From molecules to behavior: towards quantitative, systems level understanding of bacterial chemotaxis

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(Work done with Dr. Bernardo Mello)

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•IBM Research
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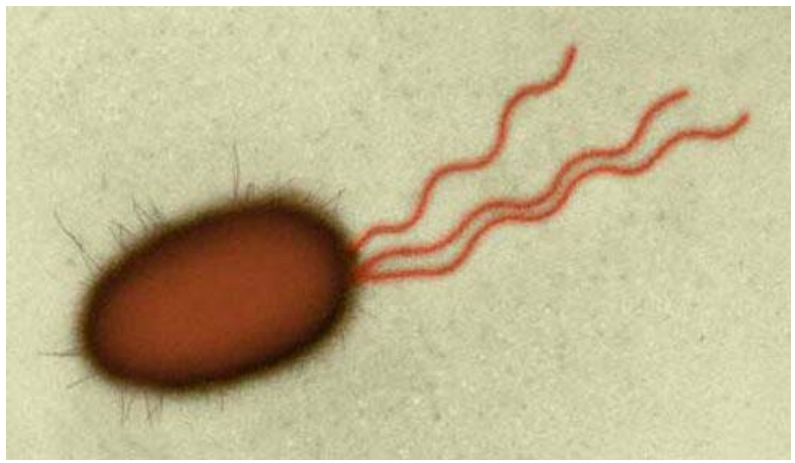
Outline

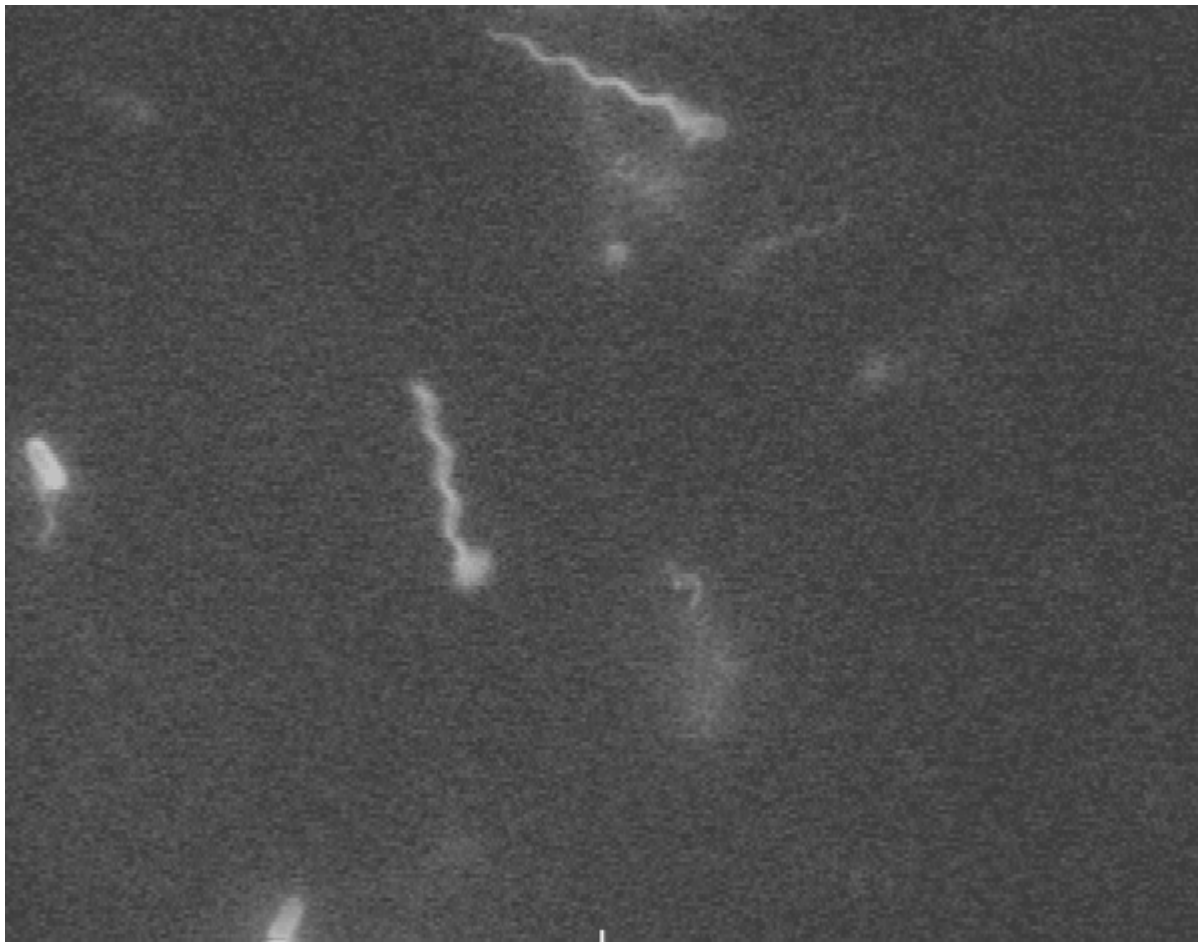
- Introduction to bacterial chemotaxis: description of behavior
- Molecular mechanisms: properties of the chemotaxis network
  - Signal amplification
  - Adaptation
  - Flagellar motor
  - Noise effects
  - Spatial effects

  …….
- Understanding behavior: responses to complex temporal signal



The behavior

A Movies of E. Coli Motion



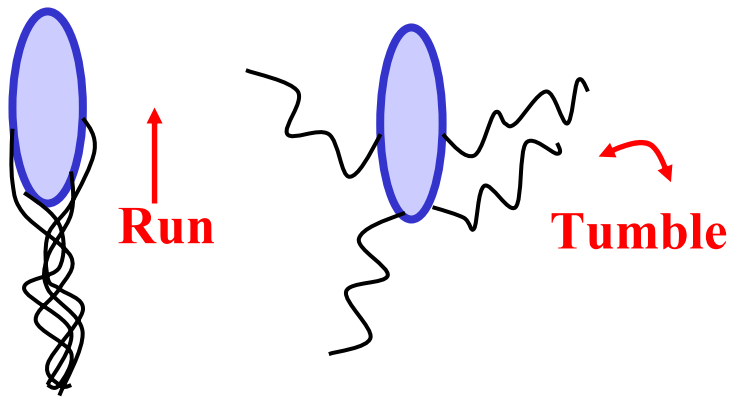
(from Howard Berg's Lab, Harvard University)

Background on Bacterial Chemotaxis

(The sensory system of bacteria)

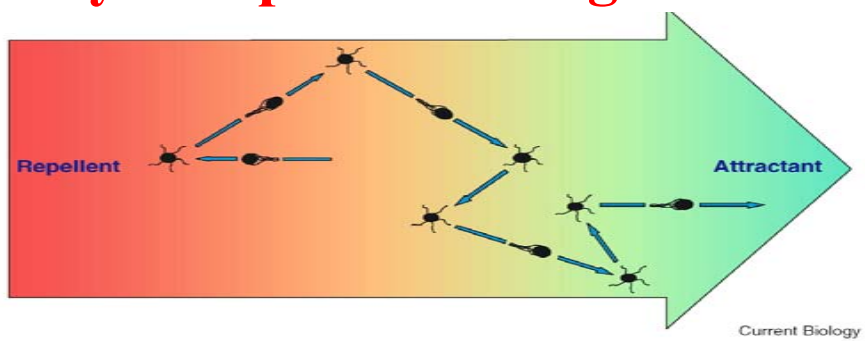
How do bacteria follow gradient of attractant concentration?

- Two modes of motion
  (1)**Run**: flagella rotate counter clockwise
  smooth swimming ~20μm/s
  (2)**Tumble**: flagella rotate clockwise
  tumbling (randomly change direction)



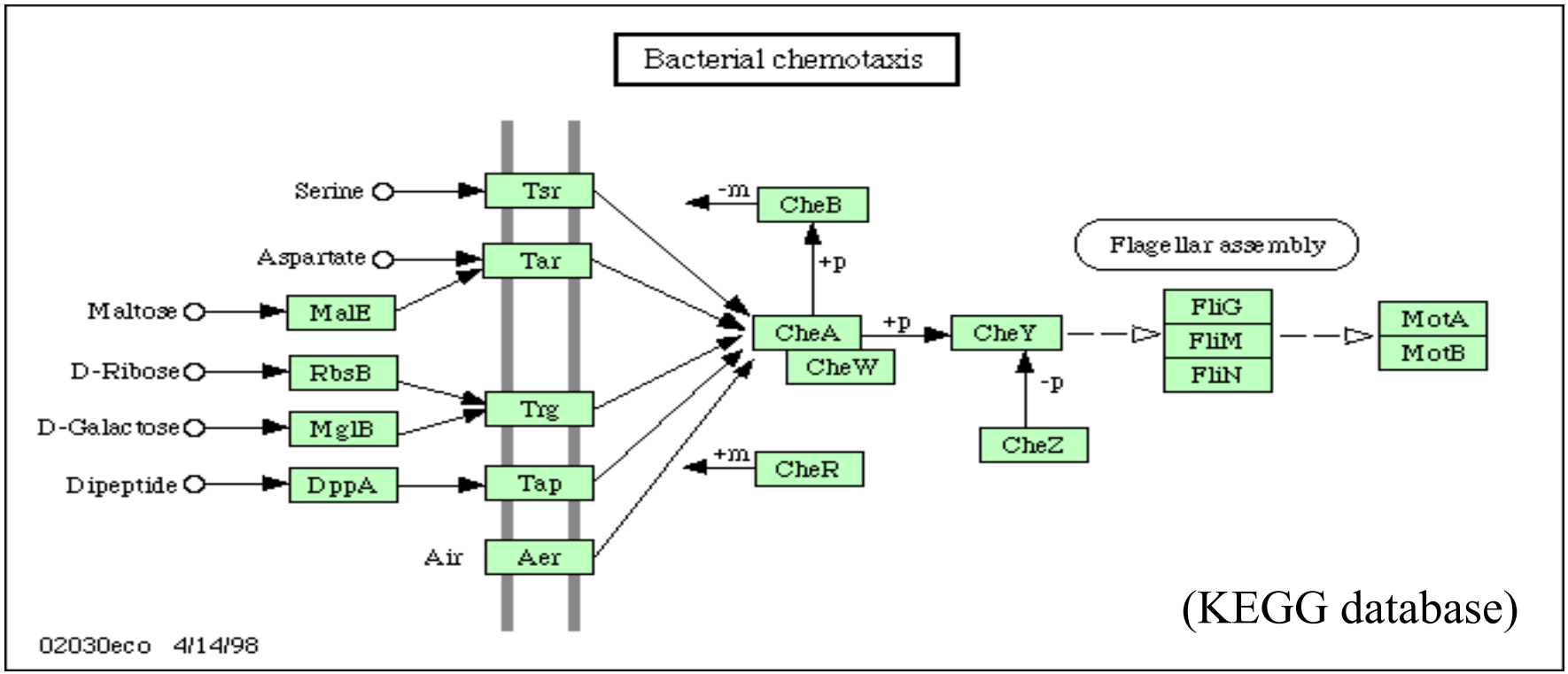
- Switch frequency set by comparing instantaneous attractant concentration and some **memory**: **temporal sensing**

Biased Random walk



E. Coli Chemotaxis Signaling Pathway : The relevant molecules and their interactions

How does signal pass from outside to inside the cell and further control the flagella motion



(KEGG database)

Sensing

Adaptation

Signal transport

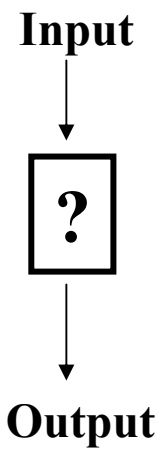
Motor kinetics

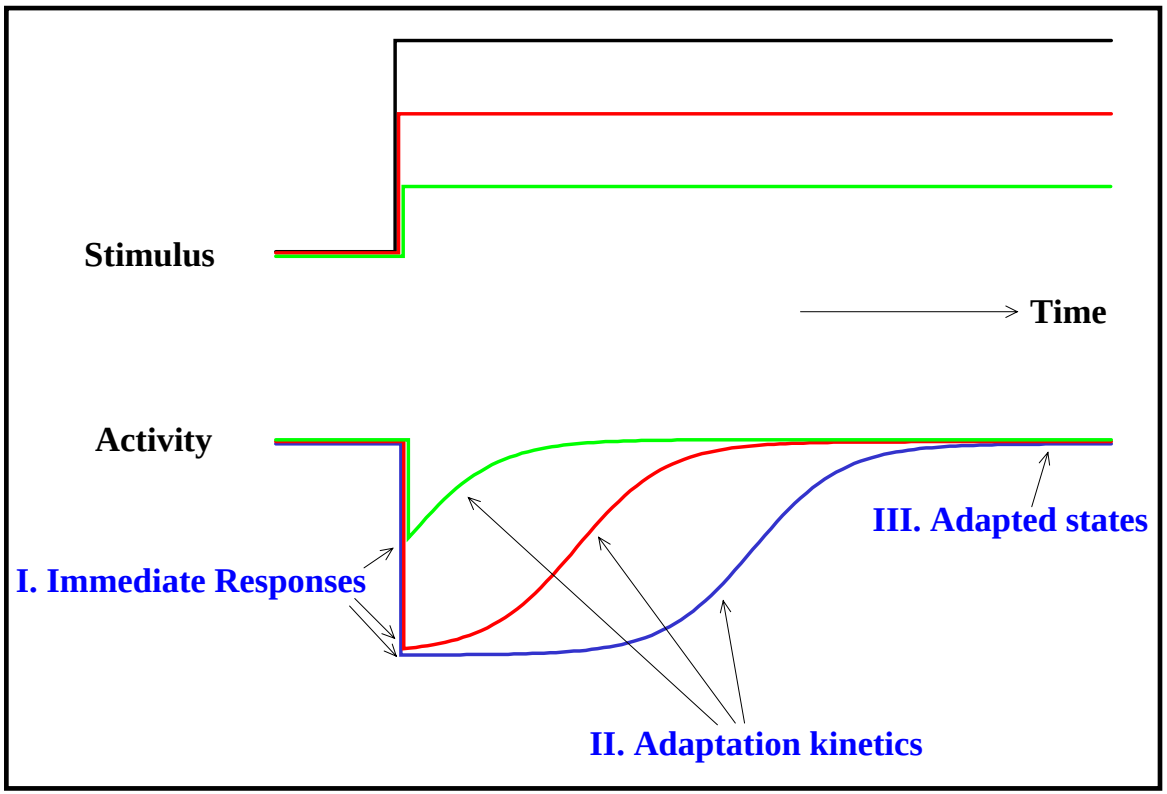
Signal amplification

Motor assembly

Quantitative Characteristics of Chemotaxis Response

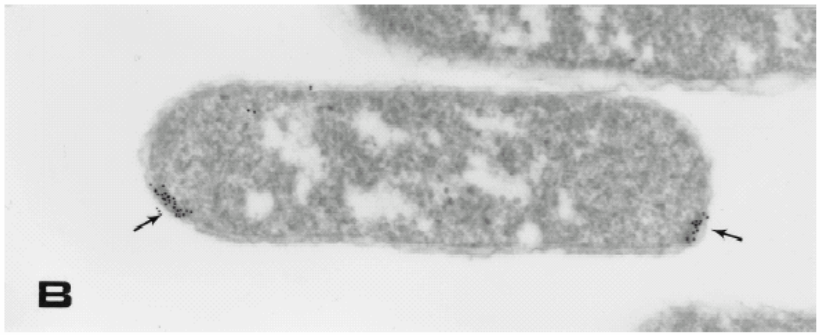
- High sensitivity (~10's nM, a few ligand molecules)
- Signal amplification (~40X)
- High sensitivity exists in a wide range of backgrounds
- Wide dynamic range (10nM→1mM)
- Near perfect adaptation





