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Review

Dynamic signal encoding—From cells to organisms

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ABSTRACT

Encoding information at the level of signal dynamics is characterized by distinct features, such as robustness to noise and high information content. Currently, a growing number of studies are unravelling the functional importance of signalling dynamics at the single cell level. In addition, first insights are emerging into how the principles of dynamic signal encoding apply to a multicellular context, such as development. In this review, we will first discuss general concepts of information transmission via signalling dynamics and recent experimental examples focusing on underlying principles, including the role of intracellular network topologies. How multicellular organisms use temporal modulation of specific signalling pathways, such as signalling gradients or oscillations, to faithfully control cell fate decisions and pattern formation will also be addressed. Finally, we will consider how technical advancements in the detection and perturbation of signalling dynamics contribute to reshaping our understanding of dynamic signalling in developing organisms.

Contents

Abbreviations: NGF, nerve growth factor; DSB, double strand break; SSB, single strand break; ATR, ataxia telangiectasia and Rad3 related protein; ATM, ataxia telangiectasia mutated protein; Shh, sonic hedgehog; DPP, decapentaplegic; NPC, neuronal progenitor cell; PSM, presomitic mesoderm; RA, retinoic acid.

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1. Introduction

In 1957, Conrad Waddington (1905–1975) noted that "the main respect in which the biological picture is more complicated than the physical one is the way time is involved in it" [1]. This is particularly apparent during development of a multicellular organism. Starting from a single cell, the generation of a complex organism requires not only tight regulation in space, but also in time. How a multitude of complex information (both in identity and intensity) is processed to allow development is a central question that is still not fully understood. Strikingly, this is accomplished by only a limited number of conserved signalling pathways.

Theoretical considerations implied early on that signalling dynamics might offer additional properties and layers of information encoding. Signalling dynamics, in contrast to a static "either or" perspective, describes the temporal evolution of a signalling system [2]. Excitingly, technical advancements in visualizing and perturbing intracellular signalling now enable experimental approaches to investigate the significance of dynamics at the signalling level. Indeed, experimental evidence indicates that upstream stimuli can be encoded in the dynamic properties of signals, such as delay, duration, fold-change or frequency (see Fig. 1). Here, we discuss recent experimental progress in understanding signalling dynamics, signal encoding and the implications for development of multicellular organisms. We will first review general principles of dynamic information transmission (Sections 2 and 3) before turning to specific examples in developing organisms (Section 4).

2. Properties of dynamic signal encoding

Dynamic signal encoding is characterized by robustness to noise, high information content and the possibility for temporal organization [3,4]. In recent years, it has become apparent that these general features are also an integral part of biological information encoding.

2.1. Robustness

For efficient cellular communication, the information has to be robust to noise and convey the message in identity and quantity [5]. In biology, noise is generated by random fluctuations and changes of environmental conditions such as pH or temperature, which in turn impacts on the kinetics of all cellular reactions.

In general, a digital signal is more robust to noise than an analogue one, as long as the noise amplitude is smaller than the discrete quanta of the digital signal. Several studies provide theoretical and experimental evidence that digital encoding in the signal frequency or in the fold-change of a signal is more robust and resistant to information loss by noise than detection of absolute levels [6–10]. In the human colon carcinoma cell line RKO or *Xenopus laevis* embryos a fold-change in β-Catenin levels is detected upon stimulation with Wnt [7]. Similarly, in the non-small cell carcinoma cell line H1299 a fold-change in nuclear levels of ERK2 (extracellular signal-regulated kinase 2), a mitogen-activated protein kinase (MAPK), rather than absolute ERK2 level is relevant for the downstream response upon stimulation with the epidermal growth factor (EGF) [8]. By encoding information in the fold change instead of the absolute level, cell-to-cell variations in basal signalling activity can be compensated. Indeed, perturbations of the Wnt signalling pathway, which alter the baseline but preserve β-catenin fold-change, do not interfere with the dorsoanterior development of *X. laevis* [7].

2.2. Increasing diversity through dynamic signal encoding

How a very limited number of conserved signalling pathways can encode a wide variety of distinct downstream responses is a longstanding question in the signalling field. Dynamic information encoding can be seen as powerful strategy to provide additional versatility: one and the same pathway can elicit different outcomes depending on its dynamics. Information can, for example, be encoded at the level of signal delay, duration, fold-change or periodic signalling frequency.

This concept can be exemplified using signalling gradients in development: the classical (static) view emphasizes the *amount* of stimulus as key determinant [11]. This view is currently undergoing drastic change. Accordingly, gradients can encode information in versatile ways, including the rate at which a signal changes in time [12]. In this *dynamic* view, two gradients with greatly differing absolute amounts that decay with the same kinetics over time, could elicit similar downstream responses (Fig. 1).

2.3. Temporally ordered cells as basis for higher-order spatiotemporal patterning

Within assemblies of cells, signalling dynamics, such as oscillations, have an additional, critical potential: whenever coupling between cells enables temporal synchronization, it can form the basis for subsequent patterning that requires spatial, but also temporal coherence. Development of multicellular organisms has been one context in which such coherent spatiotemporal signalling dynamics have been identified [3,11,13–16] and we will review specific examples (see Section 4).

In the following, we will discuss specific modes of dynamic information encoding in more detail as well as recent experimental work that provided novel insights into underlying mechanisms.

3. Dynamic information transmission

In engineering a message is sent by a source, encoded (by the *transmitter*), transferred and decoded (by the *receiver*) before reaching the destination [5,17]. Similar principles apply to biological information transmission, in which encoding and decoding are accomplished by complex signalling networks. The topology of the network defines signal dynamics and the consequent output. To allow information encoding in signalling dynamics, more complex molecular networks are necessary than for encoding information only in the absolute signal [4]. Interestingly, the signalling topologies that have been identified so far involve recurrent motifs, such as feedback or feedforward loops [4]. For instance, a steady stimulus can lead to oscillatory signalling based on a limited set of topological requirements, such as a delayed negative feedback loop [18].

3.1. Network topology matters

The importance of the network topology for the resulting dynamics of a signalling pathway can be illustrated at the level of p53 signalling in response to DNA breaks (Fig. 2): whereas double strand breaks (DSBs) result in *oscillations* of p53 levels with a period of 4–7 h, single strand breaks (SSBs) induce a single pulse of signalling [19–21]. The underlying mechanism that generates these different dynamic outcomes involves subtle changes in the topology being employed, in particular an additional negative feedback present in the DSB-induced network, but lacking in SSB-induced signalling (Fig. 2). While double strand breaks are digitally encoded in the *number* of p53 oscillations (damage correlates with number of oscillations), the extent of SSBs is encoded in signal *duration* and *amplitude* [22]. Interestingly, in the context of p53, the functional relevance of the different dynamic responses has been addressed. Purvis et al. [23] used a small molecule inhibitor to change p53 dynamics upon DSBs from oscillations to sustained activity reflecting SSB-specific signalling dynamics. Instead of only promoting cell