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Fold-change detection in biological systems

Miri Adler and Uri Alon

Abstract

Many sensory systems in cells and organisms share a recurring property called fold-change detection (FCD). FCD describes a system whose dynamics – including amplitude and response time – are determined only by the relative change in input signal, rather than its absolute change. FCD entails two important features – exact adaptation and the Weber–Fechner law. Systems with FCD include bacterial and eukaryotic chemotaxis, signaling pathways in mammalian cells such as NF-κB, Wnt and Tgf-β, and organismal vision, hearing and olfaction. Here, we review circuits that can provide FCD such as the incoherent type 1 feedforward loop, the non-linear integral feedback loop, and logarithmic sensor. We review experimental ways to test for FCD and differentiate between FCD mechanisms, and highlight theoretical studies that begin to map the space of FCD circuits and the functions they can provide. Finally, we discuss open questions on the structure and function of FCD systems.

Addresses

Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, 76100, Israel

Corresponding author: Alon, Uri (uri.alon@weizmann.ac.il)

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Introduction

The ability to sense the environment is a fundamental trait of biological systems. Sensory systems in cells include signaling pathways and the bacterial chemotaxis system that guides motion toward attractants, and sensory systems in animals include vision, hearing and smell. This review focuses on a property that many sensory systems at different scales and across organisms share: fold-change detection (FCD) [1,2]. FCD describes a system that is sensitive to the fold-change in the input signal and not to the absolute change. Therefore a step in input signal from 1 to 5 yields exactly the same dynamical response — same amplitude, shape and decay times — as a step from 5 to 25 because the fold-change is the same (Figure 1A). FCD is also sometimes called scale invariance, because it is a form of symmetry with respect to scaling the input by a multiplicative factor [3–5] (Figure 1B). The FCD property always applies to a certain range of input signals, typically of several decades. FCD breaks down when signals are very small or very large.

Systems with FCD have two important features. The first is the Weber–Fechner (WF) law. Weber performed experiments where people adapted to a weight ω_o, and then new small weights $\Delta\omega$ were added. The minimal perceptible change in weight $\Delta\omega$ was proportional to the background weight ω_o. Fechner further found that peoples' subjective perception of stimuli, such as visual stimuli, depends on the stimulus level divided by the background stimulus level [6]. Here, we mean by 'WF law' that the response amplitude (maximal output level) to a change in signal Δu depends on the fold-change $R = f(\Delta u/u_o)$, where u_o is the background signal level (Figure 1C).