Receptor Clustering as a Possible Mechanism for Gain

Chemoreceptors cluster in bacteria
(~20,000 chemo-receptors in a E. Coli cell)



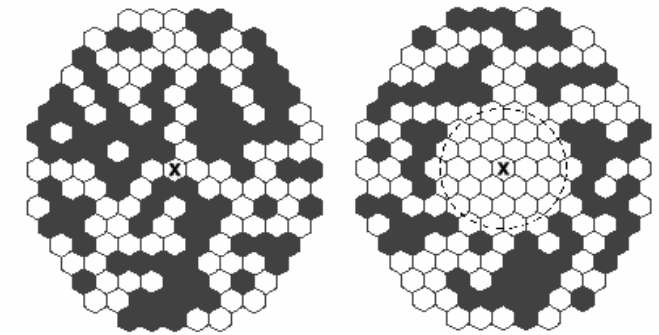
(Maddock & Shapiro, 1993)
(Lybarger & Maddock)

- Clustering of MCP+CheA+CheW
- Independent of CheR or CheB

Receptor clustering as a cellular mechanism to control sensitivity

Dennis Bray, Matthew D. Levin & Carl J. Morton-Firth

(Nature, **393**, 85-88, 1998)



Coupling through conformational spreading?

One Problem: High gain against wide dynamic range

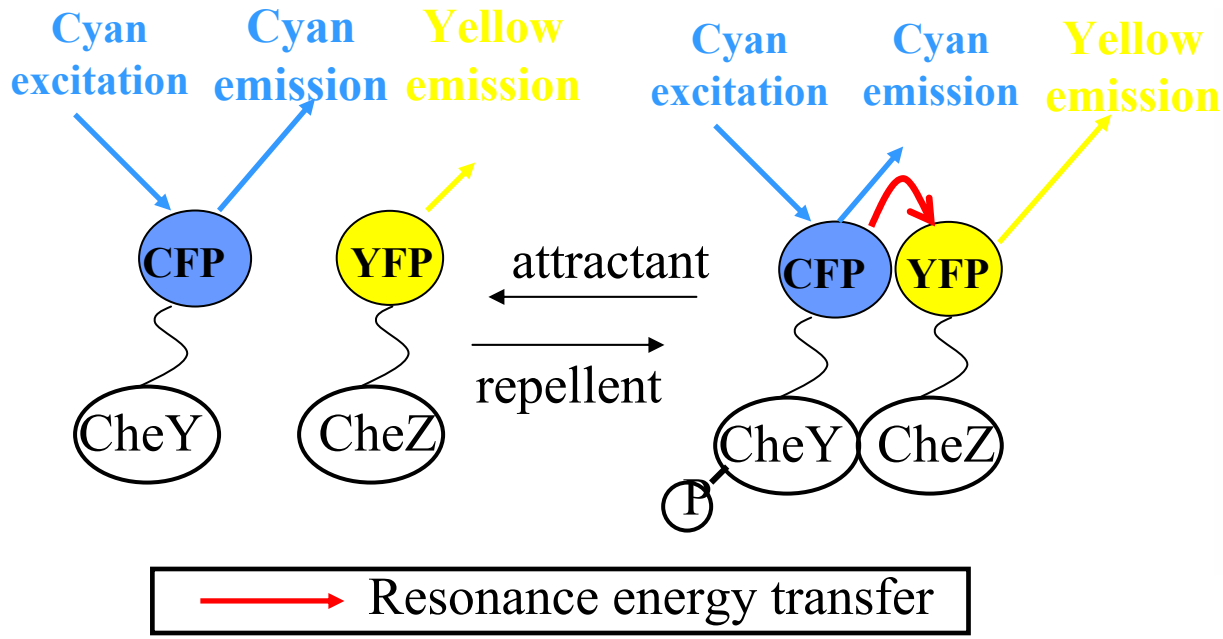
concept → quantitative model → direct compare with data

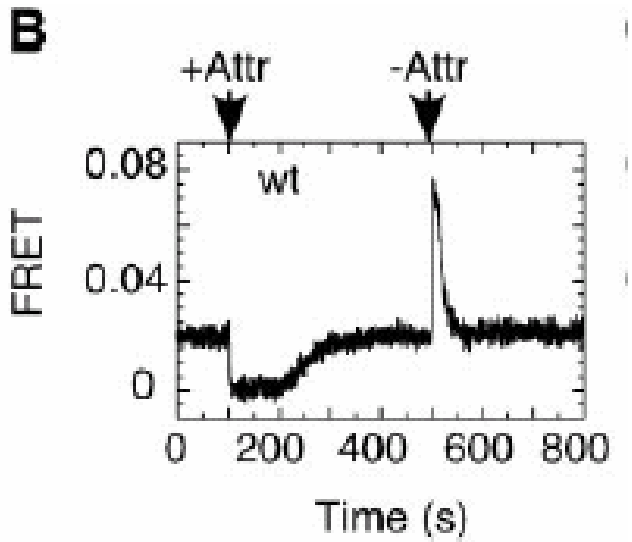
↑

Needs quantitative data

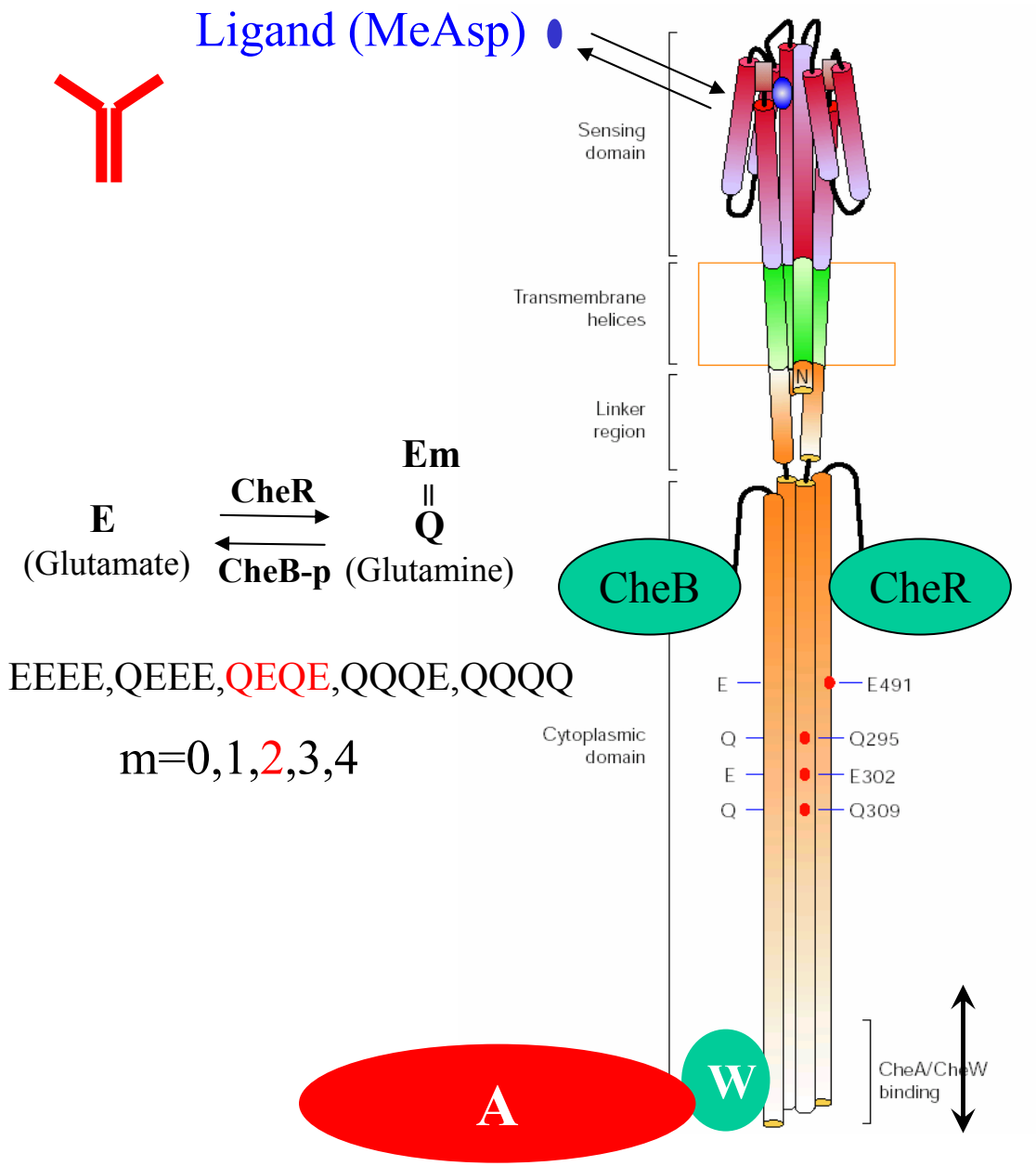
Recent *in vivo* Response Measurements Using FRET

Direct *in vivo* measurement of $CheY^P$ level by FRET
(Fluorescence Resonance Energy Transfer)
(Sourjik&Berg, PNAS 99 123-127 (2002))





Properties of an Individual Chemo-receptor Dimer



Input — **Ligand binding**

Control — **Covalent Modification (Methylation level)**

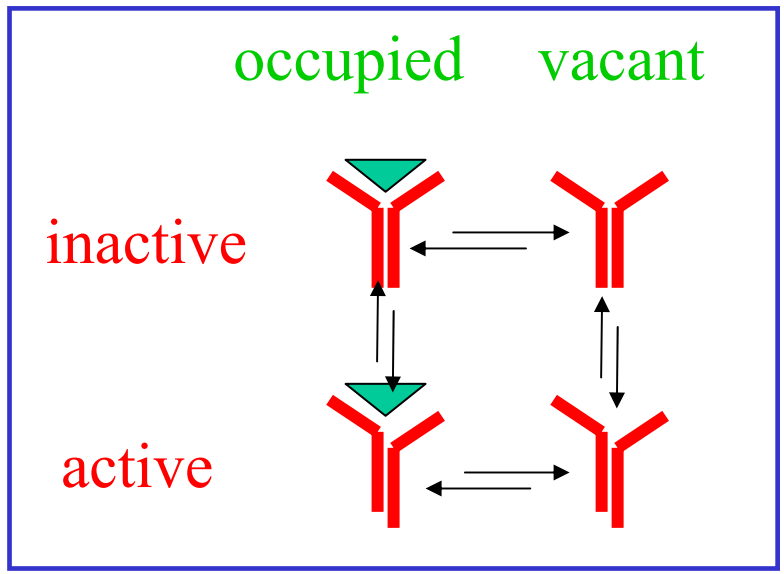
Output — **Conformation change (Kinase Activity)**

The 4-state Receptor Model

•4 states for each individual receptor i

•Activity $a_i = 0,1$

•Ligand binding $l_i = 0,1$



Energy (Hamiltonian) of the states:

$$H_i = a_i(E_m(m_i) + E_L(m_i)l_i) + \mu_l(m_i)l_i + coupling\_term$$

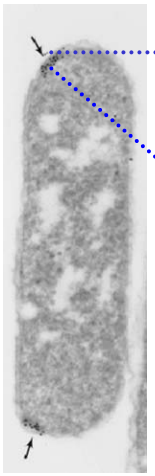
Probability in each of the 4 states: $P(a_i, l_i) \propto \exp(-H_i(a_i, l_i))$

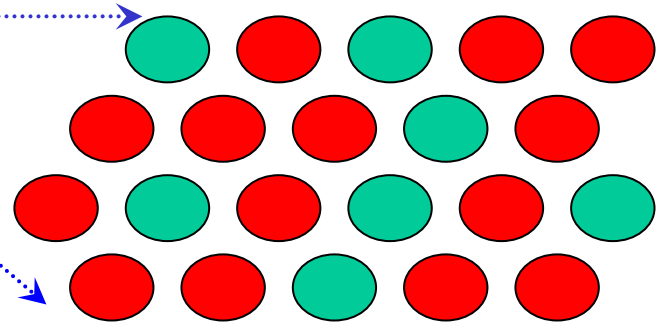
•3 independent parameters for each individual methylation level

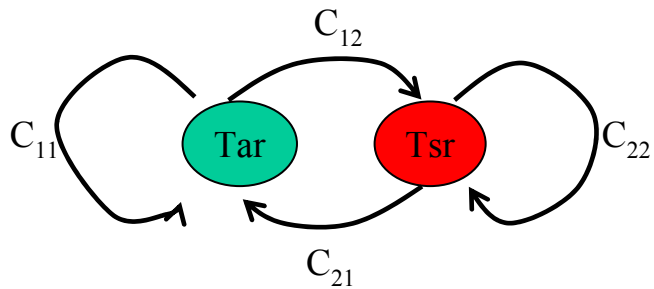
$$K_a; K_i; E_v; E_o (= E_v - \ln \frac{K_a}{K_i})$$

