Sensing Multiple Ligands with a Single Receptor

Vijay Singh[1] and Ilya Nemenman[1, 2]

***Short Abstract* — Cells use surface receptors to estimate the concentration of external ligands. Limits on the accuracy of such estimations have been well studied for cases of single ligand-receptor species. However, cell surface contains many species of receptors that measure the concentration of several external ligands, and non-cognate ligands can bind to receptors, resulting in the phenomenon of cross-talk. We show that the cross-talk does not interfere substantially with determination of ligand concentrations if one is allowed to use the entire temporal sequence of receptor binding-unbinding instead of only the receptor's average occupancy. In fact, concentrations of two different chemical ligands can be measured with just one receptor with an accuracy approaching the limit set by basic statistical considerations. We argue that a high-accuracy approximation to such inference of multiple chemical concentrations can be done using the kinetic proofreading mechanism that is abundant in real cells.**

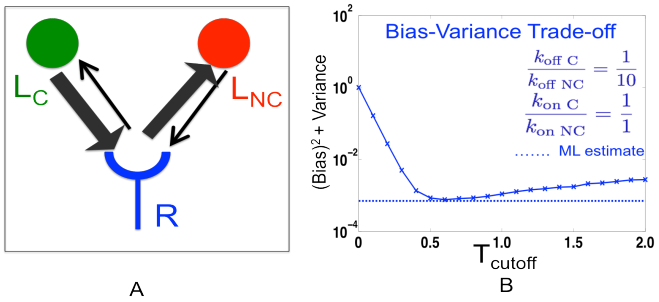
***Keywords* — ligand concentration estimation, maximum-likelihood, kinetic proofreading.**

I. Motivation

Cells estimate the concentration of external ligands by capturing the ligand molecules with cell-surface receptors. Limit on the accuracy of such estimation has been a subject of interest since the seminal work of Berg and Purcell [1], with several substantial improvements found in the recent years [2-5]. All these estimates assume one ligand species coupled to a single receptor species. However, realistically, there are many species of ligands present in the vicinity of a cell. Similarly, the cell surface contains several types of receptors. In principle, each ligand can bind to each receptor, albeit with different affinities. Does this cross-talk affect the accuracy of estimation of ligand concentrations by the cell? Is it always detrimental, or can it be used to improve the estimation?

II. Model

We answer these questions in the context of a simplified model of a single receptor estimating concentration of two chemical ligands (cognate and non-cognate) (Fig. A). The on-rates for both ligands are assumed to be diffusion-limited and hence are nearly the same. However, the cognate ligand has a smaller off-rate and hence stays bound to the receptor for longer periods of time, generally. Writing down the master equation for the system allows us to calculate the probability of each particular sequence of binding-unbinding events for the receptor, which we then use for estimation of ligand concentrations.



A B

III. Results and Conclusions

We observe that the time series of binding-unbinding events carries information about both ligand concentrations, where the number of long binding events carries information about cognate ligand, and short binding events can be used to estimate the concentration of the non-cognate ones. We write down the maximum-likelihood (ML) solution [6] for this estimation, and an approximate solution that assumes that *all* long binding duration events come from cognate receptors. This results in a simplified estimation that can be implemented by cells using the kinetic-proofreading mechanism, which is an abundant motif in protein signaling. We use analytical and stochastic simulation methods to investigate the bias and the variance of the approximate estimator as a function of the cutoff time above which all binding events are considered cognate. The minimum of the bias-variance tradeoff curve is very close to the perfect estimation (see Fig. B). This shows that the cross-talk allows to estimate concentrations of two ligands simultaneously and efficiently by one type of receptors. Multiple ligand concentrations can be estimated similarly by setting up multiple kinetic proofreading cascades. Finally we argue that cross-talk can be beneficial in concentration estimation problems allowing to extend the dynamic range of the system by measuring concentration of a ligand on a non-cognate receptor when the cognate one is saturated.

Acknowledgements: This work was funded by Human Frontier Science

[1]Department of Physics, Emory University, Atlanta, GA 30322. E-mail: vijay.singh@emory.edu

[2] Department of Physics and Biology, Emory University, Atlanta, GA 30322. E-mail: ilya.nemenman@emory.edu

References

[1] Berg HC, Purcell EM (1977) Physics of chemoreception. In *Biophysics J.* **20**, 193–219.

[2] Bialek W, Setayeshgar S (2005) Physical limits to biochemical sensing. *PNAS.* 102, **29**, 10040-10045.

[3] Kaizu K, et. al (2014) The Berg-Purcell limit revisited. *Biophysics J.* **106**, 976-85.

[4] Endres RG, Wingreen NS (2008) Accuracy of direct gradient sensing by single cells. *PNAS.* **105,** 15749.

[5] Hu B, et. al (2010) Physical limits on cellular sensing of spatial gradients. *PRL* **105** 048104.

[6] Endres RG, Wingreen NS (2009) Maximum likelihood and the single receptor. *PRL.* **103,** 158101.