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Scale-Invariance in Biological Sensing

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Abstract

The phenomenon of fold-change detection, or scale invariance, is exhibited by a variety of sensory systems, in both bacterial and eukaryotic signaling pathways. This entry gives a short introduction to the subject.

Keywords

Perfect adaptation · Fold-change detection · Scale invariance

Introduction

It is often the case that a physiological signal returns to a pre-stimulus value after a transient input has been sensed. This input, for example, an impulse or pulse, could be physical or biochemical in nature. Examples are a ligand to an olfactory receptor or a light input to a photoreceptor. This is a stability property. A much more interesting phenomenon is that of *exact adaptation* to a persistent input, the subject of much investigation from both a modeling and experimental perspective (Alon 2007). This phenomenon occurs when the return to such a steady-state value of the output happens even in the face of a *sustained* step or periodic excitation. Physiological adaptation is a trait of many sensory systems. It allows them to accurately detect changes in input signals and to distinguish meaningful information from background, by appropriately shifting their dynamic range. For example, the human eye distinguishes features across nine orders of magnitude, even though its sensors can only detect a three order of magnitude contrast; this is achieved through both the pupillary light reflex and the adjustment of sensitivity of rods and cones. Similarly, humans adapt to constant touches, smells, or background noises, detecting new information only when a substantial change occurs. At a cellular scale of behavior, a very well-studied example of physiological adaptation is that of the response of the *E. coli* chemotactic pathway response to stepwise addition and subsequent removal of attractant.

In terms of control theory, perfect adaptation can be thought of as a particular instance of *disturbance rejection*, which for linear systems is translated as zero gain at zero or other frequencies. Disturbance rejection implies, for linear as well as some classes of nonlinear systems, the existence of "internal models" of inputs (Huang et al. 2018). For simplicity, we restrict to step responses in this short discussion, but similar questions can be studied for persistent oscillatory inputs.

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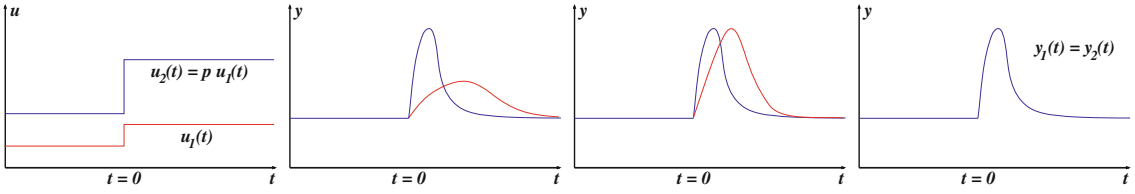
Scale Invariance

There is a finer property than mere adaptation, called scale invariance of responses or "fold-change detection". To explain this property intuitively, consider two step inputs u_1 and u_2 which are scaled versions of each other: $u_2(t) = pu_1(t)$, for some positive number or "scale factor" p, see Fig. 1a. Adaptation means that, whether the input is u_1 or u_2, the output will return to the same value (Fig. 1b). Scale invariance means that the entire actual transient response will be the same under either excitation (Fig. 1d). An intermediate property between mere adaptation and scale invariance is the "Weber-like" property in which temporal, transient responses may be different but peak intensities coincide (Fig. 1c). This intermediate property is one version of the Weber-Fechner law in psychophysics of human sensing, which relates physical magnitudes of stimuli to perceived intensities. Ernst Weber in the 1840s performed experiments in which subjects were asked to hold a weight, and the weight was gradually increased until a change was first noticed. He found that the smallest noticeable difference was proportional to the starting value, and not to the absolute weight: two scaled versions of the input result in the same reaction. A similar phenomenon has been observed in other sensory systems, including perception of pitch in sound, light intensity, smell, pain, and taste. Gustav Fechner went on to establish a logarithmic relation between physical and perceived quantities (Weber 1905).

A pair of papers published in late 2009 led to a focus on scale invariance in cell biology. These papers dealt with the Wnt and EGF signaling pathways, which are highly conserved eukaryotic signaling pathways that play roles in embryonic patterning, stem cell homeostasis, cell division, and other central processes, the misregulation of which results in diseases including several types of cancer. The paper Goentoro and Kirschner (2009) focused on the effect of binding of Wnt ligand on the levels of a key protein in the Wnt signal transduction pathway, β-catenin, which in turn activates transcription of specific target genes. It was observed that, in a given population, cells might differ substantially in the β-catenin level after stimulation by Wnt but that the effects downstream, measured either through gene expression or phenotype (in *Xenopus* embryos), appear to be a function only of the relative changes in Wnt, and not its absolute amount. Analogous results, for an EGFR pathway, were reported in the paper Cohen-Saidon et al. (2009). Scale invariance is also found in certain bacterial signaling systems. A prediction, for the *E. coli* chemotaxis sensory circuit in response to the ligand α-methylaspartate, was made in Shoval et al. (2011), based on a model proposed by Tu, Shimizu, and Berg (2008). This prediction was later verified in a microfluidics population experiment carried out in Stocker's lab as well as an in FRET measurements on genetically altered bacteria in Shimizu's lab (Lazova et al. 2011).