A Simple Representation of Receptor Interaction

- Activity of a receptor will be affected by the activities of its neighbor in the receptor cluster.







$$\text{Interaction energy} = a_i \sum_j C_{q_i q_j} (a_j - \tfrac{1}{2})$$

- j labels all the "neighboring" receptors of i'th receptor

$$H = \sum_i a_i [E_m(m_i) + E_L(m_i) l_i + \sum_{j(i)} C_{q_i q_j} (a_j - \tfrac{1}{2})] + \mu_l(m_i) l_i$$

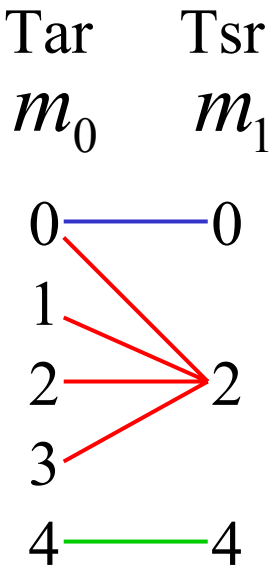
"Spin" "Magnetic field" "Ising coupling"

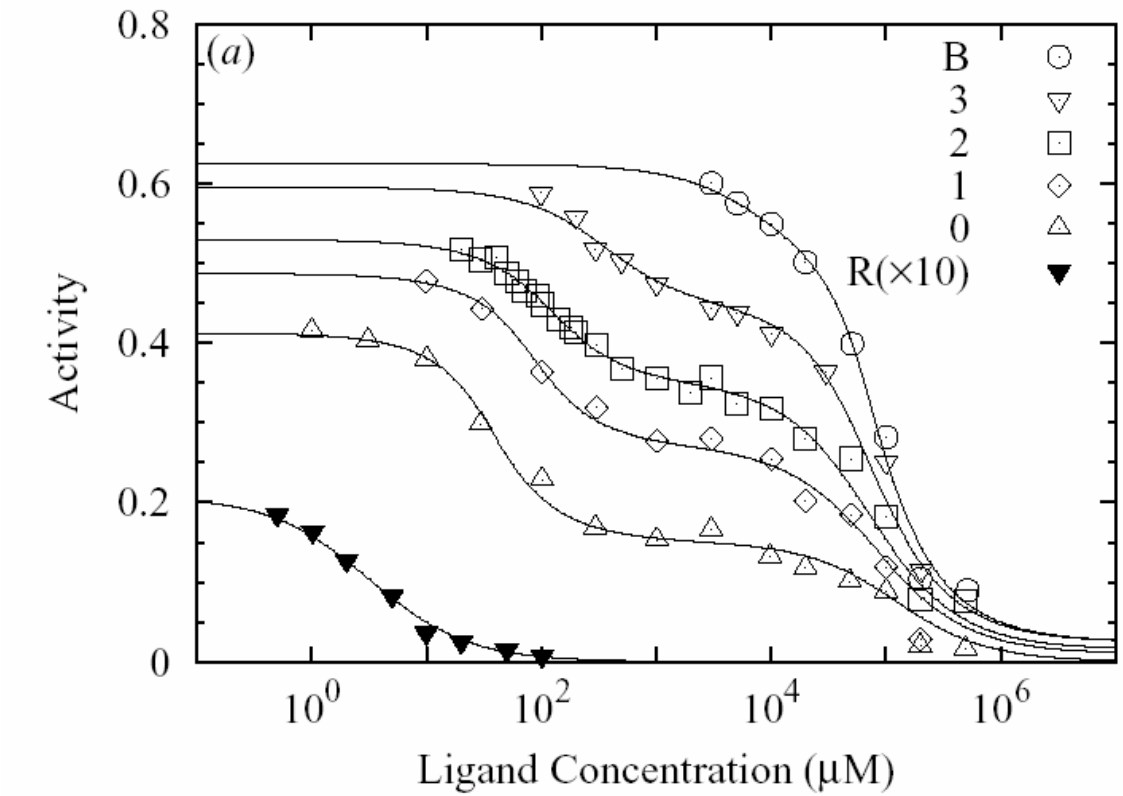
The "mixed Ising model"

The Modeling Results for the 6 CheRB- Mutant Strains

Adaptation disabled: Receptor methylation level fixed

- ***Solve our model by mean field theory, MC simulation***
- ***Find parameters to fit to all 6 mutant strains together***





Exp.---symbols
Theory ---lines

# of parameters in the model: 3x8+4=28

# of independent data parameters: ~6x7=42

Not overfitting!

What Do We Learn from Modeling the Responses of the CheRB- Mutants?

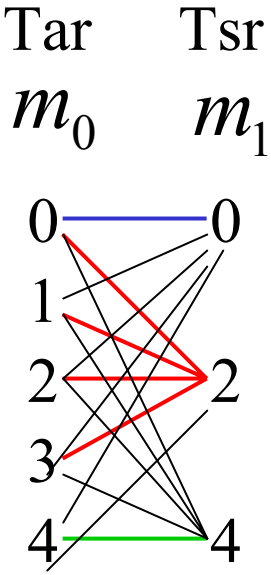
•We "prove" the existence of direct receptor-receptor interaction: Receptor-receptor coupling is necessary to explain the in vivo data.

there is no need for "new function/players" in the pathway, e.g., CheB is not involved in direct inactivation of the kinase activity.

•The model fitted to exp. response data is the most promising way to determine in vivo parameters.

More experiments are needed in pinning down these parameters, such as other combinations of Tar/Tsr methylation states, i.e., complete the graph!

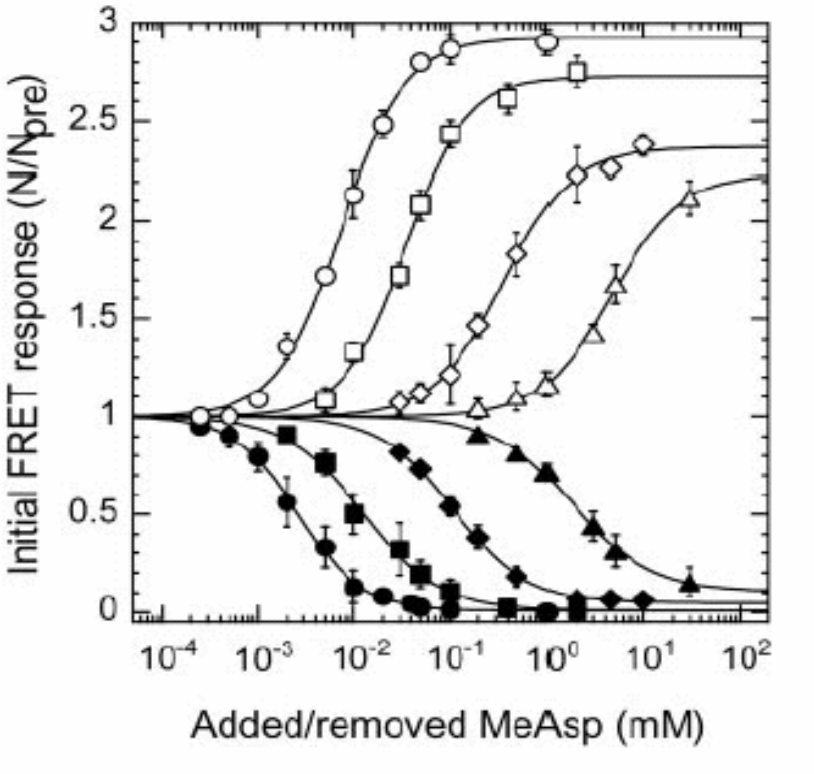
•Strong interaction between different types of chemoreceptors



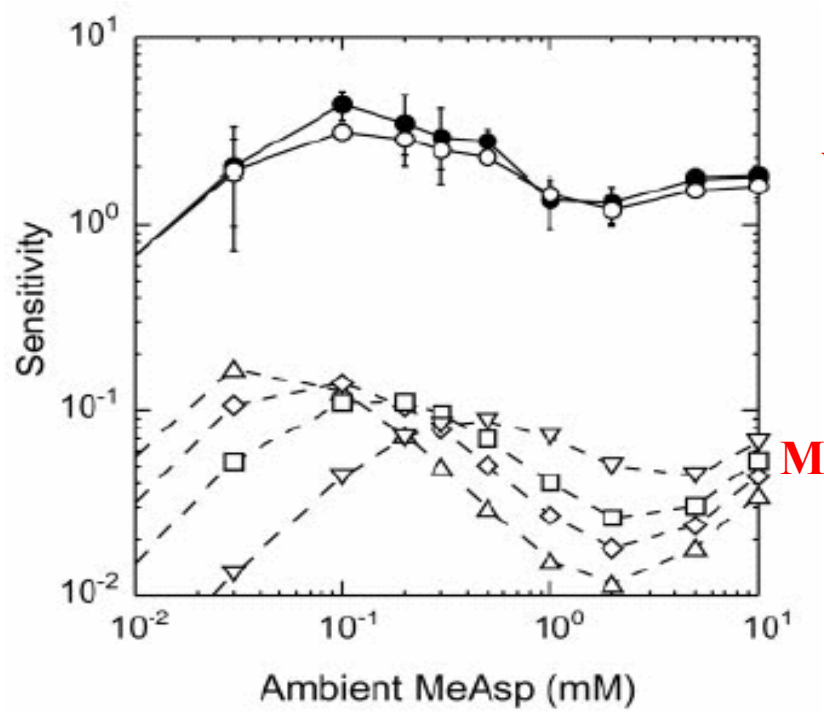
Strong Tsr-Tar coupling: receptor level cross talk

The Response of Wild-type Cell: Sustained High Sensitivity by Adaptation

Response



Sensitivity



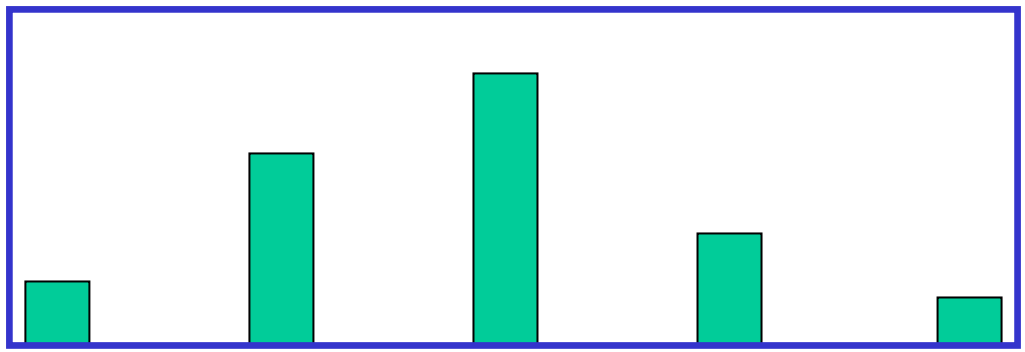
Ambient MeAsp $[L]_0$ = **0, 0.1, 0.5, 5 mM**

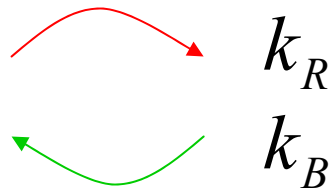
$$S \equiv \frac{\Delta A / A_0}{\Delta[L]/[L]_0}$$

(Sourjik&Berg, PNAS, 2002)

The Model for the Wild-type Cell (with CheR & CheB)

- f_{qml} is a distribution, determined by methylation/demethylation kinetics.





Assuming only active receptor can be demethylated; only inactive receptor can be methylated

Perfect adaptation

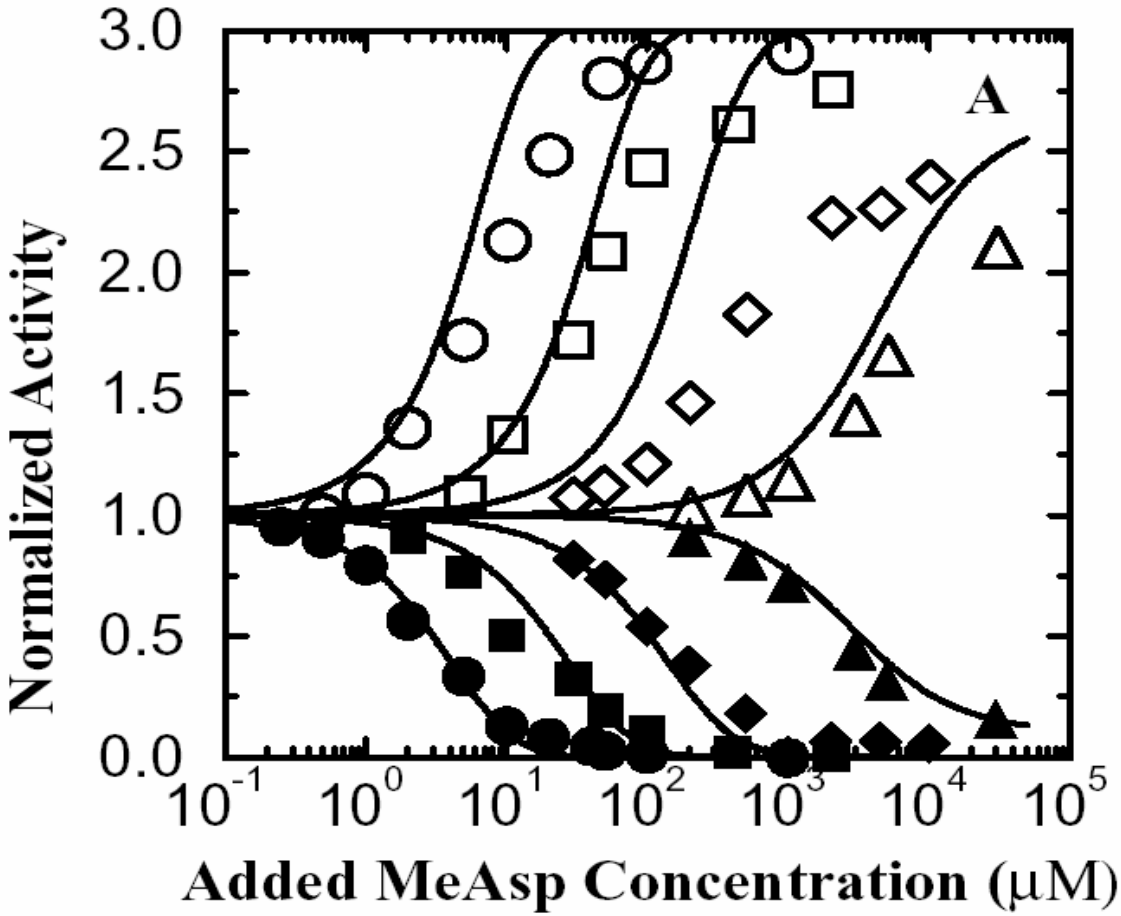
(Barkai and Leibler, Nature, 1997)

