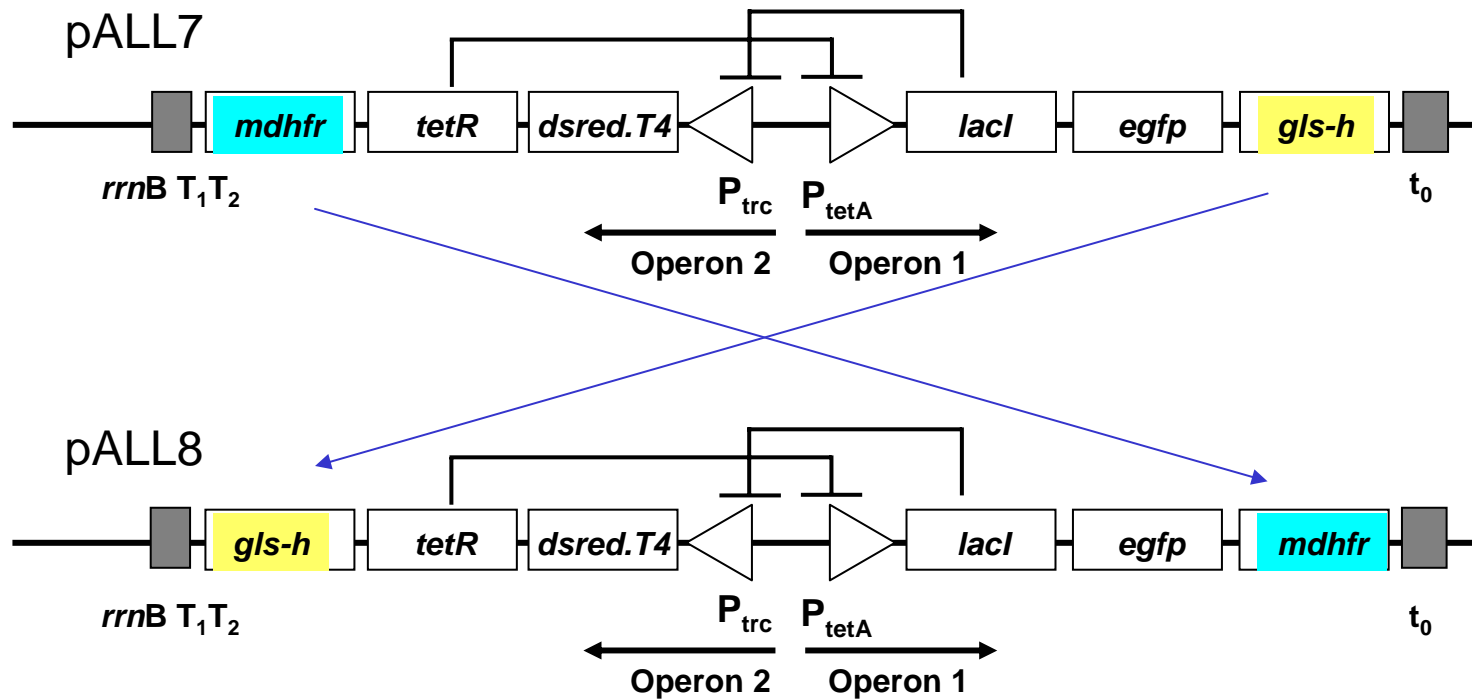
# Summary

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.

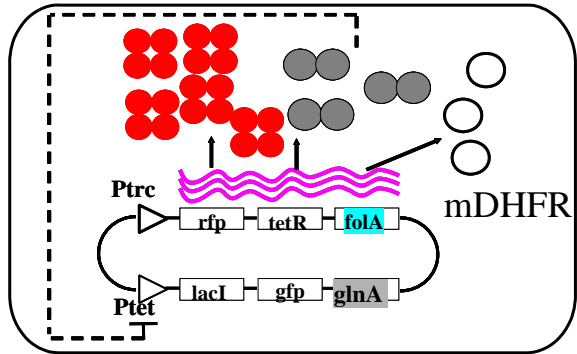
$$\frac{d}{dt} \mathbf{r}_x = \mathbf{f}(\mathbf{r}_x) \times activity + \boldsymbol{\eta}$$



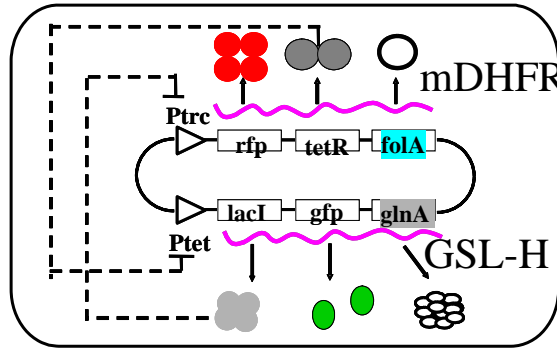
Did unknown signal transduction machineries, which could be encoded on *E.coli* genome, transfer the information of the nutrient depletion to the promoter regions in the mutually inhibitory operons?



