Do Cells Perceive Diffusion Noise?

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I. Introduction

Robert Brown discovered "Brownian motion" (the random walk of small particles in a fluid) in 1827 [1]. From a micro-scale perspective, the particles are self-propelled inside the fluid by their thermal energy. From a macroscopic perspective, the Brownian motion of individual particles leads to collective behavior of "diffusion" from a region of high concentration towards a region of lower concentration.

Diffusion is a prevalent mechanism used by cells to communicate with other cells and sense their surrounding environment (extracellular matrix). Cells employ the extracellular environment and circulatory system to transmit their signaling molecules within short and long distances. The signaling pathway in the target cell senses and processes signaling molecules enabling the downstream effectors to adapt the cell's physiological state to changing conditions [2].

Systems biologists study cell signaling pathways through cell culture experiments where a specific ligand concentration stimulates cell individuals or populations and the corresponding response is measured [3]. As input signal, the levels of soluble ligand concentration observed by the individual cells fluctuate due to the Brownian motion of molecules that affects the analysis of signaling pathways and cell behavior. This raises the question whether Brownian motion is also responsible for the variability of the measured response of the cell besides intracellular noise and cell-to-cell variability? If it is how can the cells and tissues in our body reliably operate while relying on random walks of molecules?

The natural cell-to-cell communication mechanism has inspired diffusive molecular communication (DMC) among nanomachines to realize nanonetworks for various applications including healthcare [4]. The biological, synthetic, or biosynthetic cells may be used as nanomachines in these systems. In DMC, molecules as carriers of information are released from the transmitter cell (nanomachine) and propagate in the environment due to diffusion. The receiver cell (nanomachine) receives propagating molecules through the reception mechanism. While diffusion noise has been theoretically modeled and studied by MC community [5], [6], the practical constraints on the sensitivity or computational capacity of the receiver nanomachine has been less considered.

The fundamental physical limit to chemical sensing by cells has been proposed by Berg and Purcell [7] in which the sensing precision of the cell is related to the concentration magnitude and the cell physical properties like its size. Their limits have been refined and extended in many works including [8], [9]. Some of these works investigate the contribution of specific binding mechanisms at the cell to define bounds on the cell precision to measure the concentration. Following the original work of Berg and Purcell, they measure statistical uncertainty using variance.

In this paper, we investigate a different but related question that impacts the study of cell signaling pathways and molecular communication systems: Given a certain level of cell sensitivity to measure concentration, how much uncertainty observed by the cell is due to Brownian motion of molecules? We propose a universal information-theoretic measure based on *normalized entropy* that is built upon probabilities instead of variance and is independent of the physics of the system. The proposed measure has the following properties:

- This metric is independent of the type of cell's reception mechanism. We define the cell sensitivity as the concentration difference that the cell is able to measure which can be obtained based on the cell response curve and dynamic range of the cell's response.
- This metric is normalized to the range of $[0, 1]$ enabling comparison between different cells and stimuli. The lowest value corresponds to a deterministic (non-random) concentration perceived by the cell with its sensitivity level. Maximum value of 1 determines the maximum randomness of concentration observed by the cell.

II. Proposed Normalized Entropy Measure

Assume that a cell is located in an environment filled with fluid media. Using its transmembrane mechanisms, e.g., receptors, the cell senses the molecule type A in its sensing region. The cell's sensing region is the region where the cell reception mechanism is impacted by the signaling molecules A. The size of the sensing region is within the same order of magnitude as the cell volume denoted by V_c in l liters.[1]

Consider that X Molar (M) is the average concentration of A molecules in the sensing region of the cell at a specific time. For the sake of generality, we do not discuss the source of A molecules in the environment or its concentration profile. The average concentration of molecules at the recipient cells can be computed using the partial differential equations based on Fick's law characterizing the spatial-temproal concentration profile of molecules in the environment subject to the applied release source and boundary conditions.

[1]To justify this assumption, one may assume a transparent cell that counts molecules fallen in its volume.

The average number of molecules in the sensing region of the cell is then XV_cN_0 where N_0 is Avogadro's number. Brownian motion affects the movement of individual molecules through the random walk process. Thereby, the number of molecules within the sensing region of the cell at given time instance is a random variable with an average of $N = XV_cN_0$. Diffusion leads to the Poisson distribution of molecules [12] which is the maximum entropy discrete random variable given the mean value. Therefore, $E(\mathbf{N}) = \sigma^2_{\mathbf{N}} = XV_cN_0$.