(B. Mello and Yuhai Tu, *Biophysical Journal*, 84(5), 2843-2856 (2003))

•Steady state distribution can be determined

$$k_R \sum_l (1 - a_{0ml}) f_{0ml} = k_B \sum_l a_{0(m+1)l} f_{0(m+1)l}$$

Wild-type Responses: Theory versus Experiments



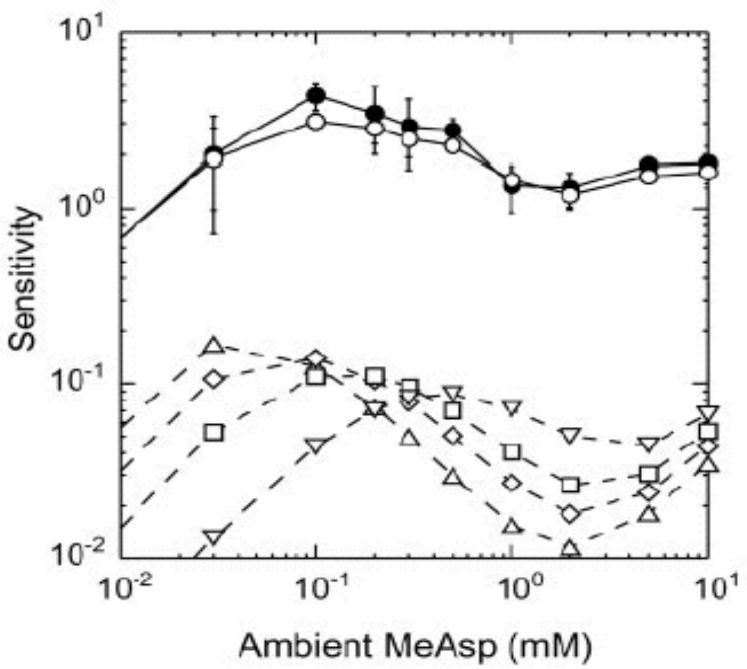
Exp: Symbols
Theory: Lines

$[L]_0$=0, 0.1, 0.5, 5 mM

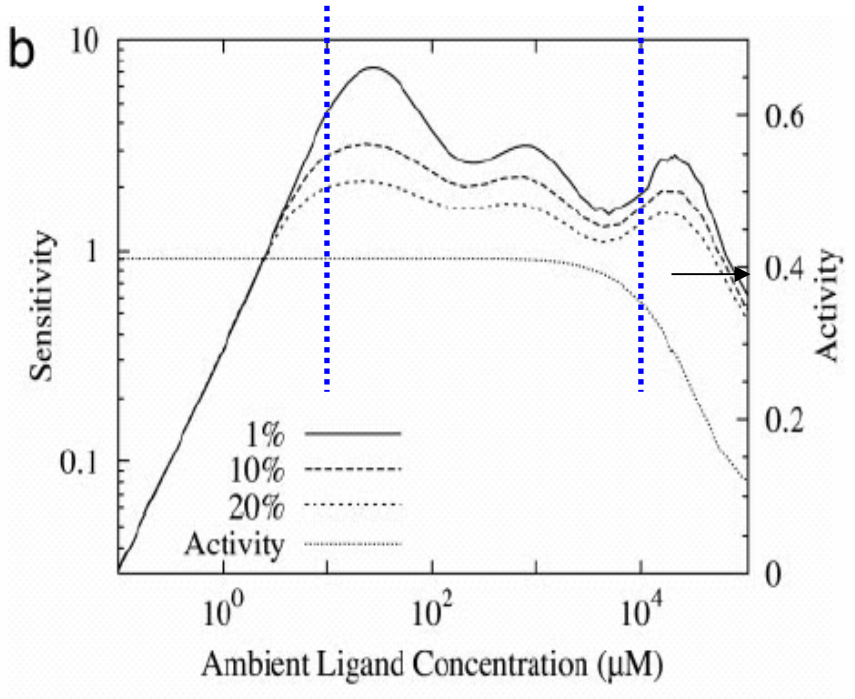
- Consistent with experimental data over full range of ambient concentration
- **Reveal mechanism for the wide dynamical range over which high sensitivity is sustained.**

Sensitivity: Thoery versus Experiments

Experiment



Theory

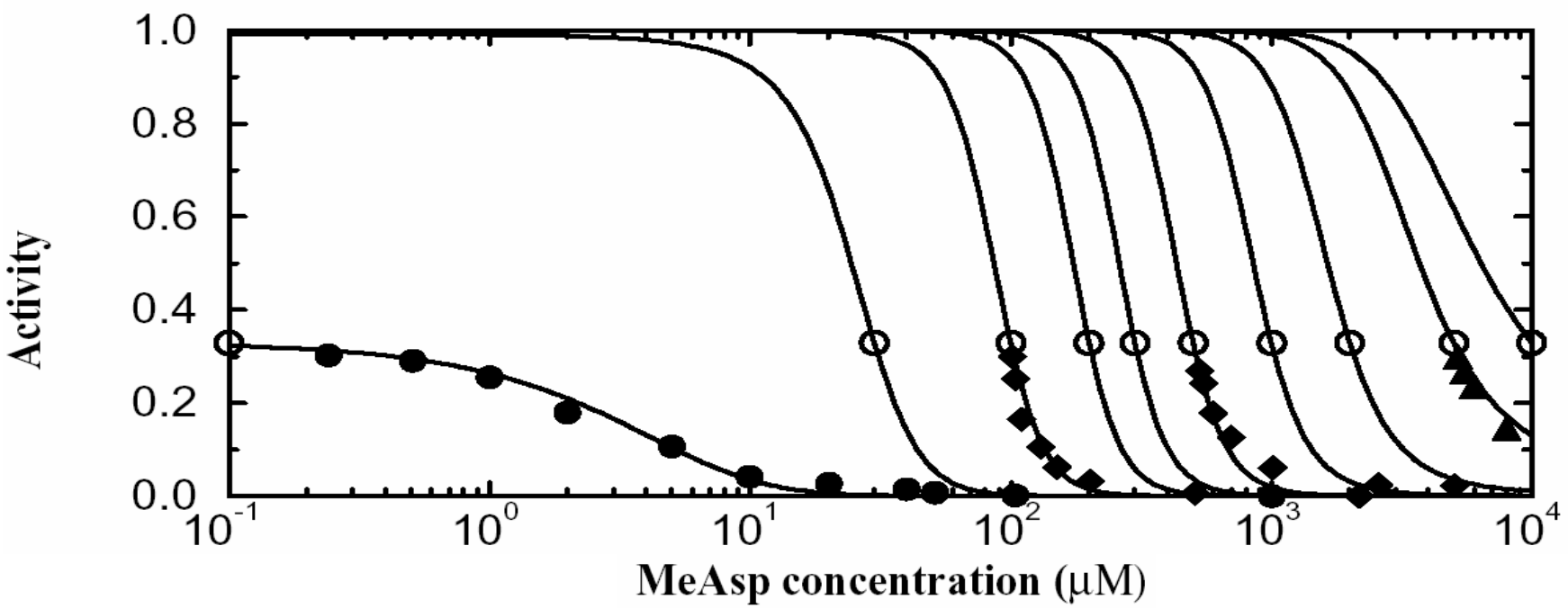


$$\text{Sensitivity} \quad S \equiv \frac{\Delta A / A_0}{\Delta [L] / [L]_0}$$

agreement over full range of ambient MeAsp concentrations

High Gain over a Wide Range of Backgrounds: The Role of Sensory Adaptation

Increasing receptor methylation level →
(higher background concentrations)



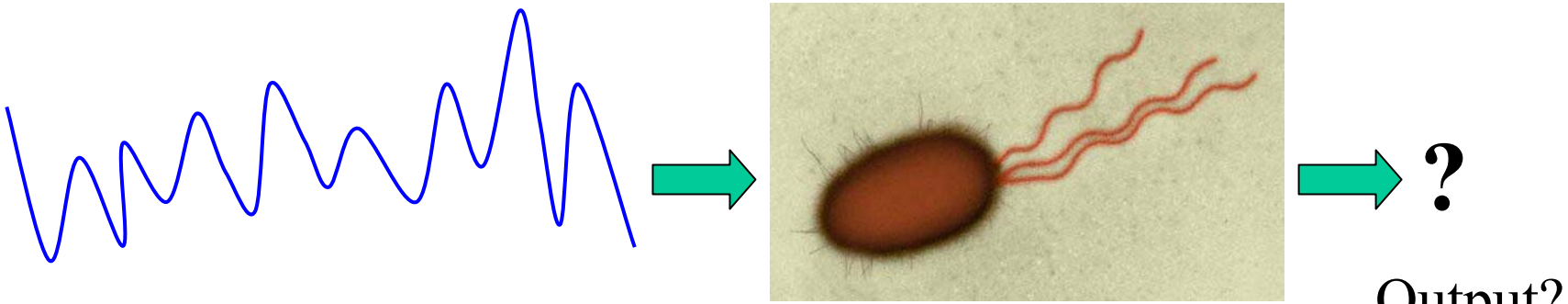
$$H = \sum_i a_i [E_m(m_i) + E_L(m_i) l_i + \sum_{j(i)} C_{q_i q_j} (a_j - \tfrac{1}{2})] + \mu_l(m_i) l_i$$

The "smart" Ising model: Self-tuned near-critical behavior

- **Receptor interaction results to high gain: PHYSICS**
- **Adaptation maintain the high gain: BIOLOGY**

Responses to complex temporal signals

Simple step function stimulus is useful to understand the pathway.
However, such simple stimuli is un-physiological.



- **What kind of signal processor is bacterial chemotaxis pathway?**

Amplifier; filter; nonlinear effects; signal integration/differentiation

- **Why is it designed the way it is?**

What is it good for?

Some "forgotten" experiments

Experiments done in the 80's by Howard Berg's group

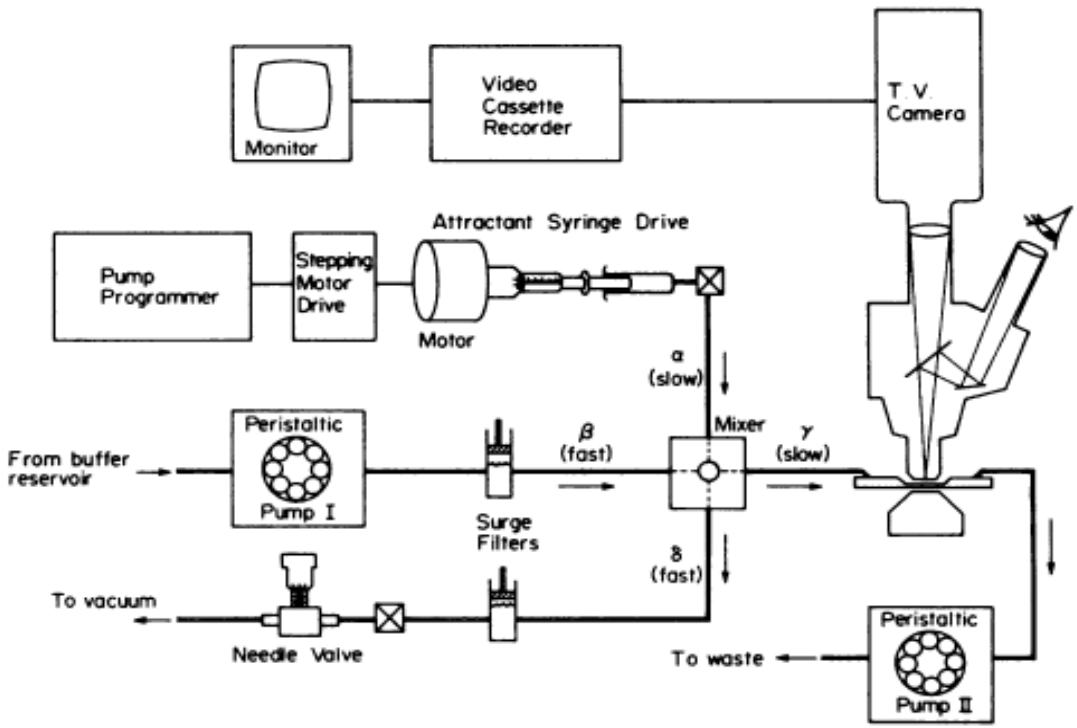
JOURNAL OF BACTERIOLOGY, Apr. 1983, p. 312–323
0021-9193/83/040312-12$02.00/0