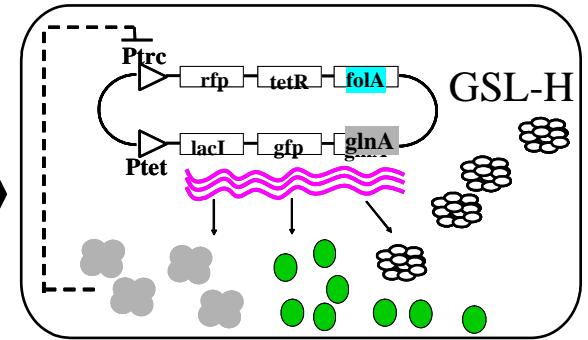
Medium T  
Tetrahydrofolate depletion



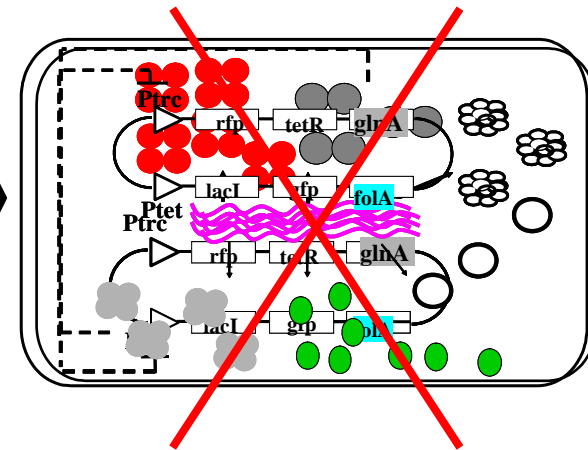
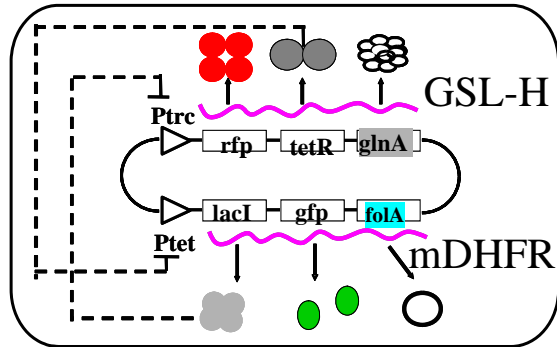
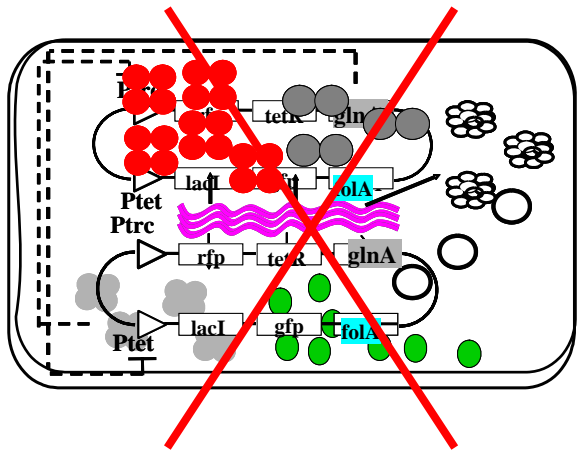
Medium N  
No nutrient depletion



Medium M  
Glutamine depletion

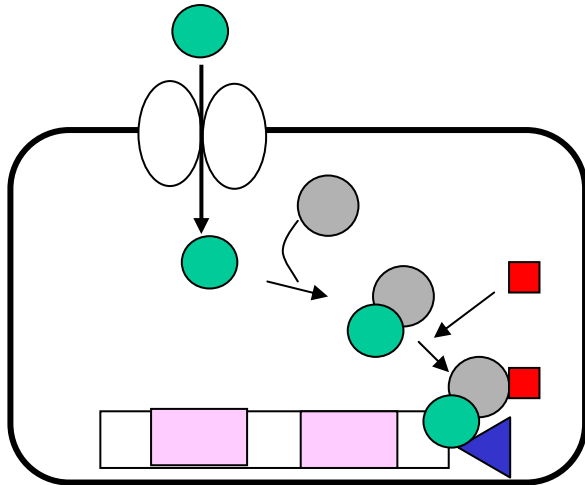


Position exchange of  
Glutamine synthetase gene and  
mDHFR gene



# Two complimentary mechanisms for adaptive response to environmental changes

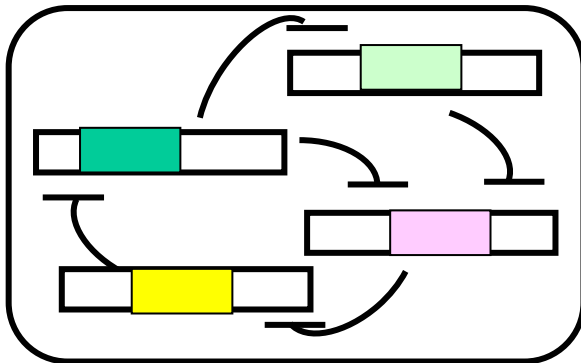
## Signal transduction from environment to promoters



- 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.

