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Review

Analysis of cellular signal transduction from an information theoretic approach

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ABSTRACT

Signal transduction processes the information of various cellular functions, including cell proliferation, differentiation, and death. The information for controlling cell fate is transmitted by concentrations of cellular signaling molecules. However, how much information is transmitted in signaling pathways has thus far not been investigated. Shannon's information theory paves the way to quantitatively analyze information transmission in signaling pathways. The theory has recently been applied to signal transduction, and mutual information of signal transduction has been determined to be a measure of information transmission. We review this work and provide an overview of how signal transduction transmits informational input and exerts biological output.

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1. Introduction

Information processing is necessary for survival of living systems as well as the energy consumption, and it plays an important role in their adaptation to environmental conditions. Generally, information processing can be seen at multiple levels in living systems, from the single-cell level to multicellular interactions, including brain activity. In this review, we focus on the information processing of signal transduction at the single-cell level that controls cell fates such as proliferation, differentiation, and death.

Information processing at a single-cell level remains poorly understood. However, signal transduction is considered to be a core mechanism of cellular information processing, that is thought to garner information from concentrations of molecules. For example, epidermal growth factor (EGF) stimulation has been reported to induce transient phosphorylation of extracellular signal-regulated kinase (pERK) and cell proliferation, while nerve growth factor (NGF) stimulation induces sustained pERK and cell differentiation [1–4]. This means that information for distinct growth factors is encoded into distinct patterns of pERK concentration that are selectively decoded by downstream molecules and lead to proper

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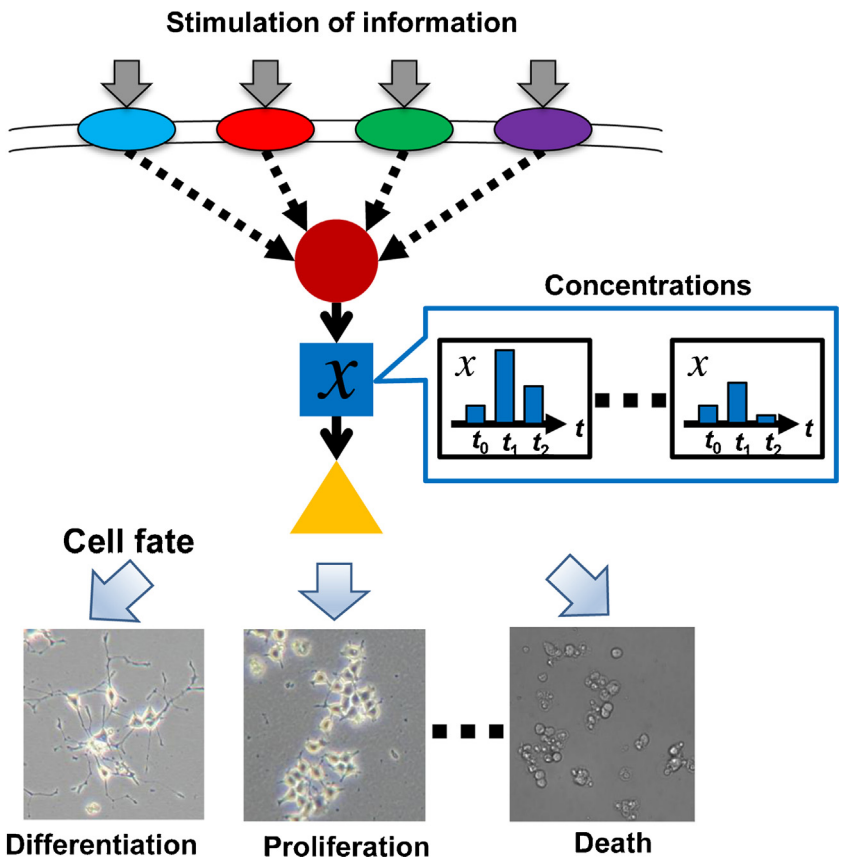

Fig. 1. The information transmission in signal transduction. Given that x represents pERK concentrations, pERK can be regarded as a sender for downstream gene expression, and as a receiver for upstream growth factors. Whether pERK is a sender or a receiver depends on the problem setting for analysis.

cell fate decisions [5] (Fig. 1). For example, ERK activation can transmit information about various types of cell fates. Thus, signaling pathway can be regarded as a communication system that involves encoding, communicating, and decoding variable information.

Information transmission of a cellular system is mediated by concentrations of molecules serving as signals, with chemical interactions between upstream molecules (senders) and downstream molecules (receivers) underlying the transmission. Thus, the concentrations of upstream molecules need to be distinguished from concentrations of downstream molecules. More precisely, the difference in concentrations of upstream molecules rather than their absolute quantity needs to be known for information transmission to occur. In other words, the amount of information transmitted between upstream and downstream molecules is measured by how much upstream information is known downstream based on interactions between chemicals. Mutual information – that is, information from senders that receivers can interpret – is defined based on this idea, and is widely used in various fields such as communication theory and information science [6–8]. Mutual information has recently been begun to be measured in signal transduction (Table 1).

The first example of mutual information being applied in a cellular system is the study of information processing in morphogenesis in *Drosophila*, in which mutual information between concentrations of upstream transcription factors and downstream gene expression based on snapshot population data at separate time points has been measured [9,10]. Similarly, mutual information of tumor necrosis factor (TNF) dependent signal transduction [11] and ERK-dependent signal transduction [12] has been determined by snapshot population data in mammalian cells. Recently, mutual information of ERK, calcium (Ca^{2+}), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) using time series data in a live cell – imaging technique has also been measured [13] (see Section 5).

In this review, we assume wide readership from biologists to information scientists. The rest of this paper is organized as follows. In Sections 2 and 3, we explain the concept of mutual information for signal transduction and how to calculate mutual information respectively, for biologists who are not familiar with information theory. Thus, others can skip these section. In Section 4, we describe data acquisition. This section may be informative for information scientists rather than biologists. In Section 5, we introduce previous works. In Section 6, we describe summary and future perspective.

2. Mutual information for signal transduction

Mutual information is used as a general measure of information between random variables in an array of fields, including communication theory, statistical science, and machine learning [6–8,14]. Thus, the interpretation of mutual information depends on the problem setting in each field. For example, mutual information in statistical science is interpreted as a measure of independency between random variables – in other words, a general correlation including nonlinear relationships. In this section, we introduce mutual information as a measure of the amount of information transmission, which requires only the statistical property of signals.

Let x and y be concentrations of an upstream molecule (a sender) and a downstream molecule (a receiver) in a signal transduction pathway, respectively. If we assume that the concentrations of molecules x and y behave deterministically, the concentrations of molecule y is uniquely determined by $f(x)$, that is $y = f(x)$, whose

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