Vol. 154, No. 1

Adaptation Kinetics in Bacterial Chemotaxis

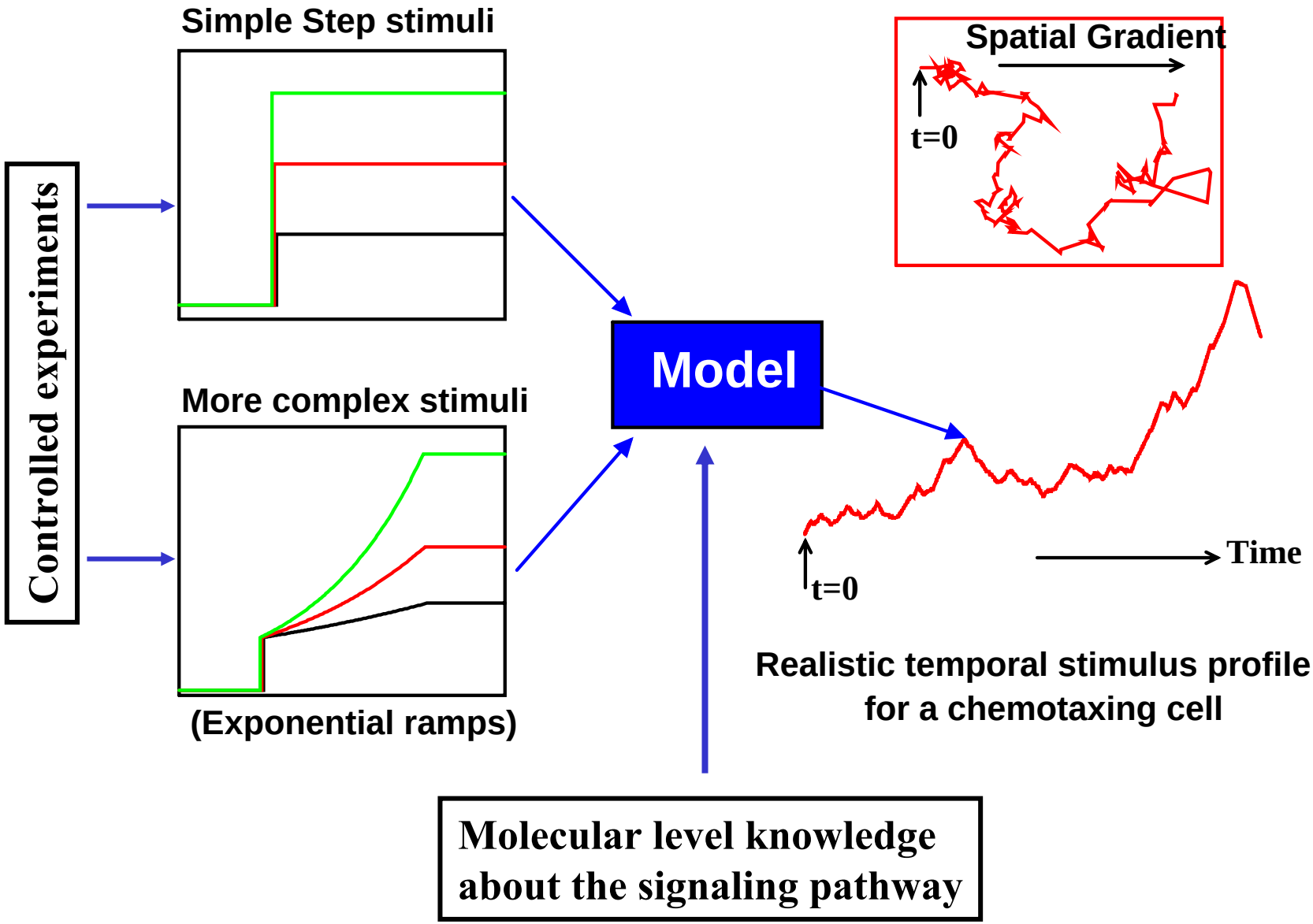
STEVEN M. BLOCK, JEFFREY E. SEGALL, AND HOWARD C. BERG*
Division of Biology, California Institute of Technology, Pasadena, California 91125

Received 18 October 1982/Accepted 21 January 1983



- **Exponential ramp**
- **Exponentiated sine wave**
- **Steps and impulses**

Theoretical model is necessary



A simple dynamical model

Receptor cooperativity

$$a = G(m,[L])$$

"Quasi-equilibrium"

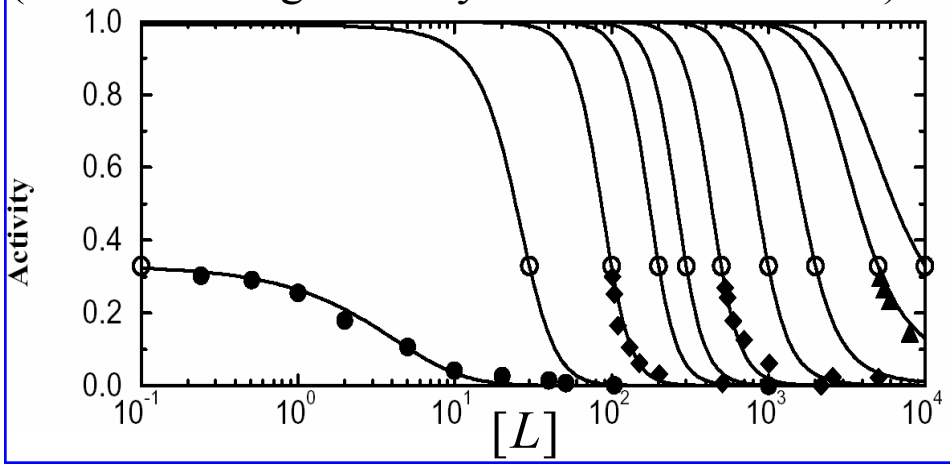
Perfect adaptation

$$\frac{dm}{dt} = F(a,\cancel{m},[\cancel{L}])$$

$$G(m,[L]) = \frac{L(1+C[L]/K)^N}{L(1+C[L]/K)^N + (1+[L]/K)^N},$$

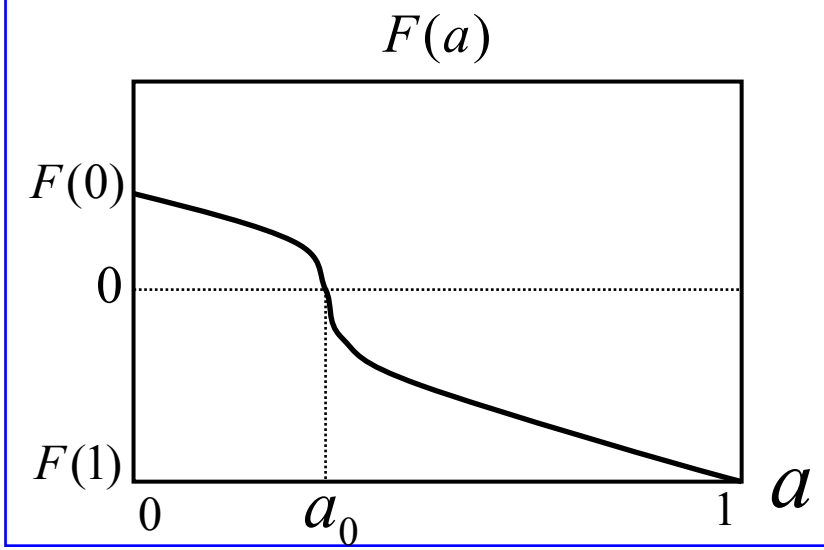
$$L = L_0(l(m))^N$$

(Monod-Changeaux-Wyman allosteric model)



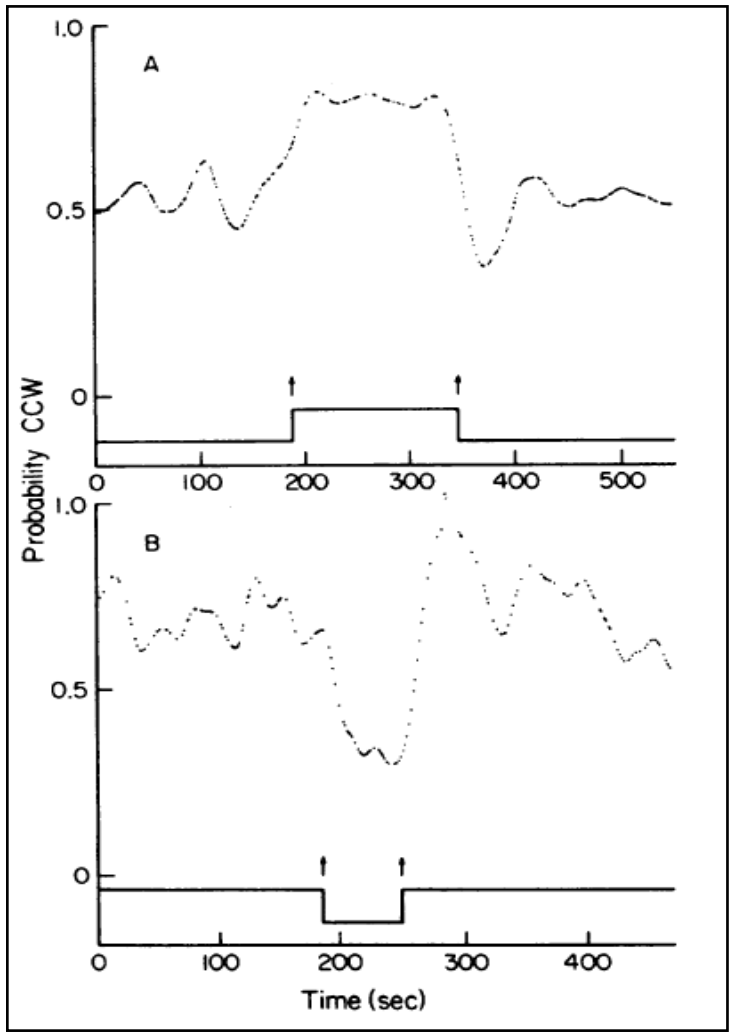
$$F(a_0) = 0, F(0) > 0, F(1) < 0$$

$$-F(1) > F(0)$$



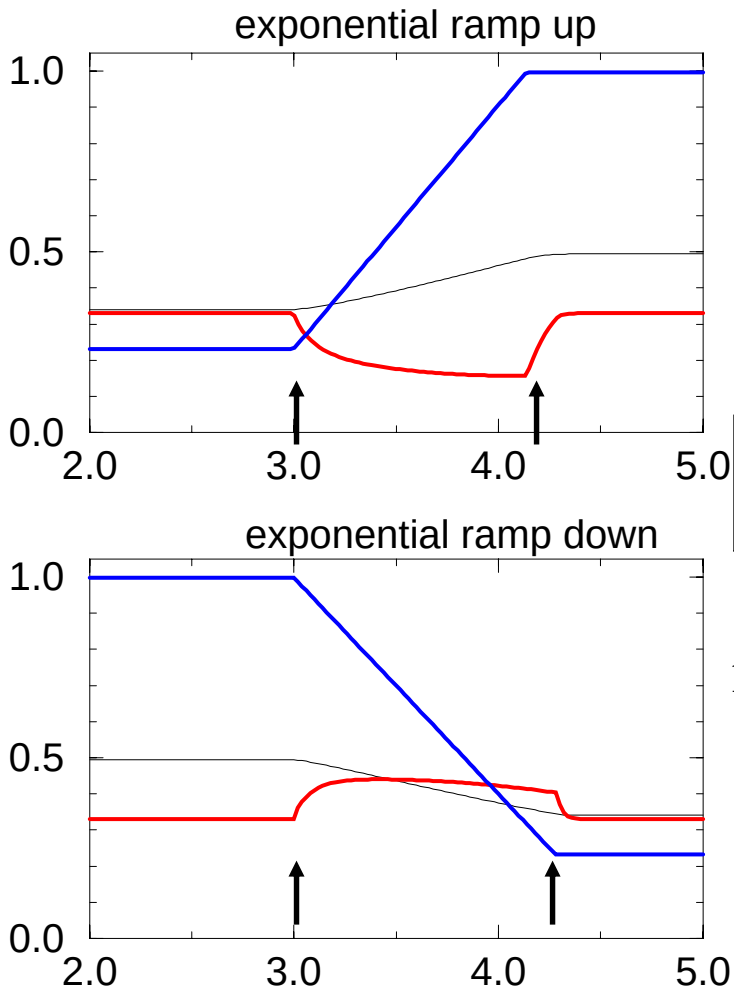
Activity shift in response to exponential ramps

(Exp.)



(S. Block et al, 1983)

(Theory)