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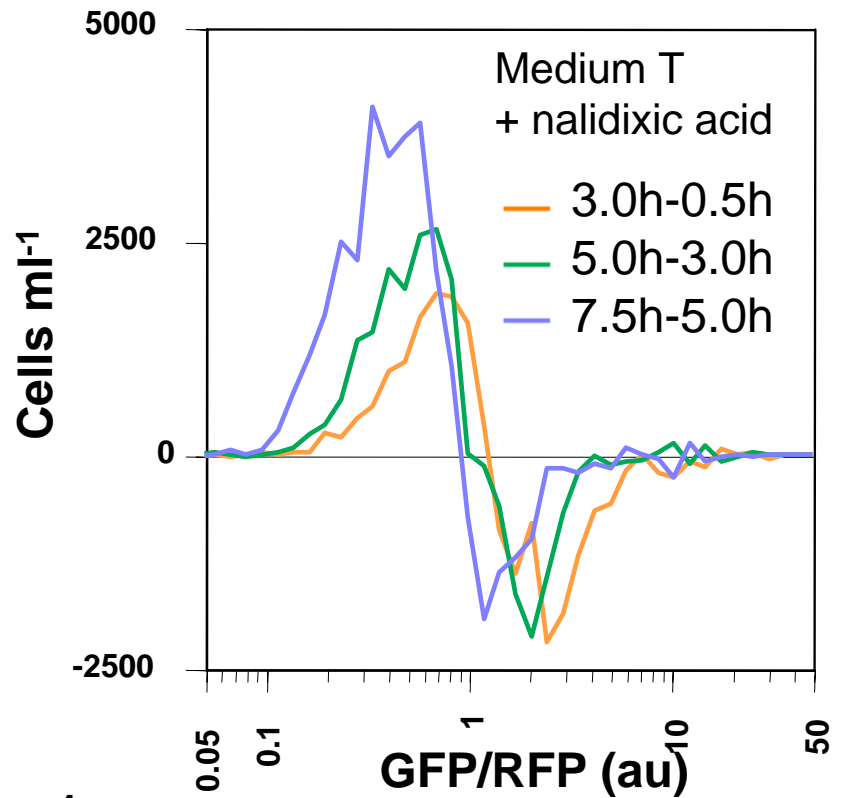
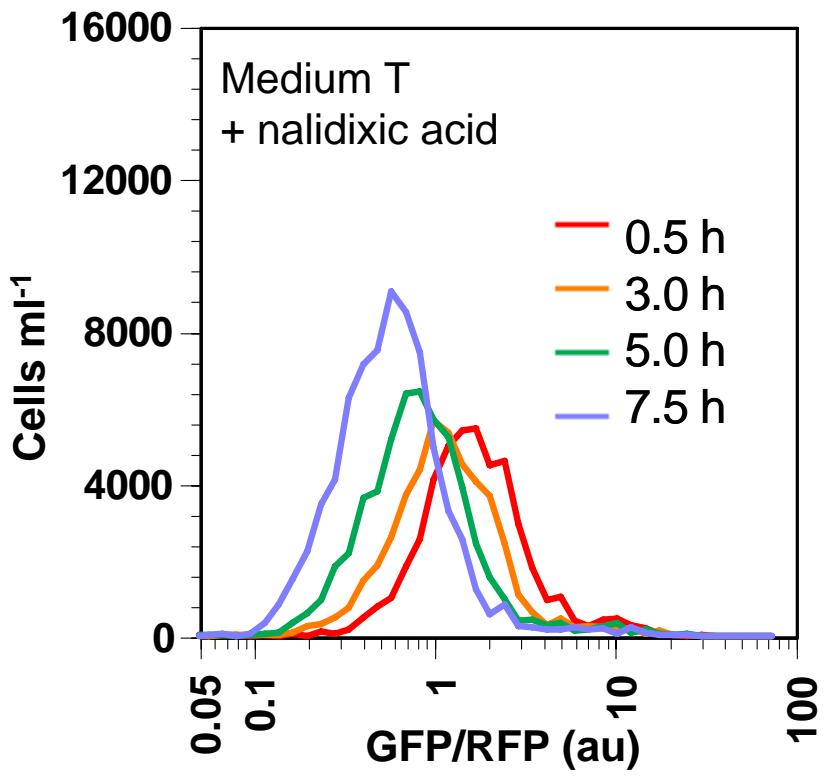
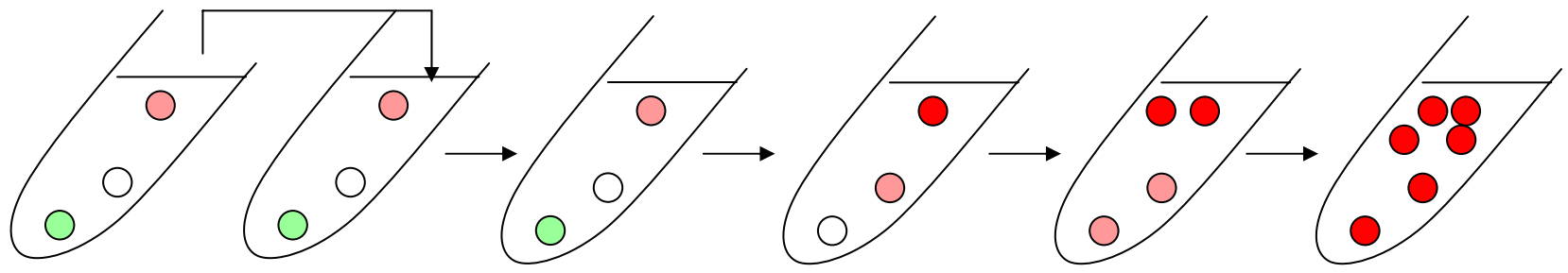
## Fitness-induced Attractor\_selection



