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Environmental sensing, information transfer, and cellular decision-making

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The recognition that gene expression can be substantially stochastic poses the question of how cells respond to dynamic environments using biochemistry that itself fluctuates. The study of cellular decision-making aims to solve this puzzle by focusing on quantitative understanding of the variation seen across isogenic populations in response to extracellular change. This behaviour is complex, and a theoretical framework within which to embed experimental results is needed. Here we review current approaches, with an emphasis on information theory, sequential data processing, and optimality arguments. We conclude by highlighting some limitations of these techniques and the importance of connecting both theory and experiment to measures of fitness.

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Introduction

Life for single cells is stochastic [1]. Cells sense fluctuating signals with biochemical networks that are themselves stochastic and history-dependent [2], and yet living organisms are able to flourish in nearly all environments. Understanding how cells prosper despite stochasticity and environmental variability is the focus of a relatively new area of systems biology, that of cellular decision-making [3,4]. By a cellular decision we mean the process by which a cell makes a 'choice' of phenotype from a range of possible phenotypes in response to or in anticipation of extracellular change. Such choices could include new gene expression, changes in cell morphology, intracellular re-arrangements, movement, or the option not to change phenotype at all.

In addition to the stochasticity of signal transduction, cells locally sense signals that fluctuate both in time and across space, whereas often it is the successful identification of broader environmental changes that is important in enabling an effective response [5]. Even bacteria appear to be able to solve this kind of inference problem, using local signals to identify, for example, that they are in the human gut and thereby anticipate likely future events [6,7].

Here we review the theoretical approaches developed so far to understand cellular decision-making. Motivated by the surge of interest in biochemical stochasticity generated by the theoretical work of McAdams and Arkin in 1997 [8], we ask if theory is now poised to have a similar effect on the experimental study of decision-making in single cells.

Dose–response and information theory

Most theorists have focused on applying ideas from information theory, often inspired by neuroscience [9]. In systems biology, the experimental confirmation that gene expression is stochastic [10,11] and the related discovery that genetically identical cells can vary significantly in their response to the same stimulus [12–14] implies that dose–response, or 'input–output', relationships are also often substantially stochastic. Information theory, through mutual information, provides an objective means to quantify the influence of this stochasticity [15].

Mutual information is perhaps the most principled measure of statistical dependence between two stochastic variables, such as the signal and response of a biochemical network [16–19]. We discuss its interpretation as a measure of information in Boxes 1 and 2. Mutual information can be related to the quality of the optimal prediction, or inference, of the signal from the response (Box 1 and Figure 1), does not require knowledge of transduction mechanisms, and is invariant to nonlinear, one-to-one transformations of either the signal or response. It does, however, require measurement of the probability distribution of the signal and the response. Collecting sufficient data to accurately estimate probability distributions and mutual information can be difficult, and for most organisms we know little about the distribution of signals experienced in the wild. An approach often taken in an attempt to circumvent this lack of knowledge is to calculate the information capacity (Box 2), which is the maximum value of the mutual information over all possible, plausible signal distributions.

Recently, the development of fluorescent reporters and microfluidics have enabled unprecedented characterization

Box 1 Interpreting mutual information

Mutual information can be interpreted in several different ways.

Mutual information is the difference between the entropy of the input and the entropy of the input given the output. For discrete systems, the entropy of a random variable is a measure of uncertainty, and mutual information therefore quantifies the reduction in uncertainty about the input gained from measuring the output. For example, if the entropy of the input is, say, 3 bits, a signalling output with a mutual information of 2 bits implies less impeded 'information flow' than an output with a mutual information of 1 bit. For continuous systems, entropy as a measure of uncertainty is more problematic. We would expect the extent of our uncertainty about a random variable not to change if the variable is transformed by a one-to-one mapping, but the entropy of a continuous variable generally does change under such transformations [20].