ramp up

$$[L] = [L]_{low} e^{rt}$$

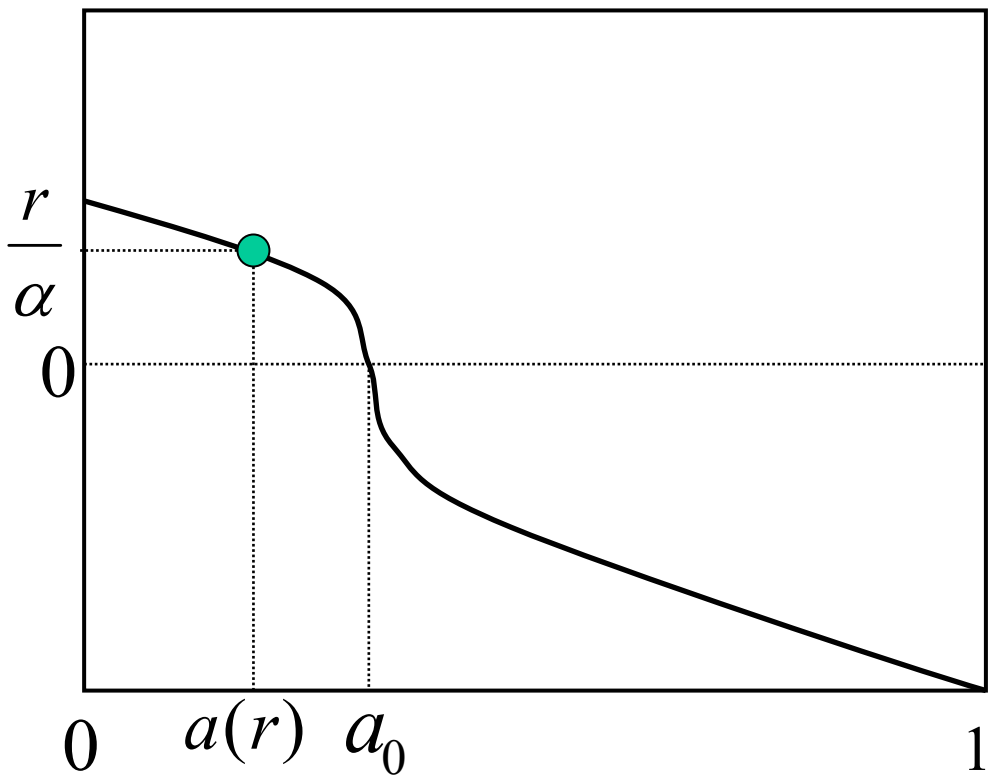
ramp down

$$[L] = [L]_{high} e^{-rt}$$

The mechanism for the activity shift

$$\frac{dm}{dt} = F(a)$$

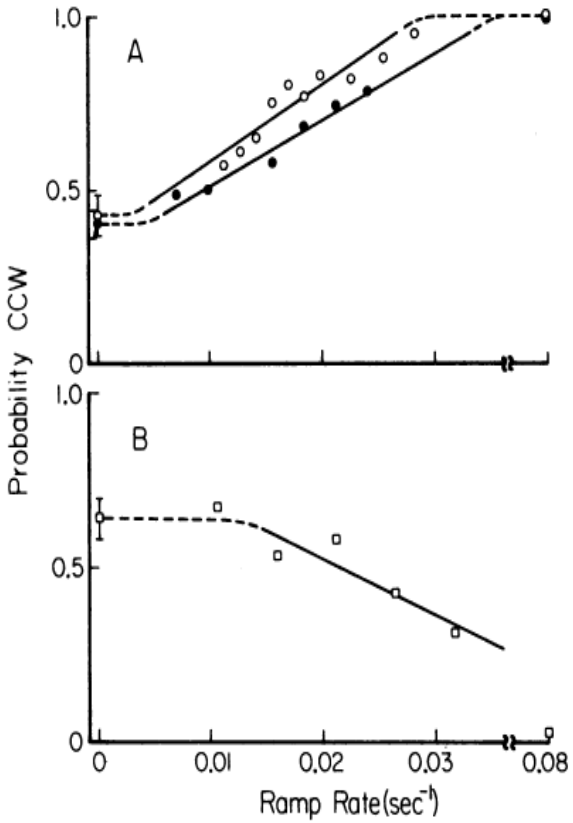
$$F(a) = \frac{r}{\alpha}$$



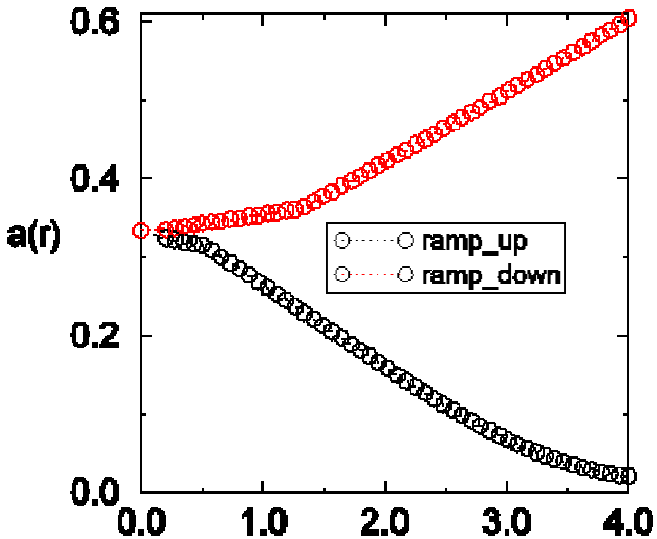
Methylation tries to catch up with the exponentially changing external stimulus
But it lag behind it, which leads to the activity shift

The dependence of the activity shift on ramp rate

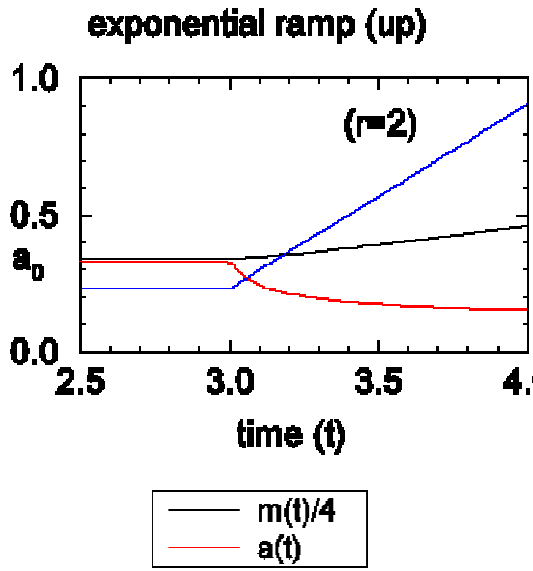
Experiment

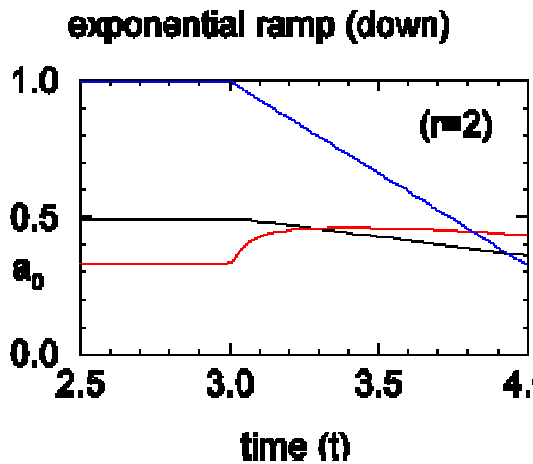


Theory



$(\varepsilon_1=0.05;\varepsilon_2=0.1;f_1=0.15)$



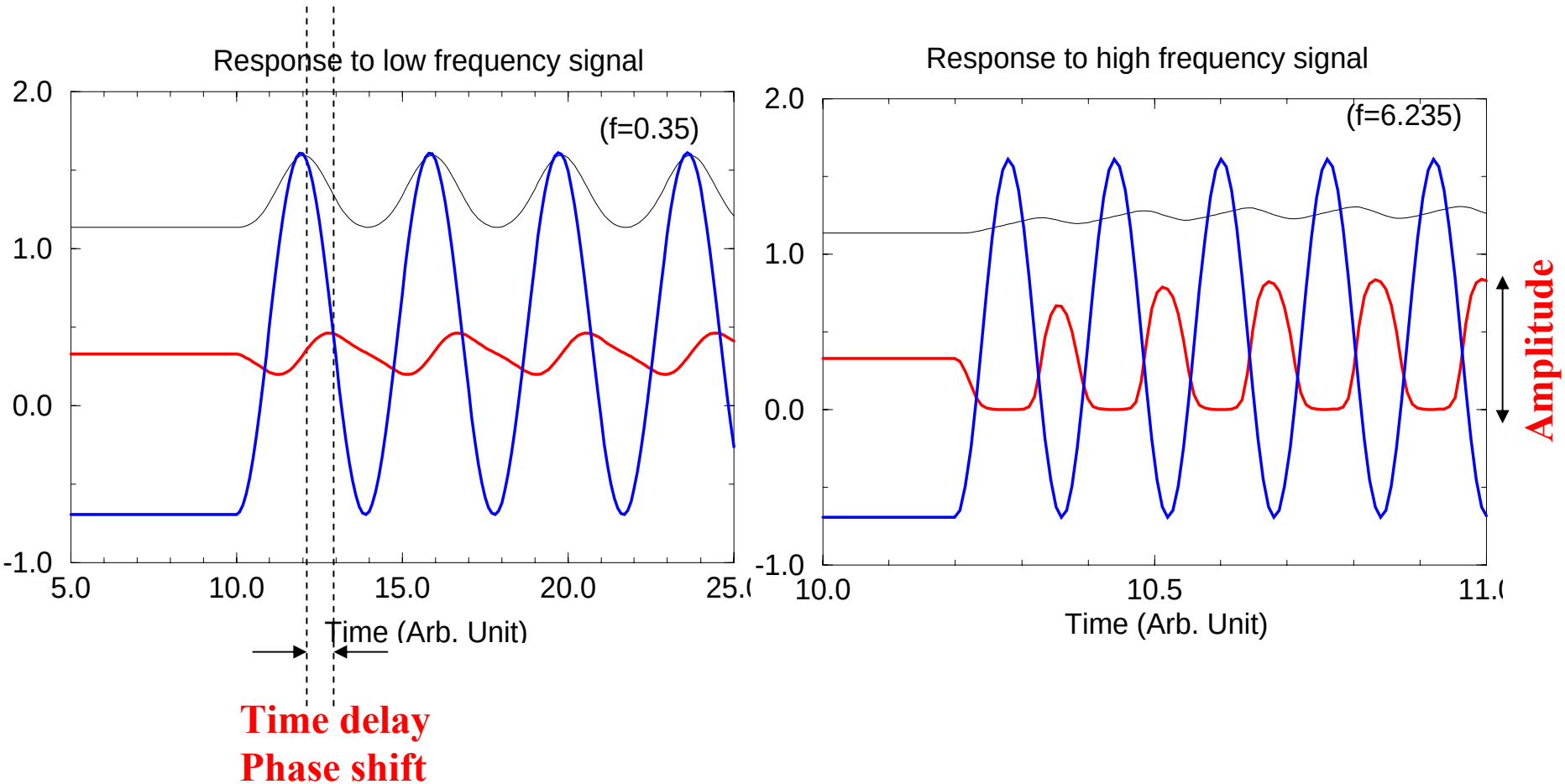


Responses to exponentiated sine waves

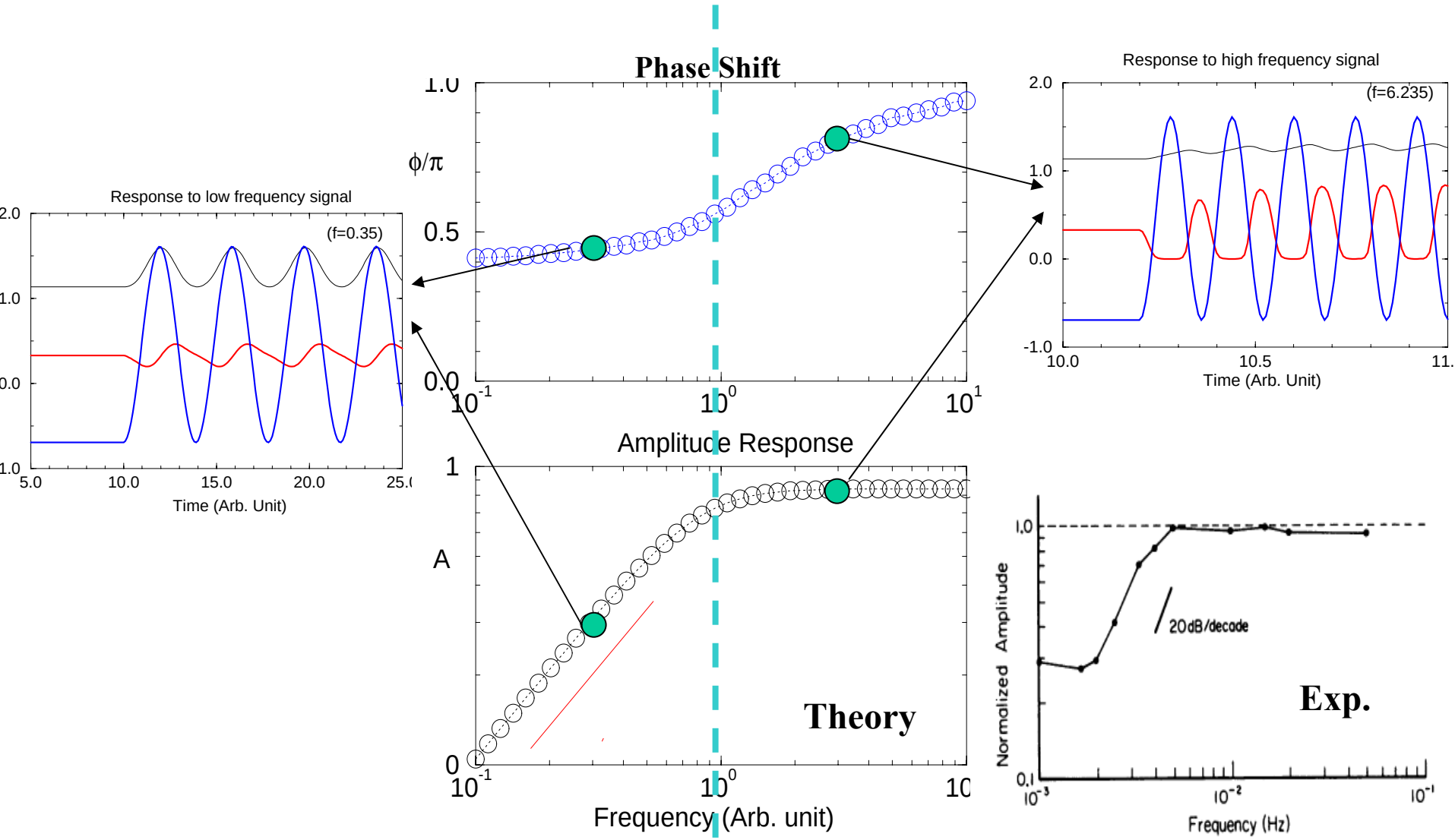
Input: $[L](t) = [L]_0 e^{\beta \sin^2(\pi f t)}$

Output: kinase activity a(t)

Control: methylation m(t)