We define the cell sensitivity (i.e., accuracy of distinguishing the different number of molecules A) as Δ. If we consider the quantized version of the the number of molecules by the step Δ, then the entropy of the quantized version of $\mathbf{N}$, $\mathbf{N}^{\Delta}$, is given by $H(\mathbf{N}^{\Delta}) = -\sum_i (P_{\mathbf{N}}(n_i) \log P_{\mathbf{N}}(n_i))$ in which we have $P_{\mathbf{N}}(n_i) = \sum_{n_i<n<n_i+\Delta} e^{-E(\mathbf{N})} E(\mathbf{N})^n/n!$.

Given that we define the cell dynamic range as the range the molecule numbers that results different cell responses is $[N_1, N_2]$, the normalized entropy metric is given by

$$\bar{H} = \frac{H(\mathbf{N}^{\Delta})}{\log(\frac{N_2-N_1}{\Delta})}, \tag{1}$$

where the denominator is the maximum entropy of the discrete uniform distribution over $[N_1 : \Delta : N_2]$. Obviously, the normalized entropy falls within $[0, 1]$.

The value of normailized entropy determines the maximum uncertainty implied by the diffusion process. If the entropy is much smaller than 1, then this implies uncertainity due to diffusion noise is negligible. In other words, the cell distinguishes the corresponding quantized input level correctly.

III. Results and Discussion

To gain some insights into the proposed metric, we consider two natural extreme scenarios in the human blood with very low and very high molecule concentrations.

Glucose is a highly-concentrated molecule in blood with different target cells including hepatocyte cells in the liver. The dynamic range for glucose is assumed to be between 2.8 mM and 11 mM corresponding to representative levels of hypoglycemia and hyperglycemia, respectively [11]. The typical hepatocyte cell volume is around 3 picoliter (pL). In contrast, parathyroid hormone has a very low dynamic range of concentration in blood, around 0-10 picomolar (pM). It mainly targets bone and kidney cells including podocytes with parathyroid hormone 1 receptors. The volume of a matured podocyte cell has been reported on the order of 100 pL [10]. Fig. 1 demonstrates the normalized entropy versus the cell sensitivity, Δ, given in (1) for hepatocyte and podocyte cells sensing glucose and parathyroid hormones of concentrations $X = 6$ mM and 5 pM, respectively.

We observe that for the highly-concentrated glucose, the hepatocyte cell does not perceive any noise even with high sensitivity on the order of 10^{-4} times $N_2 - N_1$ (equivalently, 10^{-3} mM). For the very low concentration of parathyroid hormone, the cells should be much less sensitive, e.g., 10^{-1} times $N_2 - N_1$ (equivalently, around 1 pM) to not perceive diffusion noise given observing one sample.

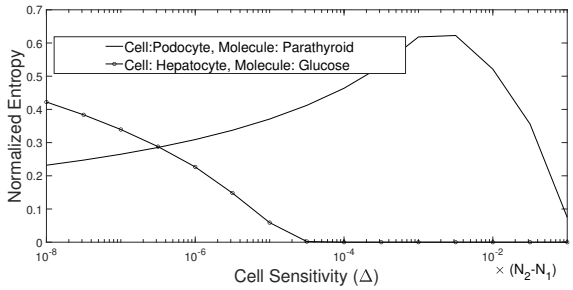

Fig. 1. Normalized entropy for hepatocyte and podocyte receiving glucose and parathyroid hormunes, respectively, versus the cell sensitivity.

As illustrated by the two examples, the normalized entropy measure allows us to quantify the impact of Brownian motion on cell perception of noise and to reason about its biological impact, in principle, on any cell type and signaling molecule.

The proposed metric in this paper only considers observation of one sample by a cell while cells may take multiple samples from the concentration signal. Also, the cells are in communities and respond to stimuli in populations not individually. In the future, we intend to extend this single sample metric to multi-sample observations and consider cell population perception of diffusion noise. Another direction for future work is to account and accommodate for quantitative limitations of computational complexity and energy of the cell for sensitivity in the proposed metric.

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