- 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

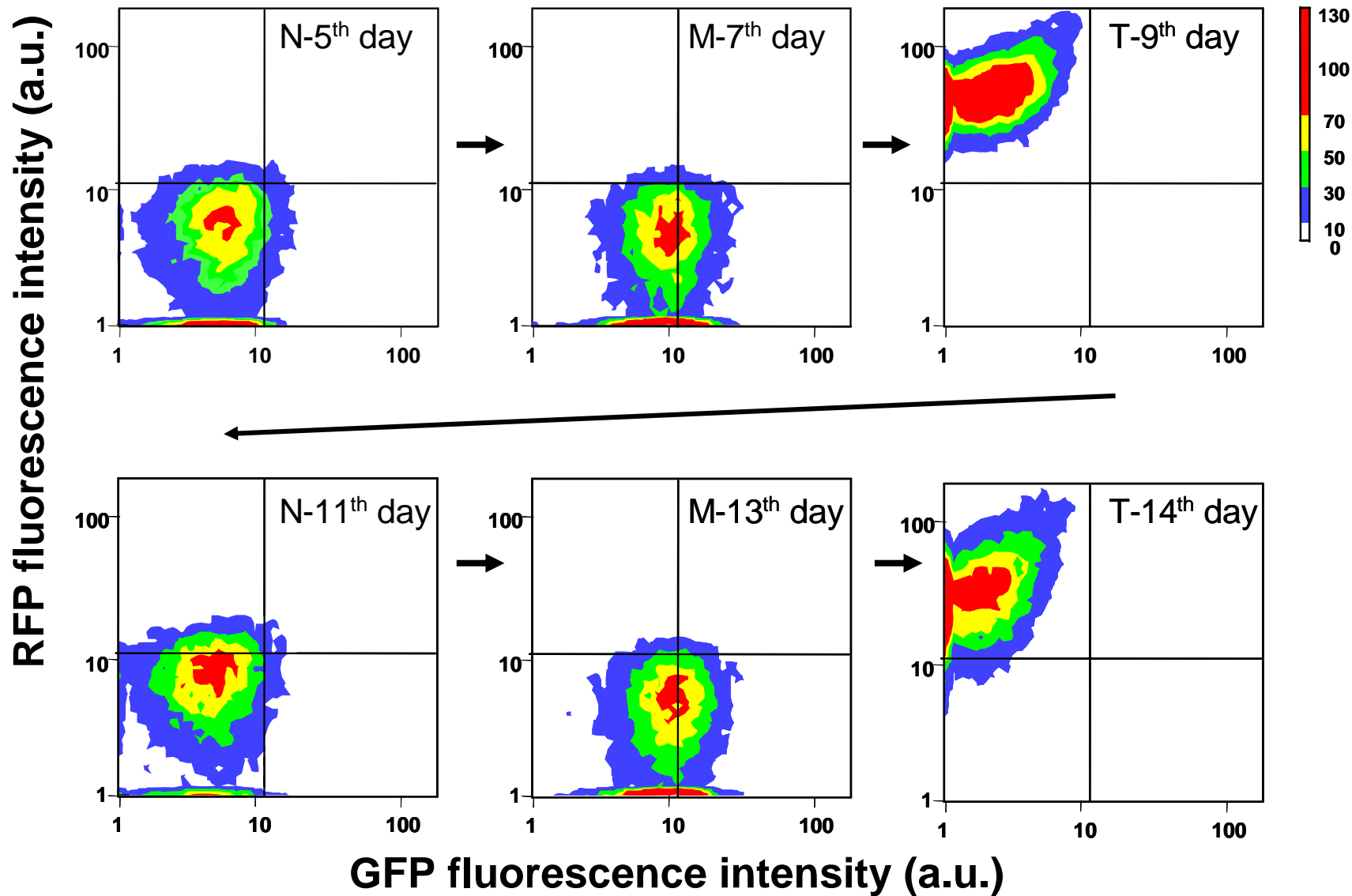
Medium N      Medium T      0.5 h      2.0 h      5.0 h      7.5 h

