Fold-change detection in biological systems
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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.

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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
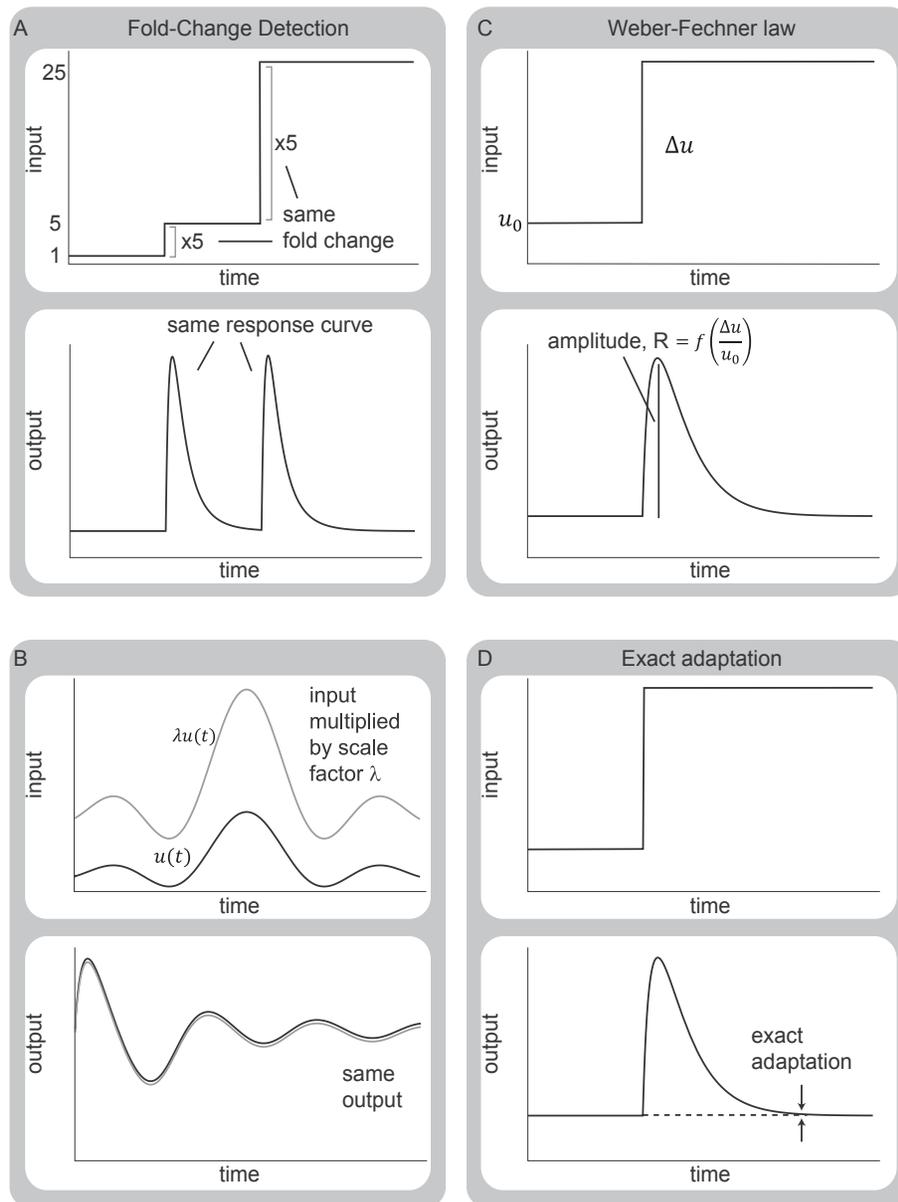
Fold-change detection (FCD) systems have identical dynamical response to signals with the same fold-change. (A) The response of an FCD system is identical for two steps of input signal with different absolute change but the same fold-change, or (B) for two input profiles that are identical except for 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

Table 1

Biological systems that show evidence of FCD. Summary of selected experimental and theoretical studies. We denote experimental evidence for exact adaptation, WF law and FCD as 'E', evidence from modeling as 'M', and 'NS' when no evidence was shown.