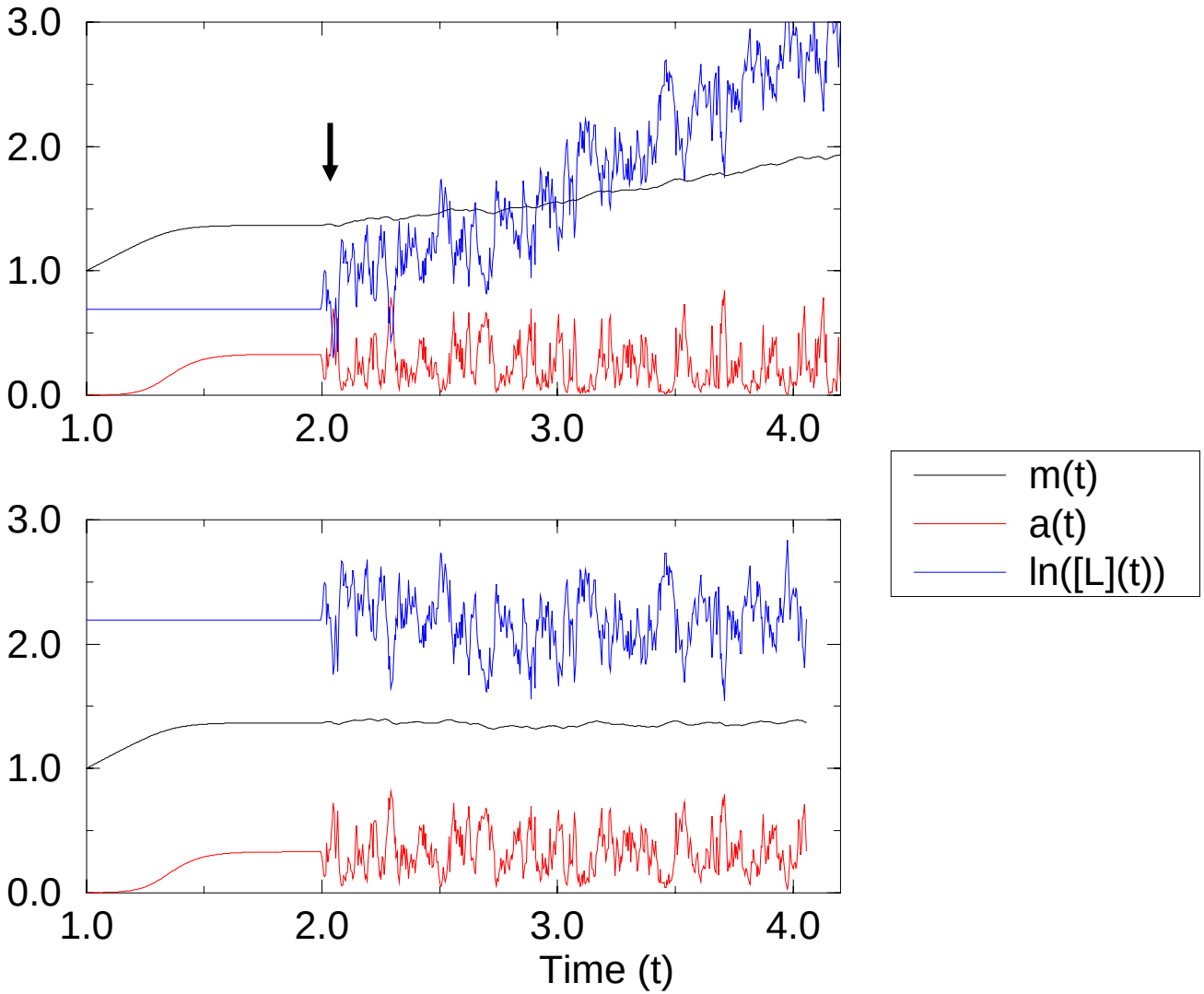
Frequency dependence of responses



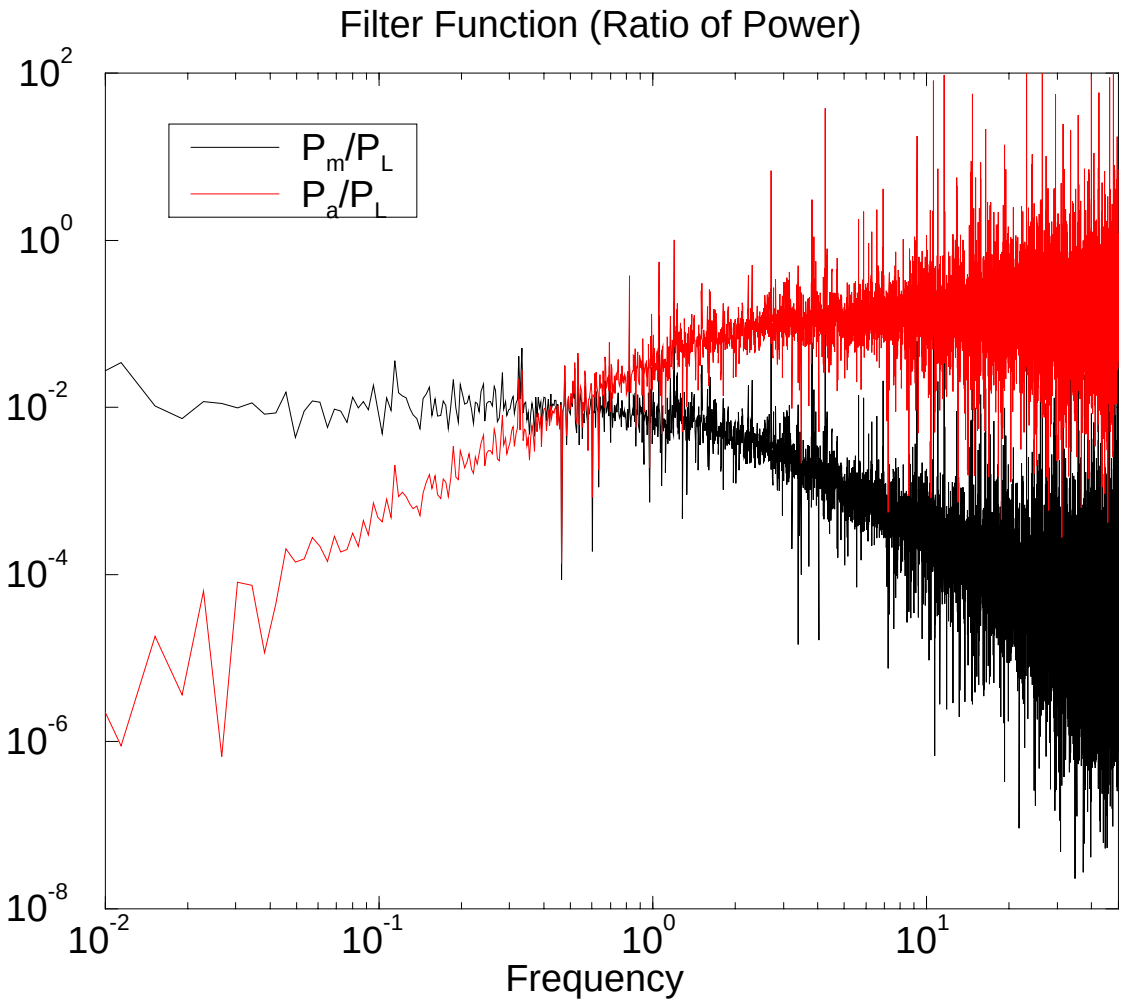
(S. Block et al, 1983)

"calculate" derivative ⟵ ⟶ **"slave" of input**

Response to noisy signal

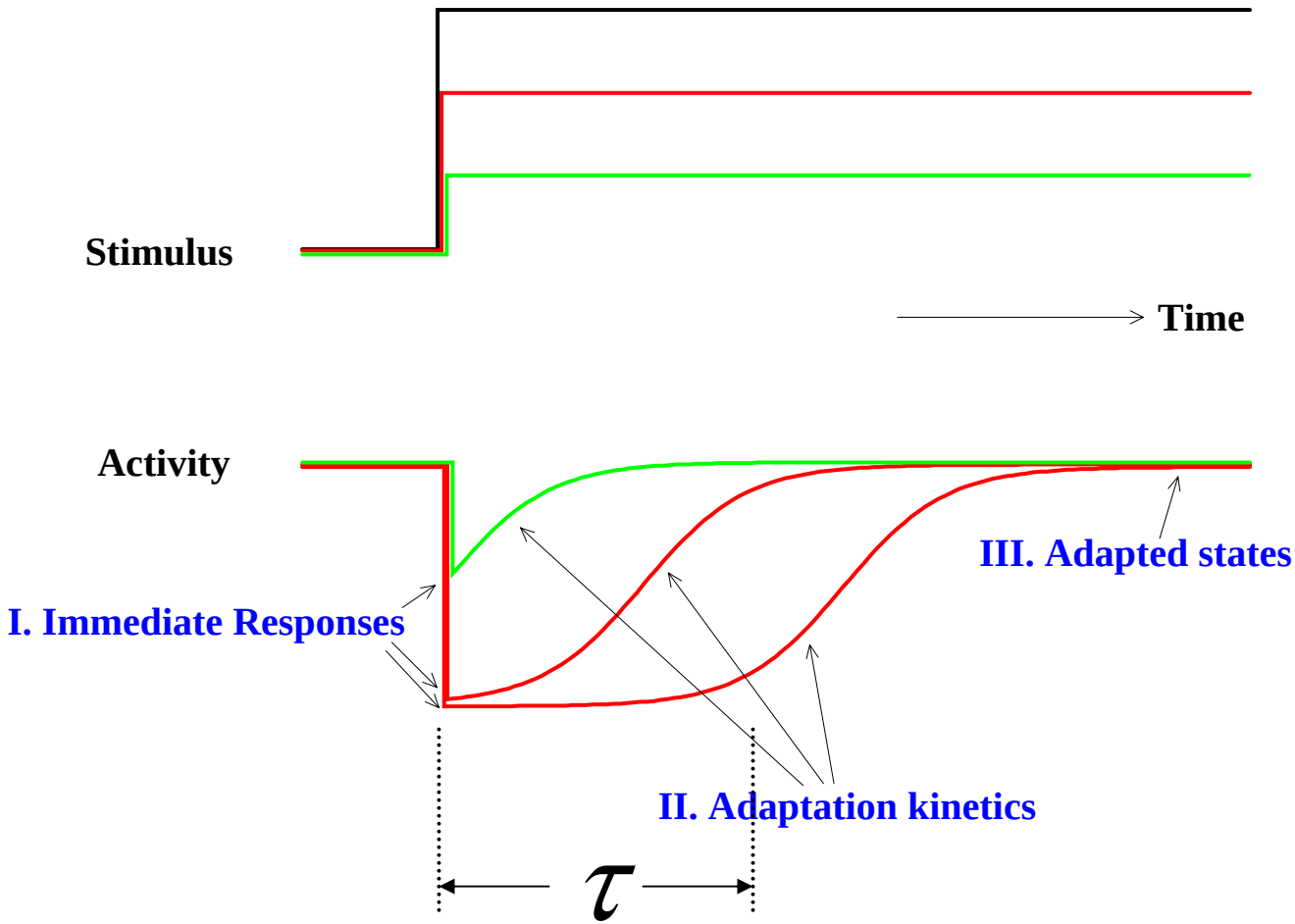


The chemotaxis filter function

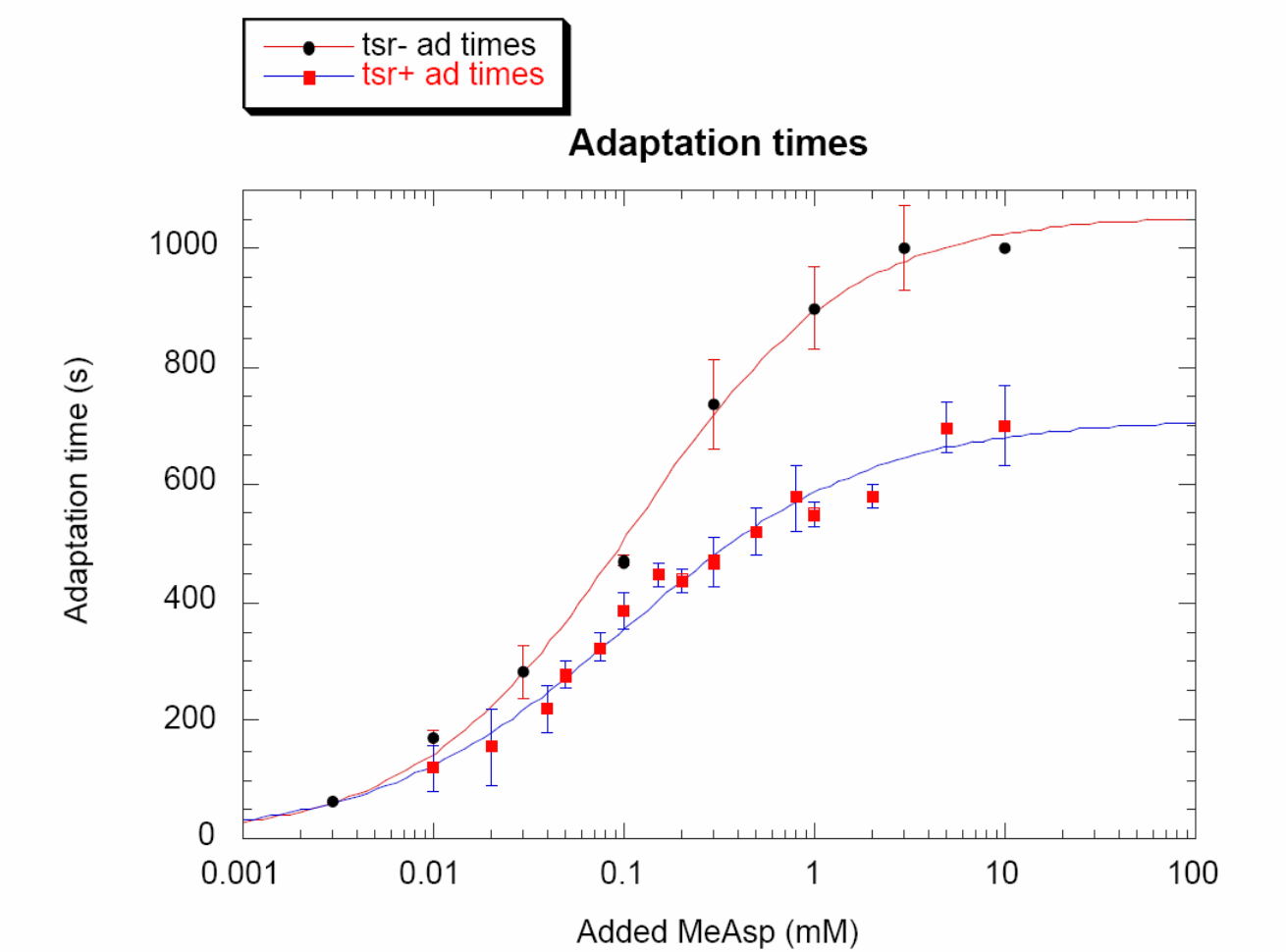


- Methylation level: Low pass filter
- Kinase activity: Calculate derivative in low frequency regime.