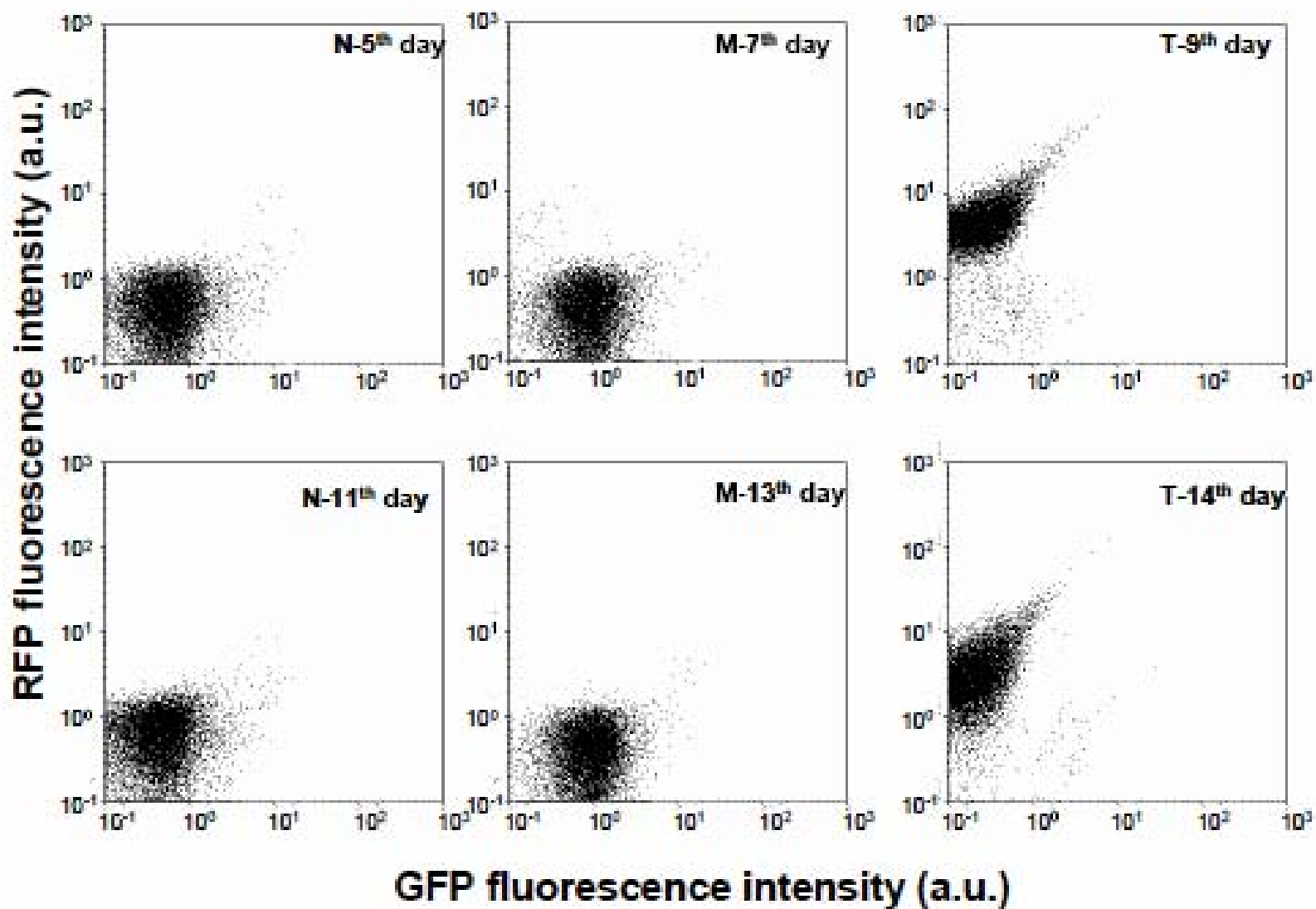


Attractor 2 ← AttractorW → Attractor 1



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



**B**

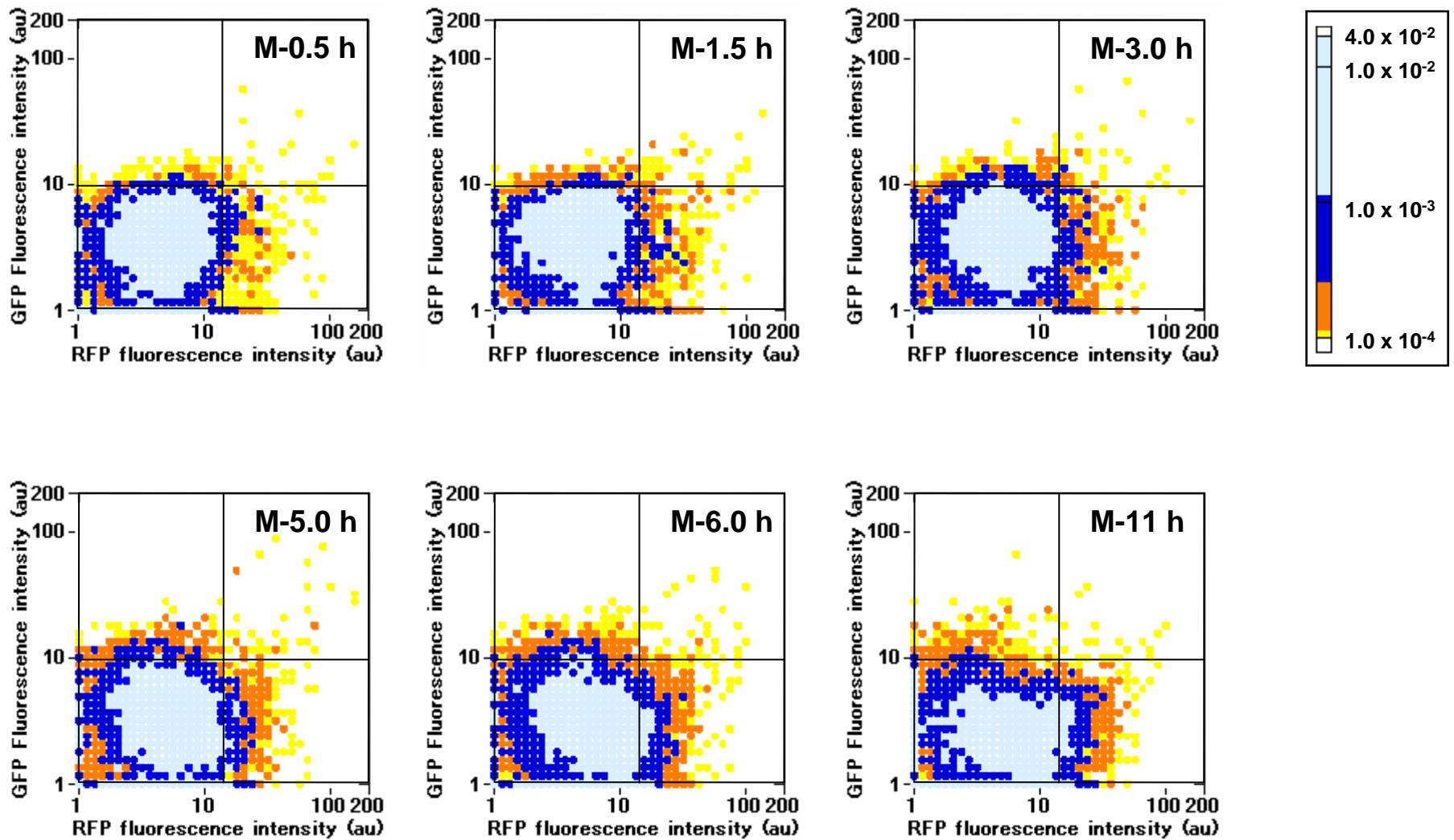


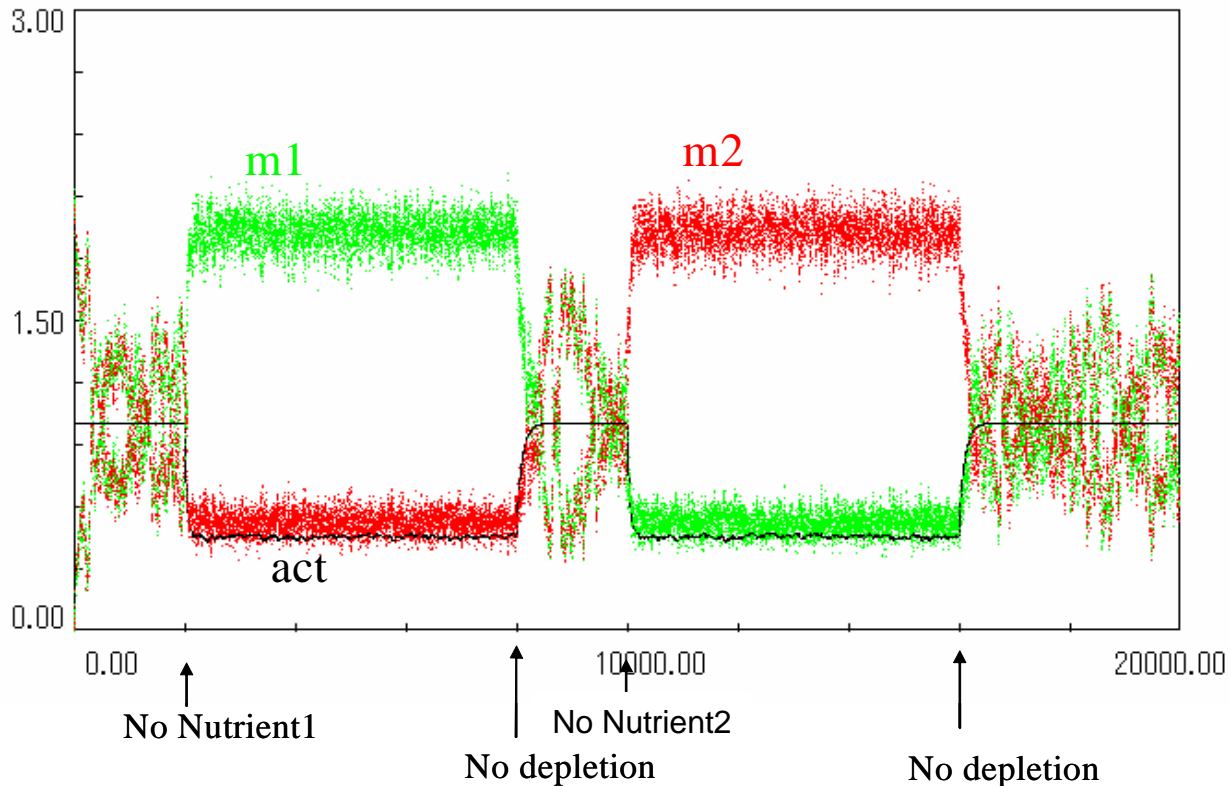
Fig. R1-2-1 The temporal change of the cell population inoculated from Medium N to Medium M. The density is presented by the ratio of the number of dots at each window to the total dots observed.

