Why are chemotaxis receptors clustered but other receptors aren't?

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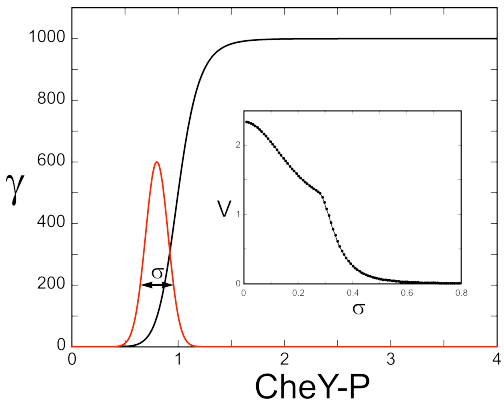
The chemotaxis network of bacteria such as *E. coli* is remarkable for its sensitivity to minute relative changes in chemical concentrations in the environment. Indeed, *E. coli* cells can detect concentration changes as low as 3.2 nM of the attractant aspartate [1], corresponding to only ~3 molecules in the volume of a cell. Much of this acute sensitivity can be traced to the collective behavior of teams of chemoreceptors on the cell surface. Instead of receptors switching individually between active and inactive configurations, teams of 6-20 receptors switch on and off, and bind or unbind ligand, collectively. Similar to the binding and unbinding of oxygen molecules by tetramers of hemoglobin, the result is a sigmoidal binding curve. Coupled with a system for adaptation that tunes the operating point to the steep region of this sigmoidal curve, the advantage for chemotaxis is *gain – i.e.*, small relative changes in chemical concentrations are transduced into large relative changes in signaling activity (specifically, the rate of phosphorylation of the response regulator CheY). However, something is troubling about this simple explanation: in addition to providing gain, the coupling of receptors into teams also increases noise, and the net result is a *decrease* in the signal-to-noise ratio of the network. Why then are chemoreceptors observed to form cooperative teams? We present a novel hypothesis that the run-and-tumble chemotactic strategy of bacteria leads to a "noise threshold", below which noise does not significantly decrease chemotactic velocity, but above which noise dramatically decreases this velocity (Fig. 1). This conjecture predicts that the sizes of receptor signaling teams are optimized with respect to this noise threshold; teams are as large as possible to maximize gain, but not so large as to cross this threshold. In practice, we have calculated the chemotactic velocity in shallow gradients, including rotational diffusion of bacteria, the signaling pathway, and the sigmoidal response of the flagellar motor. Our results, shown in the inset to Fig. 1 strongly support the hypothesis of a noise threshold. Where does this threshold come from? Chemotactic drift up a chemical gradient occurs if cells tumble less frequently when moving up the gradient, and more frequently when traveling down the gradient. The larger this difference in tumbling rates, the faster cells progress up the gradient. However, variation in the *mean* tumbling rate does not strongly affect this progress, as long as the difference between up- and down-gradient tumbling rates is preserved. It is exactly this lack of sensitivity to the mean tumbling rate that leads to a noise threshold. As long as noise from all sources does not change the mean tumbling rate too much (as set by the nonlinearity of the tumbling rate versus CheY-P), chemotactic velocity remains high. Indeed, many features of the chemotaxis network – including receptor cooperativity, number of methylation states, and protein level variations – can be understood in terms of the design principle of maximizing signal, while remaining below a hard noise threshold. In this regard, the chemotaxis network, which is designed to measure concentration *differences,* contrasts with other networks, *e.g.* quorum sensing, which are designed to measure *absolute* concentrations. We expect that comparisons of other differential versus absolute sensing systems in cells may lead to further insights into distinct novel design principles for optimal sensing.



Noise threshold in chemotaxis. For swimming *E. coli* cells, the tumbling rate γ (black curve) is a strongly sigmoidal function of the internal signaling molecule CheY-P [2]. As noise in CheY-P levels increases, measured by the width σ of the CheY-P distribution (red curve), the chemotactic drift velocity V remains high until the noise σ passes a threshold (see inset). Quantitatively, the threshold is set by the nonlinearity of the tumbling rate versus CheY-P concentration. Because sub-threshold noise does not significantly limit performance, components of the network, e.g. receptor signaling teams, may have evolved to optimize signal, rather than signal-to-noise ratio, while not exceeding the noise threshold

1. Mao, H., P.S. Cremer, and M.D. Manson, *A sensitive, versatile microfluidic assay for bacterial chemotaxis.* Proc Natl Acad Sci U S A, 2003. **100**(9): p. 5449-54.
2. Cluzel, P., M. Surette, and S. Leibler, *An ultrasensitive bacterial motor revealed by monitoring signaling proteins in single cells.* Science, 2000. **287**(5458): p. 1652-5.