System	Input	Output	Circuit	Exact adaptation	WF law	FCD	Ref.
Bacterial chemotaxis (*E. coli*)	Chemoattractant	CheY-P (protein)	NLIFL	E	E	E	[13]
Bacterial chemotaxis (*Rhodobacter sphaeroides*)	Chemoattractant	Che proteins	NLIFL	E	E	M	[18]
Eukaryotic chemotaxis (*Dictyostelium discoideum*)	Extracellular cAMP	Ras-GTP (protein)	I1FFL	E	E	NS	[24]
		Intracellular cAMP	NS	E	E	E	[25]
Green algae phototaxis (*Chlamydomonas reinhardtii*)	Light	Cell density	NS	E	M	M	[71]
Nematode chemotaxis (*C. elegans*)	Odorant	AIA (neuron)	feedback	E	E	E	[26]
Signaling, ERK2 (H1299 cells)	EGF	ERK2 (protein)	NS	E	E	NS	[28]
Signaling, Wnt (RKO cells and Xenopus embryos)	Wnt	β-catenin	NS	E	E	NS	[72]
Signaling, NF-κB (HeLa cells)	NF-κB	Inducible gene (e.g. IL8)	I1FFL	E	E	NS	[27]
Signaling, Tgf-β (C2C12 cells)	Tgf-β	Smad3 (protein)	I1FFL	E	E	NS	[29]
Signaling, Akt (MCF10A cells)	EGF	P-Akt (protein)	NS	E	E	M	[73]
Sea urchin developmental gene regulation	TFs (e.g. GCM)	Target genes (e.g. gataE)	feedforward and feedback	E	E	NS	[74]
Drosophila wing development	DPP morphogen	Cell number	I1FFL with NLIFL	NS	E	M	[41,75]
Salamander (*Ambystoma tigrinum*) olfaction and vision and Frog (*Xenopus*) vision	IBMX (odorant)	Sensory neuron	feedback	E	E	NS	[76,77]

strategy [23]). Population-level studies showed that cAMP sensing shows hallmarks of FCD [24]: response was similar for step stimuli with the same fold-change, and response time mildly decreased with the fold-change. A recent study by Kamino et al. at the single-cell level established FCD by presenting individual *Dictyostelium* cells with steps of cAMP [25]. Kamino et al. showed that an FCD circuit combined with a secrete-and-sense mechanism provides robustness to the frequency of the cAMP oscillations with respect to variations in cell densities, explaining how oscillations can work as a reliable guiding signal across a wide range of cell densities. Evidence of FCD in animal chemotaxis was obtained by providing odorant steps to *Caenorhabditis elegans* in micro-fluidic setups, and tracking neuronal activity [26].

FCD has also been documented in signaling pathways in mammalian cells. An elegant study by the Gaudet group examined the NF-κB pathway, in which the transcription factor NF-κB enters the nucleus to regulate genes in response to signals such as TNF [27]. A step of TNF elicits an adapting pulse of NF-κB nuclear entry. Lee et al. used fluorescent microscopy to show that basal NF-κB nuclear levels vary widely (3-fold) between cells, as does the amplitude of the post-stimulus pulse — and

that basal and post-stimulus levels are highly correlated (similar findings apply to the ERK2 pathway [28], and the Tgf-β pathway [29]). Cells seem to use an FCD mechanism to filter out the basal cell—cell differences: downstream gene expression in each individual cell, measured by smFISH on fixed cells at the end of the movies, matched the fold-change in NF-κB nuclear entry in each cell, and not the absolute change.

Specific feedforward and feedback circuits can provide FCD

Two mechanisms for FCD have been studied most extensively. The first is the incoherent type-1 feedforward loop (I1FFL), a common network motif [30] in which the input u activates both the output y and an internal node x that inhibits y [1,2] (Figure 2A). Details matter: an I1FFL-like circuit in which x inhibits y by accelerating its degradation [11] does not show FCD [31], whereas the I1FFL in which x reduces y production (e.g. transcription) does.

The second FCD circuit is the nonlinear integral feedback loop (NLIFL) in which the input activates the output, and the output activates its autocatalytic inhibitor x [1,2] (Figure 2B). In both circuits, the inhibitor