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

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

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

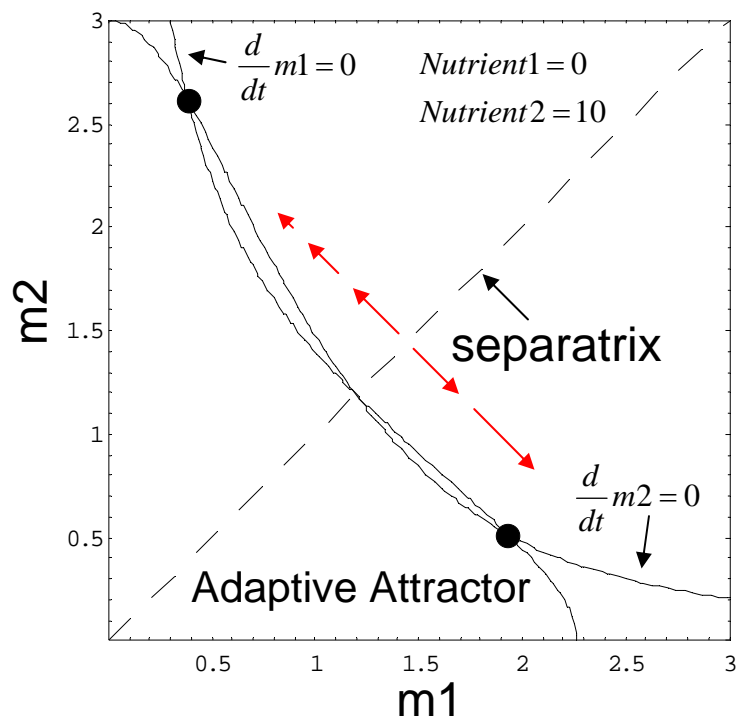
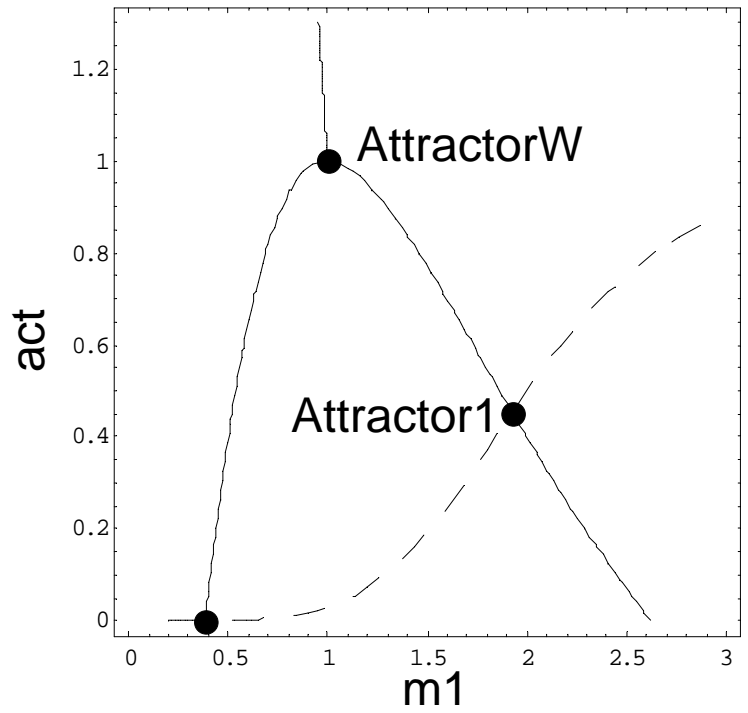
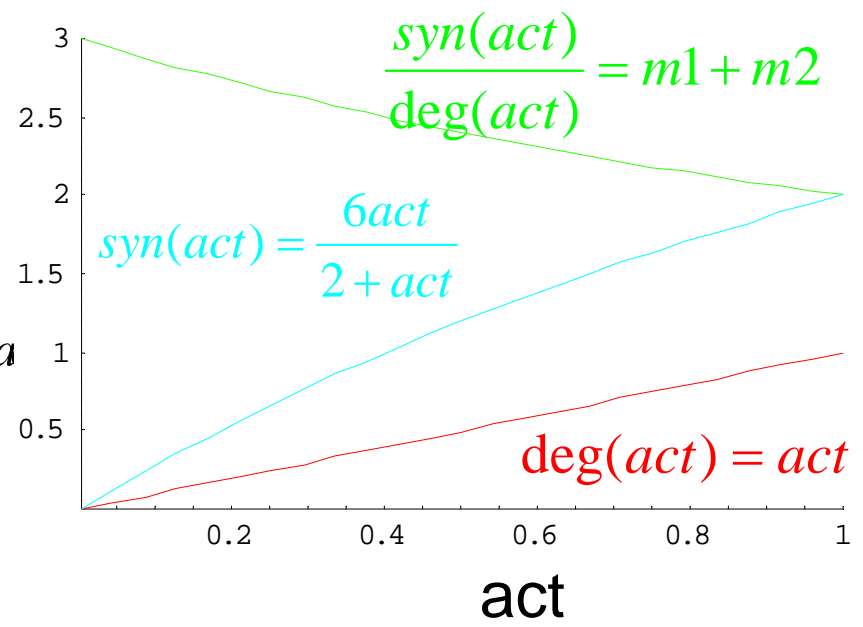
$$\frac{d}{dt} act = \frac{\text{pro}}{\left(\left(\frac{\text{Nut\_thread}_1}{m1 + \text{Nutrient1}}\right)^{n_1} + 1\right) \times \left(\left(\frac{\text{Nut\_thread}_2}{m2 + \text{Nutrient2}}\right)^{n_2} + 1\right)} - \text{cons} \times act$$