Scale invariance means that the system cannot distinguish between an input $u(t)$ and a scaled version $v(t) = pu(t)$. For step inputs that jump at $t = 0$, we can reformulate this property by saying that the response can *only* depend on the "*fold change*" of the input at time 0: $v(t)/v(0) = pu(t)/pu(0) = u(t)/u(0)$, hence motivating the alternative terminology "fold change detection"



Scale-Invariance in Biological Sensing, Fig. 1 (**a**) Scaled step inputs and corresponding responses: (**b**) perfect adaptation; (**c**) Weber-like (same peak amplitude responses); (**d**) scale invariance (same transient responses)

(FCD). Another way to phrase this is that FCD systems only depend on $\log(u(t)) - \log(u(0))$, that is, on logarithmic changes in inputs (hence sometimes the use of the term "log sensing").

Example: Feedforward Circuits

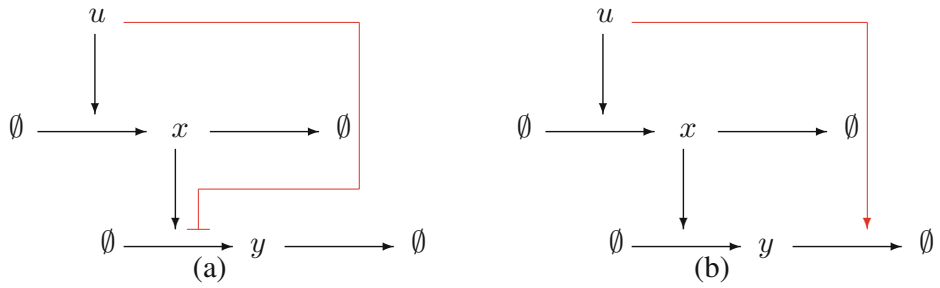
Let us focus on one rich source of practical examples of FCD systems, feedforward motifs. These circuits, popularized by the textbook Alon (2007), play a central role in metabolic pathways, signaling networks, and genetic circuits. Feedforward loops come in two flavors, coherent and incoherent. The *IFFL (incoherent feedforward loop)* motif, represented by the graphs in Fig. 2, is one of the two main biomolecular mechanisms (another is nonlinear integral feedback) that can lead to FCD (Goentoro et al. 2009; Shoval et al. 2010, 2011). In these circuits, the input u activates a regulatory variable (molecular species) x that in turn activates or represses a downstream species y. Through a different path, the signal u represses or activates, respectively, the species y. This antagonistic ("incoherent") effect endows the IFFL motif with powerful signal processing properties (Alon 2007). Similar circuits may play a role in how the immune system distinguishes between "self" and "nonself" antigens (Shoval et al. 2017).

An important subtlety is that the purely conceptual diagrams in Fig. 2 may obscure the fact that alternative molecular realizations may have different properties when viewed in the scale invariance setting. As an illustration, take the two realizations shown in Fig. 3 of the diagram in Fig. 2b. These two realizations differ in a fundamental way in regard to their scale invariance (FCD) properties. The biological mechanism in Fig. 3a exhibits FCD, but the one in Fig. 3b does not. To be more precise, we study the simplest ordinary differential equation (ODE) models for these processes, in which the concentrations of the input u and species x and y are described by scalar time-dependent quantities. Suppose that $(x(t), y(t))$ is any solution corresponding to the input $u(t)$, for the system described by Fig. 3a. Then, $(px(t), y(t))$ is a solution corresponding to the input $pu(t)$:

$$\dot{x} = \alpha u - \delta x \Rightarrow (\dot{px}) = \alpha(pu) - \delta(px)$$
$$\dot{y} = \beta\frac{x}{u} - \gamma y \Rightarrow \dot{y} = \beta\frac{\dot{px}}{\dot{pu}} - \gamma y. \qquad (1)$$

In particular, given a step input that jumps at time $t = 0$ and an initial state at time $t = 0$ that has been preadapted to the input $u(t)$ for $t < 0$ (that is, $x(0) = \alpha u_0/\delta$, where u_0 is the value of

Scale-Invariance in Biological Sensing, Fig. 2 Incoherent feedforward: (**a**) Input activates and intermediate species represses output; (**b**) Input represses and intermediate species activates output



Scale-Invariance in Biological Sensing, Fig. 3 Two realizations of the "input repressing output" motif in Fig. 2b: (**a**) Input inhibits the formation of output; (**b**) Input enhances the degradation of output

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u for $t < 0$), the solution is the same as when instead applying $pu(t)$ for $t > 0$ but starting from the respective pre-adapted state $p\alpha u_0/\delta$. On the other hand, the FCD property *fails for the system in which the input enhances the degradation of output*, shown in Fig. 3b. Scaling states x by p does not work for this second system:

$$\dot{x} = \alpha u - \delta x$$
$$\dot{y} = \beta x - \gamma u y$$

since $x \mapsto px$ and $u \mapsto pu$ do not leave the y equation invariant. Actually, one can prove that no possible equivariant group action on states is compatible with output invariance, which means that no possible symmetries are satisfied by the input/output behavior of this system. These issues are carefully discussed in Shoval et al. (2011), which carried out a systematic analysis of the FCD property and proved a necessary and sufficient characterization of FCD in terms of groups of symmetries acting on the system equations. The above negative remarks notwithstanding, it has been observed that systems such as the one in Fig. 3b satisfy an *approximate* FCD property provided that the parameters β and γ are large enough so that a time-scale separation property holds. Multiple time scales, corresponding to slow and fast subsystems, are typically inherent in cellular systems. See Skataric et al. (2015) for a rigorous discussion of this topic.

Cross-References

- Deterministic Description of Biochemical Networks
- Monotone Systems in Biology
- Reverse Engineering of Gene Networks
- Robustness Analysis of Biological Models
- Spatial Description of Biochemical Networks
- Stochastic Description of Biochemical Networks

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