Figure 2
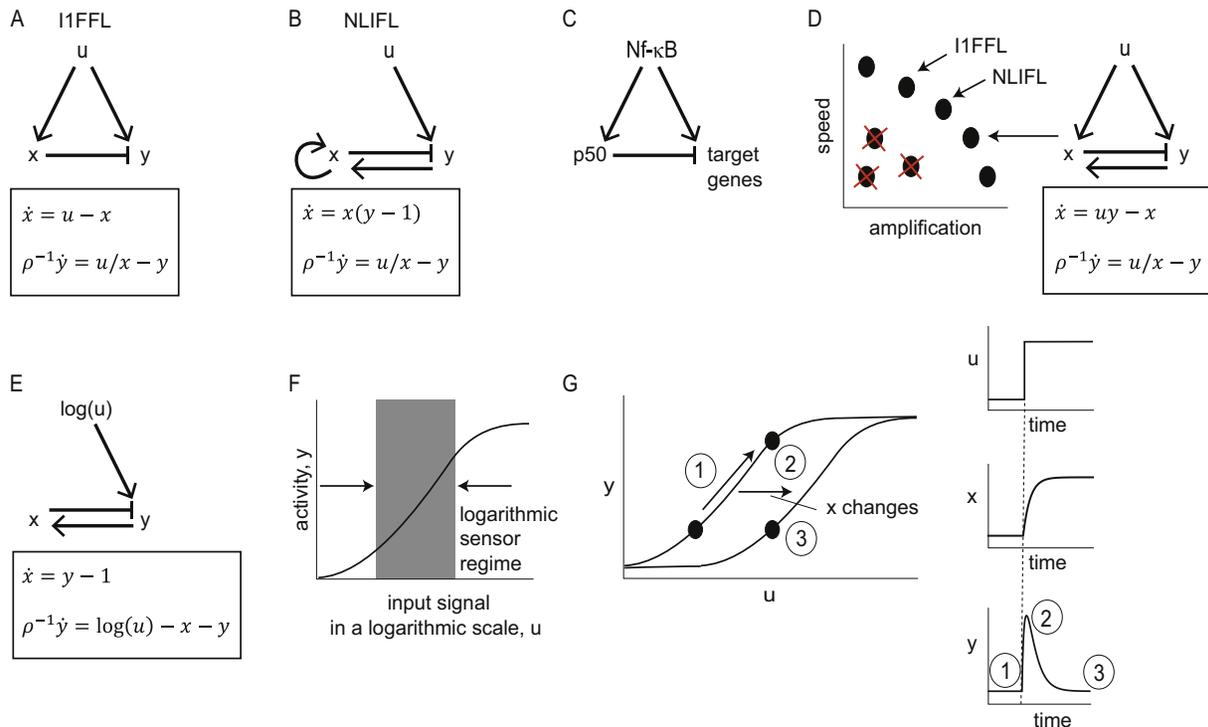
Mechanisms for FCD include the I1FFL, NLIFL and logarithmic sensors. (A) Circuit topologies of the I1FFL and the NLIFL (B) and their equations where u, x and y respectively represent input, internal node and output. The equations are shown with dimensionless variables, and have a single dimensionless parameter group ρ, which is the ratio of the removal rates of x and y [43]. Throughout, we use $\rho = 1$ in the figures. (C) A schematic of the I1FFL circuit proposed in the NF-κB system [27]. (D) An example of an additional FCD circuit that is Pareto optimal with respect to speed and amplification (speed is the inverse of the response time defined as $\int (t * (y(t) - y_{st})) / \int (y(t) - y_{st})$, and amplification is the response amplitude (or the maximal deviation of the output from its steady state) as defined in detail in Ref. [40]). (E) An FCD circuit that uses a logarithmic sensor and linear feedback. (F) Activity of an allosteric protein that shows a logarithmic regime (gray). (G) Allosteric regulation coupled to a linear feedback loop can implement FCD. An input step increases output [1], causing a slow change in the allosteric constant x that shifts the allosteric curve [2], causing output to return to baseline [3].

x acts as a memory element, tracking the previous input level and slowly building up after signal changes. The essential difference between the circuits is the lack of feedback in the I1FFL.

The response of the I1FFL and NLIFL show perfect FCD behavior in the limit of strong repression of y by x (mathematically that a u/x term approximates a $u/(k + x)$ term [1,2]). Several studies suggested additional mechanisms that show approximate FCD response assuming a separation of time scales between two variables in the system for enzymatic networks [31−36] and autocatalytic reactions in chemical networks [37].

It seems that the I1FFL circuit tends to appear in cell signaling circuits such as NF-κB (NF-κB activates its target genes as well as a repressor of these target genes [27]) (Figure 2C). In contrast, NLIFL circuits seem to appear in chemotaxis systems such as bacterial chemotaxis [38]. A theoretical study of eukaryotic chemotaxis showed that both feed-forward and feedback designs can provide FCD in temporal and spatial stimuli [39].