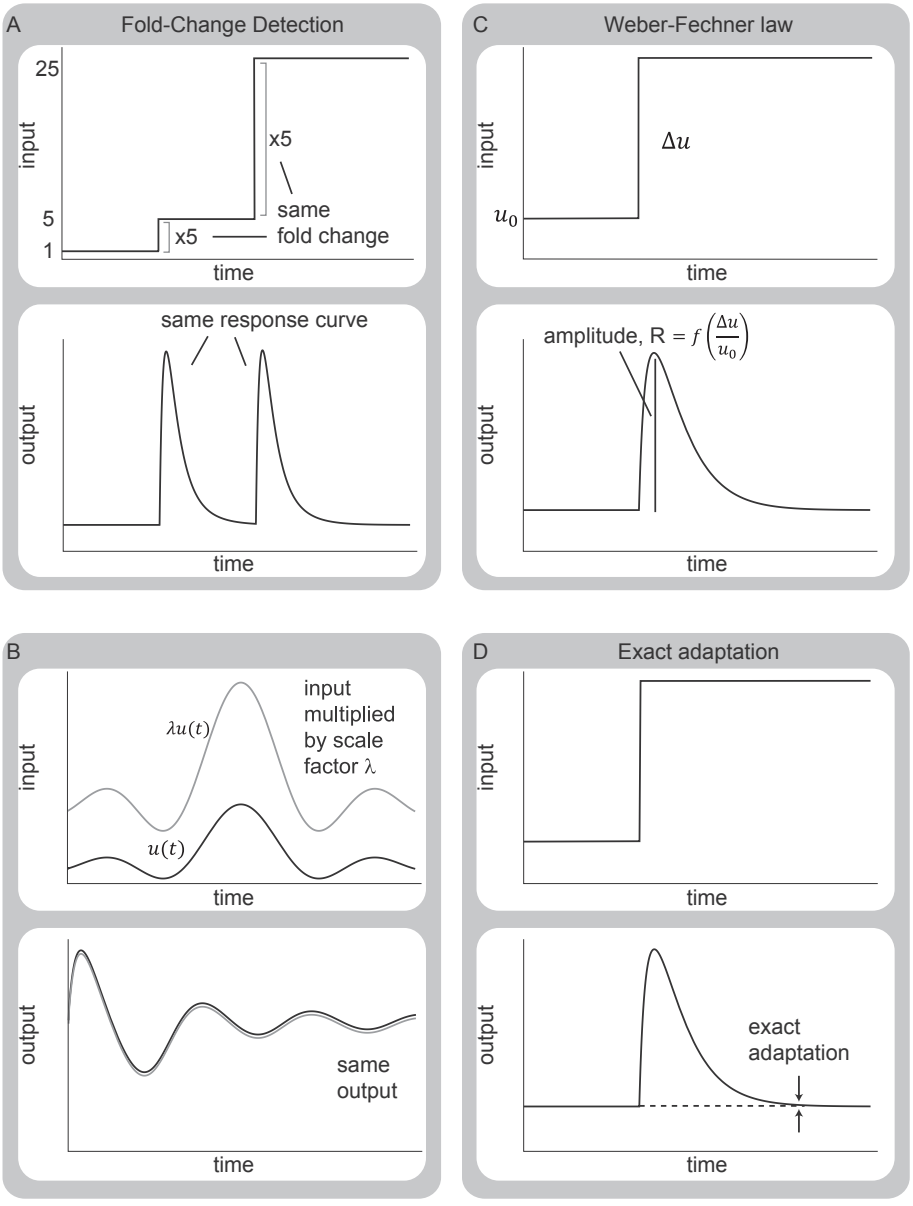
The second property found in all FCD systems is exact adaptation [7]. A system exactly adapts to a change in input signal if the response returns to the initial baseline even when the changed input persists (Figure 1D). Adaptation allows the system to respond to changes despite different baseline levels in input signal and was extensively studied in many biological systems [8–12]. FCD entails both the WF law and exact adaptation, but the opposite is not true: a system can follow a WF law, exact adaptation or both but still not have FCD — such examples are shown in Shoval et al. [2].

FCD was defined by Goentoro et al. [1], based on experiments in the Wnt [13] system from Marc Kirschner's lab and in the ERK [14] system from our lab. In the nine years since, experimental and theoretical studies deepened our understanding of FCD. Here, we aim to provide an overview of the biological systems that show hallmarks of FCD, discuss advances in understanding FCD mechanisms and functions, and discuss questions for future study.

FCD is found across scales and organisms

Some of the biological systems that show evidence of FCD are shown in Table 1. We highlight several examples that demonstrate experimental approaches to detect FCD.

Figure 1



Fold-change detection (FCD) systems have identical dynamical response to signals with the same fold-change. (A) The response of an FCD system is identical for two steps of input signal with different absolute change but the same fold-change, or (B) for two input profiles that are identical except for a multiplicative factor. In both cases, the system starts at steady-state. (C) FCD systems follow the Weber–Fechner law, with a response amplitude (R) that is a function of the change in the input (Δu) relative to the baseline of the input (u_0). (D) FCD systems show exact adaptation in which steady-state output is invariant to the level of input.

The first dynamical measurements that explicitly demonstrated FCD were presented by the Shimizu lab [13], using *Escherichia coli* chemotaxis. *E. coli* chemotaxis was known to show exact adaptation [14,15] and to show Weber's-law-like accumulation at attractant sources [16]. To test for FCD, Lazova et al. used microfluidics to provide complex temporal input (attractant) signals multiplied by different scale factors. The output was a fluorescent readout of the chemotaxis signaling, CheY-P. The output responses were found to be independent of the input scaling factor over a range of three decades of concentrations [13,17]. FCD broke down at very low and high stimuli, and, unexpectedly, two ranges of FCD were found [13]. FCD was since studied in the chemotaxis response of additional bacterial species [18–22].

FCD was also described in eukaryotic chemotaxis. The social amoeba *Dictyostelium* performs chemotaxis by following oscillatory cAMP gradients which are self-generated by the cell population (secrete-and-sense