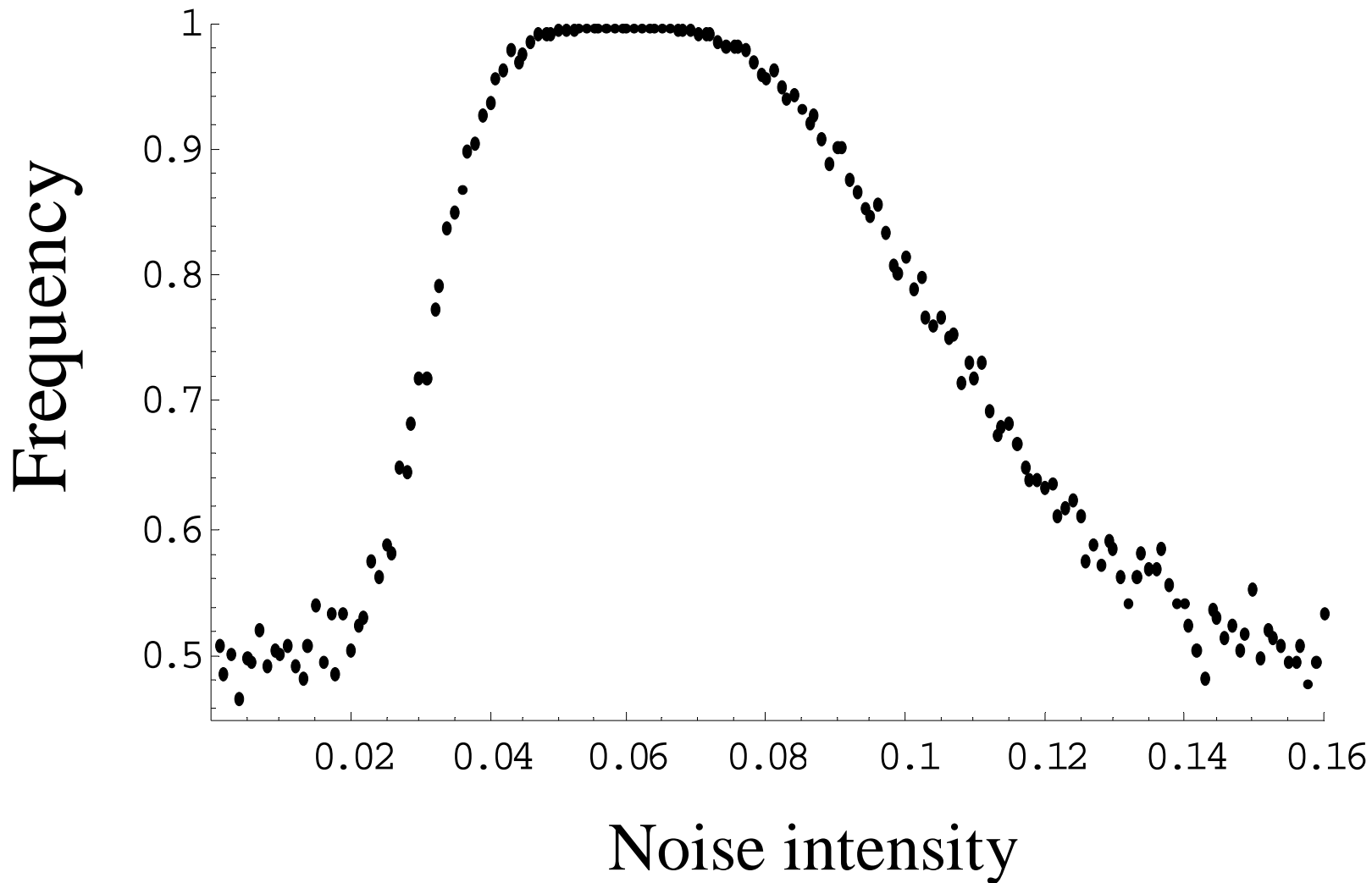


$$\frac{d}{dt} m1 = \frac{\text{syn}(act)}{1+m2^2} - \text{deg}(act) \times m1 + \eta_1$$

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

$$\frac{d}{dt} act = \frac{\text{pro}}{\left(\left(\frac{\text{Nut\_thread}_1}{m1+\text{Nutrient1}}\right)^{n_1} + 1\right) \times \left(\left(\frac{\text{Nut\_thread}_2}{m2+\text{Nutrient2}}\right)^{n_2} + 1\right)} - \text{cons} \times a$$





# Noise dependence of attractor selection