An open question is whether the type of FCD circuit found in a particular system evolves to match a specific functional requirement. For example, are NLIFLs better in some sense for chemotaxis than I1FFLs? If so, what is the mapping between functional requirement and the space of FCD circuits?

One step toward answering this question are theoretical studies which asked how many possible FCD designs exist, by screening wide classes of circuits for FCD. These studies are aided by explicit mathematical conditions necessary for a circuit to show FCD [2]. Two theoretical screens tested wide classes of three-component circuits, and found that only 0.1% show FCD [34,40]. Thus, FCD is a rare property of circuits. However, this still leaves several hundred possible FCD circuit designs, in addition to the I1FFL and NLIFL discussed above. The large number of possible designs raises the question of why the latter two designs are found most commonly (in addition to the effects of researcher bias toward known circuits). To address this, we recently used a Pareto optimality framework to

compare different FCD circuits in terms of features such as response time, amplitude and noise resistance. A set of only 5 minimal circuits, including the I1FFL and NLIFL, outperformed other circuits in multiple features [40] (Figure 2D). These findings hint at which other circuits may also be found in biological systems (one example is shown in Figure 2D). Much more work remains to be done to understand the structure–function relationship of FCD circuits.

FCD can also be understood as logarithmic sensing of the input [41]. Olsman and Goentoro, in a recent elegant study of allosteric regulation, propose a biological context for logarithmic sensing that is combined with a feedback mechanism [42] (Figure 2E). In allosteric regulation, there is a range of input signals (e.g. ligand concentration) for which the portion of active proteins is nearly logarithmic (gray area in Figure 2F — this region can span several order of magnitude of input). The internal variable x is the allosteric constant which determines the logarithmic regime of the proteins in their active state. To illustrate how FCD is implemented when ligand sensing activates linear feedback on x, consider a step increase in input signal u. Following the step, the activity of the allosteric protein y increases, which causes x to change, shifting the allosteric curve. As a result, y activity returns to baseline [42] (Figure 2G). This mechanism underlies the NLIFL in bacterial chemotaxis via the allosteric regulation by methylation of Tar receptors. Additional examples of allosteric proteins coupled to a feedback circuit include GPCR rhodopsin in vision, and EGF receptor in ERK2 signaling [42]. Thus, allosteric proteins may play an important role as logarithmic sensors in FCD systems.

Experimental tests for FCD mechanisms

In approaching a biological system, what measurements can we make to test for FCD? And if FCD is established, what tests can differentiate between different possible circuit mechanisms?

To test for FCD, one must first establish that for a wide range of steady-state input concentrations, the output pulse induced by raising the input by F-fold is identical (within experimental error). When repeated for different fold-changes (F), pulse amplitude (R) should increase with F, while response time should mildly decrease [25,43,44] (Figure 3A,B).

Once FCD is established, input–output measurements can help to distinguish between potential circuit mechanisms. One such test is the dependence of the response amplitude R on the input fold-change F. An I1FFL without cooperativity produces a logarithmic-like dependence, whereas the NLIFL produces a nearly linear dependence [43] (Figure 3A). Thus a logarithmic dependence rules out the NLIFL. We note that in this

section, I1FFL and NLIFL refer to the circuits whose equations are given in Figure 2A and B respectively.

Another potential input–output test to distinguish between circuits is the response to ramps of input, in which input increases linearly at a constant rate with time (Figure 3C). Feedforward and feedback mechanisms that show exact adaptation *but not FCD* were found to respond differently to linear input ramps [45]. The tested feedforward circuit filters out ramps whereas the feedback design loses the exact adaptation property and returns to a new baseline that depends on the slope of the ramp [45]. In contrast, the I1FFL and NLIFL which show perfect FCD both adapt exactly to the pre-stimuli baseline in response to ramps (Figure 3C). Thus linear ramps do not appear to be sensitive tests for differentiating between FCD designs. Interestingly, both FCD circuits lose exact adaptation when the ramp is exponential in time and not linear [46]. The circuits adapt to a new baseline level proportional to the rate of the exponential growth of the input (Figure 3D). The NLIFL, but not the I1FFL, often shows damped oscillations before settling down to steady state (Figure 3C,D), except when the ratio of timescales ρ in the equations of Figure 2B is very large, in which case the two circuits show similar behavior.

