# Sensitivity, feedback and fluctuations in bacterial chemotaxis

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***Short Abstract* — Combining *in vivo* FRET measurements with quantitative modeling, we study mechanisms of signal processing in the *Escherichia coli* chemotaxis system. Over a very broad range of background input, this pathway demonstrates sensitive responses and exact adaptation. A simple allosteric model of the MWC-type satisfactorily describes dose-response characteristics of adaptation-deficient mutants. We extend this model to analyze the behavior of adapting cells where receptor modification states are dynamically tuned by adaptation feedback. We study how different mechanisms of feedback contribute to steady-state fluctuations in the modification level of receptors, which, in turn, determine the sensitivity and cooperativity of receptor populations.**

***Keywords* — Fluorescence resonance energy transfer, signal amplification, MWC model, stochastic kinetics, signaling network, allosteric assemblies.**

## I. Purpose

Chemotaxis in *E. coli* has played a paradigmatic role in the transformation of cell signaling research into a quantitative discipline [1]. Three important quantitative features of this sensory system have been highlighted: exact adaptation, high sensitivity and wide dynamic range. All three are required for the problem every bacterium would like to solve: how to navigate up shallow gradients a very long way. Exact adaptation can be explained elegantly by the simple mechanism of activity-dependent feedback in the receptor modification system [2]. High sensitivity and wide dynamic range were shown to be attainable by simple physical interactions between clustered receptors [3]. Both conjectures have since been validated experimentally [4, 5].

Here we utilize dose-response curves of pathway activity ($A$) to changes in attractant concentration ($\ell$), measured *in vivo* by fluorescence resonance energy transfer (FRET), to study how these mechanisms combine in the physiology of living cells. The quality of the data is sufficient for detailed modeling of the underlying mechanisms.

## II. Results

Responses of adaptation-deficient mutants with homogeneous receptor populations are satisfactorily described by an allosteric MWC-type model of receptor interactions

$$A(m,\ell) = \frac{1}{1+e^{N(E_A(m)+\lambda(\ell))}}$$

where $m$ denotes the modification state of the receptor complex, $N$ is the number of interacting receptors, and $E_A(m)$ and $\lambda(\ell)$ measure the free-energy contribution from receptor modification and ligand, respectively. Calibrating this model with FRET experiments, we find that the modification-dependent energy $E_A(m)$ depends linearly on $m$ and the ligand-dependent energy $\lambda(\ell)$ has a finite upper bound for the attractant α-methylaspartate.

In adapting cells where modification states are feedback-regulated, the random walk of receptor complexes in modification space (coordinate $m$) is formulated as a stochastic "one-step" process [6] in which the up- and down-ward transition probabilities *f(m)* and *g(m)* are constrained by the two aforementioned theories [2,3]. A direct consequence of this mapping is that the steady-state variance in receptor modification level distribution $P(m)$, becomes inversely proportional to the sensitivity of pathway activity to receptor modification via a fluctuation-dissipation relation, i.e.,

$$\sigma_m^2 \propto \left(\frac{\partial A}{\partial m}\right)^{-1}.$$

Because $A$ is itself a function of $m$, this relation sets strong constraints on the functional forms of *f(m)* and *g(m)*. We use this relation and FRET experiments with mutants of the feedback system to study the design of the chemotaxis system.

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