Response to large steps: variable memory time scales



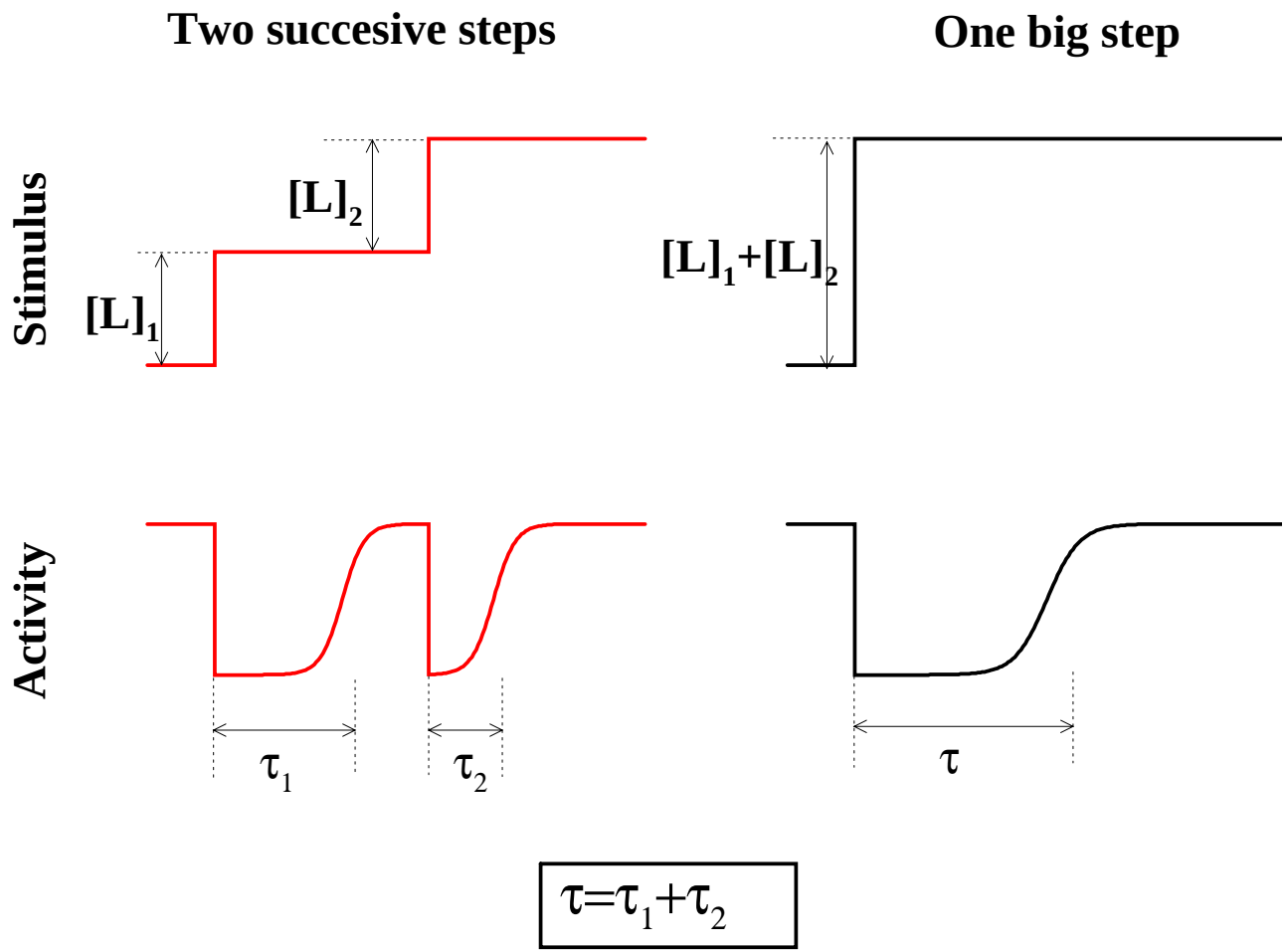
Experimental Measurements



(Sourjik, unpublished data)

Additivity of adaptation time

- Spudich & Koshland, PNAS, 1975
- Berg & Tedesco, PNAS, 1975



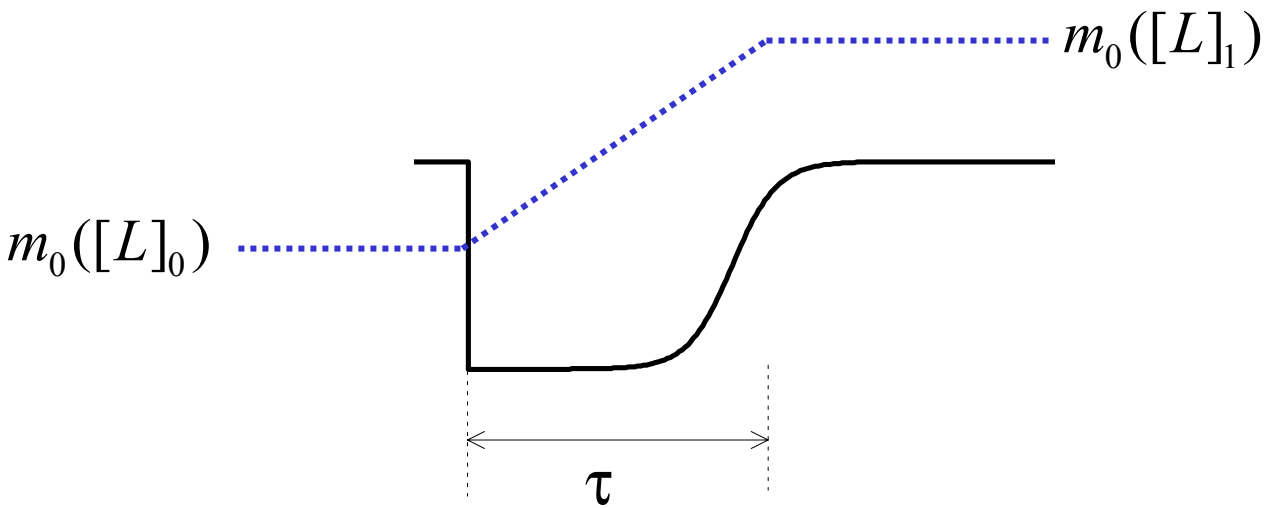
$$\tau=\tau_1+\tau_2$$

The mechanism for additivity in adaptation time

When activity is very small, the rate of change in methylation is constant. The adaptation time is therefore determined by the Rate of change in methylation level at a=0: F(0)

$$\frac{dm}{dt} = F(a) \simeq F(0)$$

$$\rightarrow \quad \tau \approx (m_0([L]_1) - m_0([L]_0)) / F(0)$$



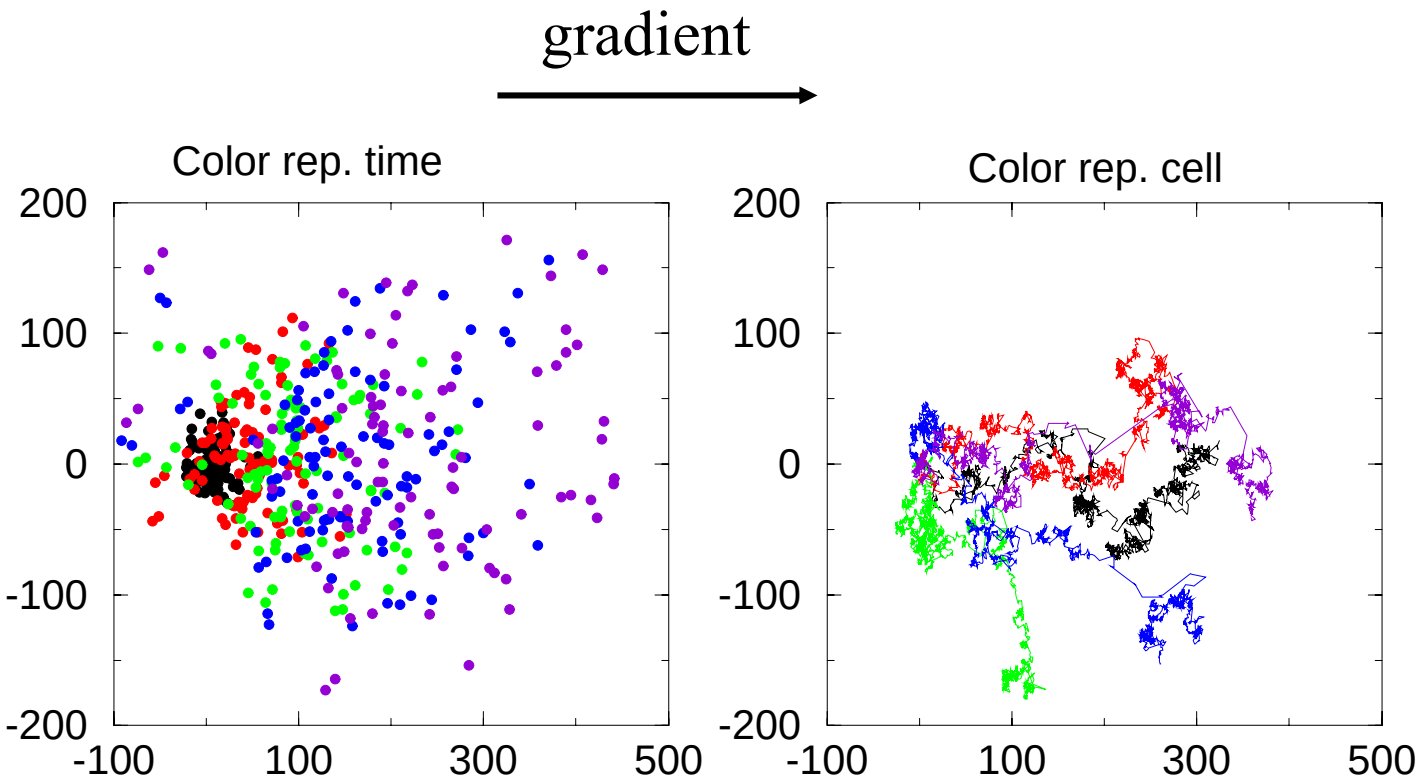
The chemotaxis signal processor

- **It calculates in log-scale**
  Responses depend on $\Delta[L]/[L]$
  The Fechner's Law in sensory system

- **It is a low pass filter for the derivative of the input**
  Calculate derivative (in log-scale) of the input in low frequency regime

- **The adaptation time depends on the stimulus strength**
  A range of time scale (seconds to minutes)
  Integral, nonlinear memory

Behavior: E Coli moving in a spatial gradient

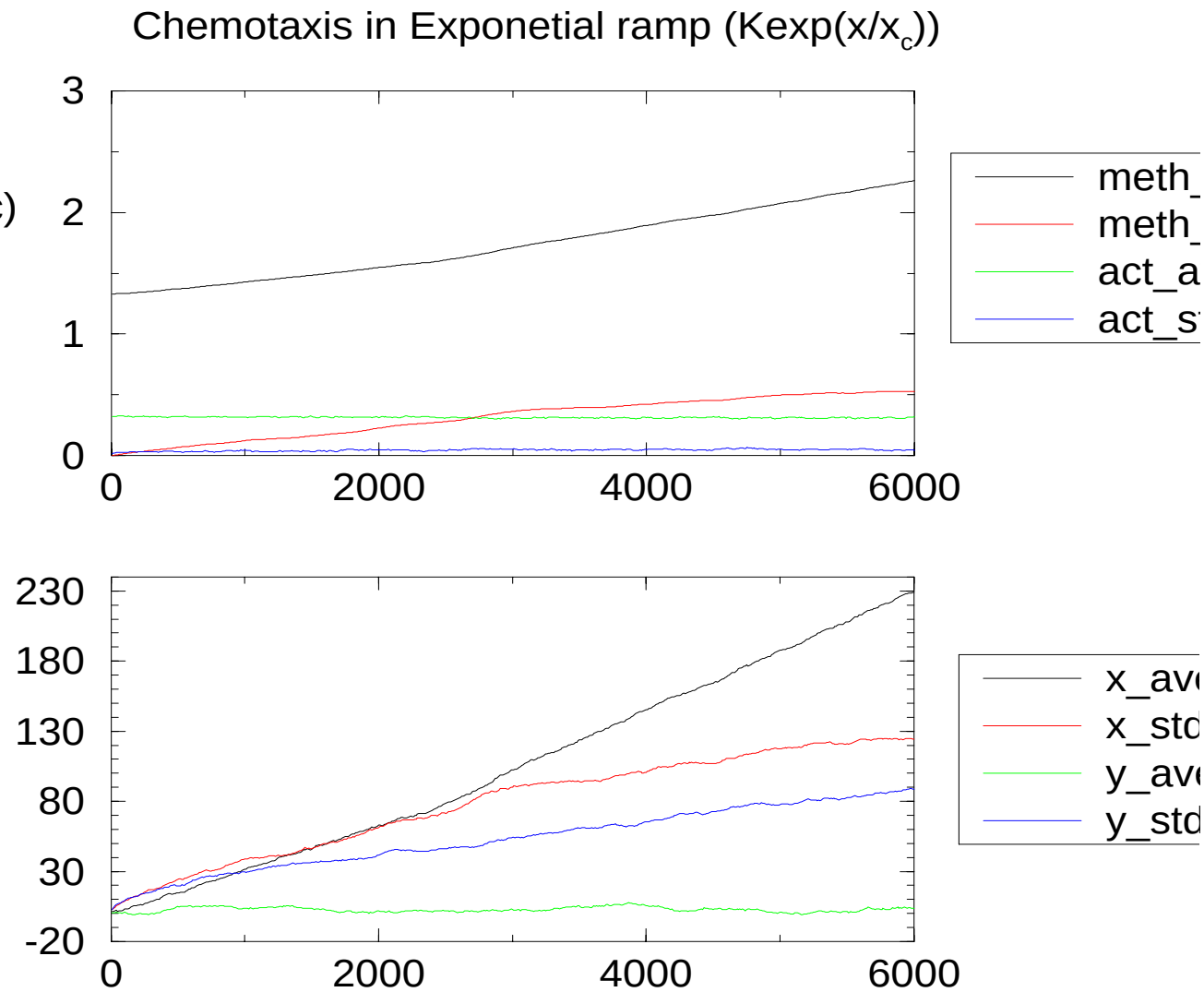


Key: we can know simulate the internal dynamics of the cell.
Methylation dynamics

The quantitative description of the internal and the positional dynamics of the cells

(x_c=100)

(t_m=100sec)



Rewrite the chemotaxis equation

The famous Segel-Keller chemotaxis equation

$$\frac{d\rho}{dt} = D\nabla^2\rho + (\vec{v} \bullet \nabla)\rho$$

$$\vec{v} = \gamma(C)\nabla C$$

Phenomenological, based on qualitative behavior: biased random walk

We are in the position to introduce the proper internal methylation (memory) kinetics to "derive" the chemotaxis equation…….

To be continued…….