Another type of FCD circuit, an I1FFL with an added feedback loop, can be inferred by studying the responses to smooth, instead of step-wise input signal changes [41]. With smooth input changes, the response amplitude of FCD circuits generally depends on both the input fold-change and its time scale [47]. Therefore, two input signals with different fold-changes and different time scales may yield the same response amplitude. An I1FFL + feedback design, which is thought to occur in the DPP signaling pathway [41,48], recovers the strict relationship with input fold-change.

In a recent study, Rahi et al. [49] showed that adapting feedback and feedforward circuits, including FCD circuits, can be distinguished (at least for some range of their parameter values) by providing a two-pulse input (or more generally oscillating inputs). The output of feedback, but not feedforward, circuits can skip periodic stimulus pulses intermittently for certain pulse frequencies. Furthermore, the response amplitude to a second stimulus pulse decreases with the first pulse duration in feedforward but not feedback circuits, which means that feedback systems 'reset' with roughly constant timing and have a stable refractory period, whereas feedforward systems do not. Rahi et al. used these criteria to establish the existence of feedback in a *C. elegans* odor sensing neuron and in a modified version of the yeast cell cycle circuit [49]. Therefore, oscillatory input profiles may be good tests for distinguishing between feedback and feedforward FCD designs.

Figure 3
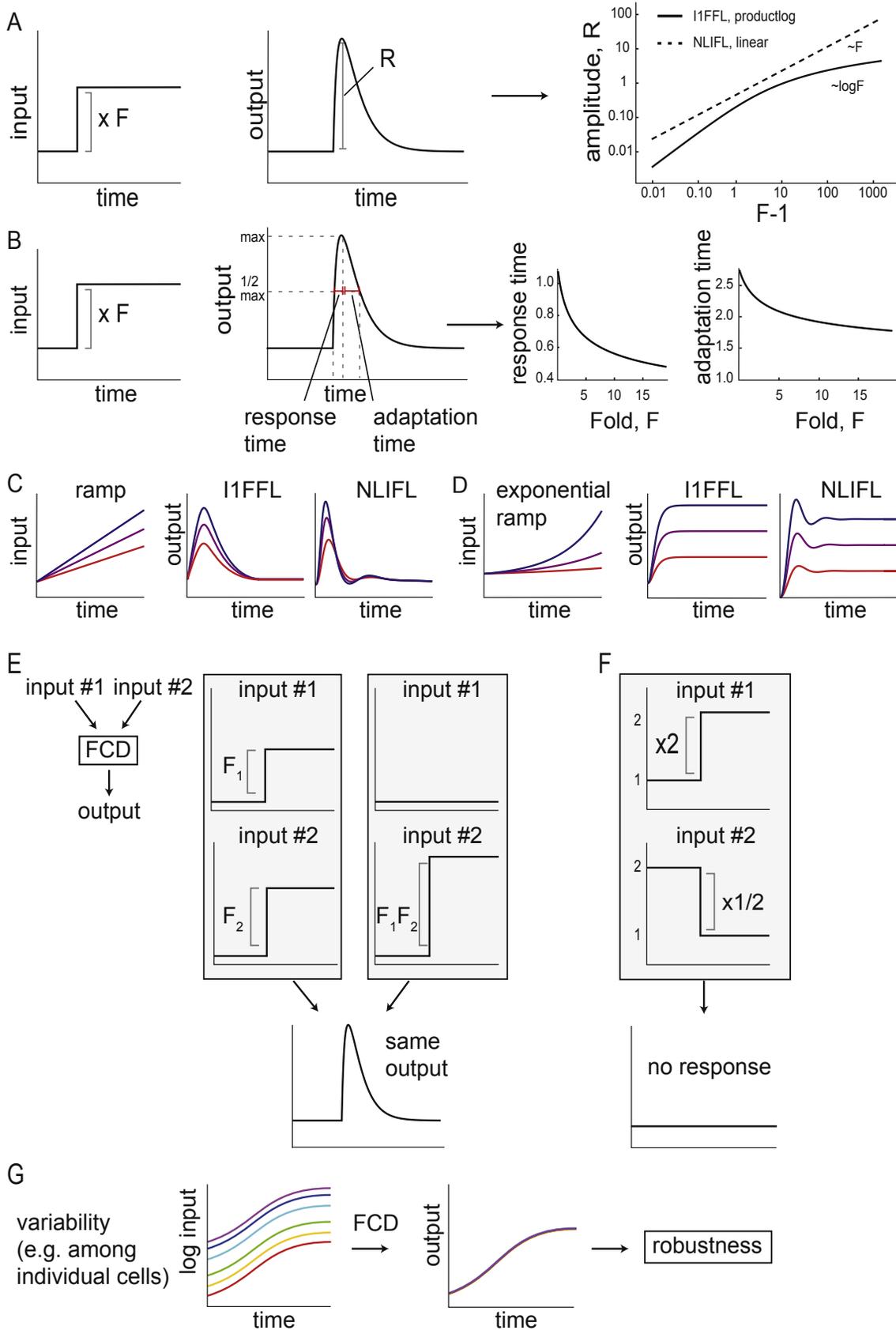
Questions for future research: the structures and functions of FCD