An alternative interpretation of mutual information, applicable to both discrete and continuous systems, comes from decision theory (summarized in Box 3). Suppose a cell must infer the state of a signal, S, from the output, Z, of a signal transduction mechanism. In general, the inference made about the signal takes the form of a probability distribution (over the possible signal values) with density function, say, q. To measure the quality of this inference, we need a means of evaluating or scoring q. If z is the measured value of the output and the inference about the signal is $q(s', z)$, a function of the possible signal states s', one possible scoring function is $\log q(s' = s, z)$, where s is the true state of the signal. This scoring function rewards inferences q that attach higher values to $s' = s$. Let the true distribution of the signal be $p(s')$ (the signal s is a sample from p) and let this distribution also be the prior distribution for any inference. Then the increase in the score that results from the inference q, when the true state of the signal happens to be s, is measured by

$$\log q(s' = s, z) - \log p(s' = s).$$

When z is measured, the expected value of this increase (averaging over all signal states) is

$$E[\text{score}|z] = \int p(s|z) \log q(s, z)\, ds - \int p(s|z) \log p(s)\, ds,$$

and averaging further over all possible values of the output, z, we have

$$E[\text{score}] = \int p(z)\, p(s|z) \log q(s, z)\, ds dz - \int p(s) \log p(s)\, ds.$$

Following decision theory (Box 3), we then ask which inference function q maximizes this expectation.

The inference that maximizes the expected score is posterior Bayesian inference, $q(s, z) = p(s|z) = p(z, s)/p(z)$ [20]. The expected score then becomes

$$E[\text{score}]_{\text{Bayes}} = \int p(z) \int p(s|z) \log p(s|z)\, ds dz - \int p(s) \log p(s)\, ds = I(S; Z)$$

which, by definition, is the mutual information. The mutual information therefore quantifies the ability, on average, to infer a given signal, S, from the output, Z, of a signal transduction mechanism, if we can assume that the prior distribution for the inference equals the actual distribution of the signal (Figure 1). For a given signal distribution, one transduction mechanism allows better inference than another if and only if it has higher mutual information. We note that different scoring functions can also result in Bayesian inference being optimal, but give an expected score that is not the mutual information. If additional requirements such as smoothness and locality are, however, imposed on the scoring function then the logarithmic function is the only possible one [20].

of the responses of individual cells [21–23], and experimental measurements of mutual information and information capacity for biochemical signalling systems are now appearing [24,25••,26••,27,28•]. A particularly close connection between mutual information and the 'function' of a signalling system is made by Bialek and colleagues in their study of development in the fruit fly [24,26••,29]. Considering the gap gene network early in development, they showed that the positional information, the mutual information between gap gene expression and the position of a nucleus, is close to the amount needed for each nucleus to identify its physical position along the anterior–posterior axis of the embryo [26••]. This system has the advantage that a uniform prior or 'input' distribution for the position of the nucleus is a natural choice. Three recent studies of signal transduction in mammalian cells report values of the mutual information of approximately 1 bit or less for a single cell under conditions of constant stimulation and using simultaneous measurement of a single stimulus and output (the studies, though, use different inputs) [25••,27,28•]. Does this value necessarily mean that the cell can therefore discriminate without error two states of the signal but not more, which would suggest the prevalence of binary decisions by cells? We believe not, for the reasons explained in the first point of Box 2. Cellular inferences of a signal must often be imperfect, and a mutual information of 1 bit is in general a quantification of the ability to infer the signal, albeit with uncertainty, from the output.

More experimentally and analytically accessible alternatives to mutual information have also been proposed, including local, variance-based measures [31] and a lower bound for information capacity based on the linear correlation coefficient [32]. The 'fidelity' is the proportion of the variance in the response that is generated by the signal rather than by, for example, biochemical stochasticity, and provides a lower bound on information capacity that accounts for non-linearity in the response [33•]. Using this approach, a study of osmosensing in yeast showed that the majority of variation in expression of a gene induced by a stress-activated kinase (up to 80%) can be due to variation in the osmotic environment [33•].