

Sensing a moving target: A new model reveals how cells sense dynamic signals

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Cells are extraordinary chemical sensors. They can detect single-molecule arrivals (1), respond to several-molecule differences between their two sides (2), and adopt distinct fates based on 1% concentration differences (3). While much of the understanding of how cells achieve this level of precision is based on static concentrations, many of the chemical signals to which cells are exposed are dynamic. Little is known about the statistical properties of these dynamic signals, let alone the precision with which cells can sense them. Now a theoretical study by Aparajita Kashyap and co-workers from Johns Hopkins University sheds important light on both questions (4). The authors work out the statistics of a dynamic concentration supplied by moving sources, and they elucidate the sensing strategies a cell should use to best estimate it. The results expand our understanding of cell sensing and could have implications for more general dynamic search problems.

The physical limit to the precision of static concentration sensing was first derived in 1977 by Howard Berg and Edward Purcell (5). Their work made clear that a cell could improve the pre-

cision of its estimate by integrating multiple measurements over time. The reason for this is that molecules diffuse; thus, after previously detected molecules are replaced by new ones, the cell has access to a statistically independent measurement of the concentration. Multiple independent measurements reduce the estimation error.

Over the past half-century, Berg and Purcell's precision limit for static concentrations has been revisited and extended many times (6), but only recently have similar limits been sought for dynamic concentrations. In 2019, Thierry Mora and Ilya Nemenman described a dynamic concentration as a geometric random walk and found that a cell should not integrate measurements indefinitely (7). Instead, the optimal integration time is the geometric mean of the random walk's timescale and the time between molecular detection events. This optimum reflects the trade-off between integrating for long amounts of time to reduce measurement error and integrating for short amounts of time to ensure that past concentrations still reflect current conditions. In 2021, Giulia Malaguti and Pieter Rein ten Wolde revealed this trade-off explicitly for Gaussian, memoryless dynamic signals by demonstrating that the estimation error decomposes into two terms, one for each of the two above effects (8). While these works were important

steps forward, it remained unclear whether these simplified dynamics reflect realistic cellular environments, and if so, how the properties of these environments affect the optimal sensory strategy.

Now, Kashyap and co-workers have derived the precision of dynamic concentration sensing for a specific, biologically plausible environment. The authors imagine a eukaryotic cell (such as an amoeba) in the presence of bacteria that secrete a chemical (such as folic acid). The bacteria execute run-and-tumble swimming motion. Because the chemical is supplied by moving sources, the concentration at the cell's location is dynamic. The statistics of the run-and-tumble motion thus determine the statistics of the dynamic concentration. Kashyap and co-workers then ask how these statistics influence the optimal sensory strategy.

The authors find that the optimal strategy can range from integrating indefinitely, to integrating for a finite time, to not integrating at all. Integrating indefinitely is best when the concentration varies weakly (i.e., is nearly static), consistent with the work of Berg and Purcell. Integrating for a finite time is best when the concentration varies slowly compared to the response time of the cell's receptors. Here, the optimal integration time scales with the geometric mean of the two timescales, consistent with

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the work of Mora and Nemenman, and the estimation error decomposes into two terms, consistent with the work of Malaguti and ten Wolde. Finally, not integrating at all is best when the concentration varies strongly—specifically, when its variance is much larger than that from the receptor binding process. Here, the cell can do no better than an instantaneous measurement because environmental fluctuations are much larger than those of its measurement device. Importantly, these results are captured in a phase diagram, generalizing the previous results and revealing the limits in which they apply.

Kashyap and co-workers then relate the above findings back to the properties of the swimming bacteria. For example, the chemical that the bacteria secrete diffuses and degrades, defining a characteristic lengthscale. The optimal integration time generally increases with this lengthscale because the concentration field becomes more uniform. A second, perhaps more surprising, example is that the optimal integration time is largely independent of the bacterial density. The reason is that both the secretion of molecules by the bacteria and the binding of molecules to the cell's receptors are Poisson processes. Both molecular amounts are proportional to the bacterial density, which thus drops out of the estimation error. These examples

relate the statistics of cellular sensing to the physics of cellular environments, providing predictions for future experiments that could test the dependencies explicitly.

The study by Kashyap and co-workers is part of a larger rethinking of Berg and Purcell's foundational contributions. In addition to investigating the best way to estimate the current value of a dynamic concentration, recent work has focused on ways to predict future values (9) or detect a point of sudden change (10). In the context of eukaryotic cells like amoebae, which can chemotax, a more relevant quantity may be the spatial derivative of a concentration. How to best measure the spatial gradient of a dynamic concentration is still an open problem.

The legacy of Berg and Purcell is the realization that because cells may have evolved to sense their environment as precisely as physically possible, the physics of their environment can be investigated to infer their sensory strategies. As more and more data corroborate this fundamental idea (11), we follow its logic to ever-deeper sensory questions. It will be fascinating to see what questions—and answers—emerge next.

DECLARATION OF INTERESTS

The author declares no competing interests.

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