We conclude with questions about FCD for future research. The first question regards the structure of FCD mechanisms, and the relative abundance of different mechanisms. Mapping the possible mechanisms and devising tests to distinguish between them will enable researchers to zero in on molecular mechanisms in natural systems [50] and to design new synthetic FCD circuits [51]. It is unclear how prevalent FCD is in biological systems, and good experimental tests can facilitate systematic searches for FCD on an organism-wide scale. It would be important to map which designs occur often and which rarely, in order to provide a dictionary of FCD motifs to guide molecular characterization. Mapping FCD designs will enable us to understand which functional context a design tends to appear in (e.g. feedback in chemotaxis, feedforward in cell signaling).

One fascinating context to search for FCD is in psychology-many human and animal behaviors show exact adaptation and invariance to input scale [52−57], and neuronal systems often adapt and scale their activity as well [58]. This hints that FCD might appear in psychology, providing strong constraints on the circuits at play.

A further question regards the response of FCD systems to multiple simultaneous signals. Many systems, including chemotaxis and signal-transduction receptors, respond to multiple ligands, whose levels can change at the same time. There is a theoretical prediction for FCD that has not yet been experimentally tested [59]: The response of an FCD system to two inputs, each varying by a different fold-change, F_1 and F_2, is predicted to be identical to the response to a fold-change F in only one signal where F is the product of the two folds, $F = F_1 F_2$. Thus a 2-fold change in one input and a 3-fold change in the other should lead to a response equal to a 6-fold change in one signal when the other stays constant [59] (Figure 3E). Similarly, there should be no response if the fold-change increase in one input is exactly the fold-change decrease in the other (Figure 3F). More generally, the system responds to an effective fold which is log-linear in the two input folds. FCD can thus provide a simple way to integrate variation in multiple inputs, by comparing each signal to its background level.

If this product rule is valid also for many simultaneous inputs, FCD can offer a way to understand how olfactory systems can respond to complex odors made up of multiple varying components, such as the smell of a rose, despite background variations in each component (a version of the binding or information-joining problem in neuroscience [60]). An FCD response to the product of fold-changes is strong only when all inputs increase at the same time (due to a whiff of air carrying all odorants together), while ignoring fluctuations in which the odorants vary in an uncorrelated way.

This leads to the more general question about the functional benefits of FCD. FCD has been suggested so far to have two main types of benefits: robustness to multiplying the input by an irrelevant factor and noise resistance across a wide dynamic range. FCD rejects a multiplicative factor such as the concentration of a transcription factor protein that varies between individual cells. It allows downstream genes to be invariant to this variation (Figure 3G). Sometimes the multiplicative factor is not noise but a feature of the signal that must be removed: for example, in vision the ambient light level multiplies the contrast field, and FCD can remove it and remain sensitive only to changes in contrast [2].

In its second main function, FCD provides resistance to noise over a wide dynamic-range of input signals, because FCD causes the signal needed for a sizable response to scale with the background level. Thus FCD can be sensitive to a small blip over a low background, and ignore the same blip when background is high (when the blip is likely to be noise).

Research in the past few years has suggested that FCD can have additional systems-level benefits when considered as part of a larger circuit [61,62]. Auditory FCD was suggested to be important for the behavior of swarms of midges, in which insects in the swarm respond to long range acoustic stimuli produced by each other [63,64]. FCD can also be at play in immune responses, based for example on an I1FFL in which immune stimulation activates T cells and at the same time activates their inhibitor, Treg cells [46,65,66]. Here, FCD can detect exponentially growing pathogen populations, by virtue of its lack of adaptation to exponential ramps as suggested by Eduardo Sontag [46]. FCD was also suggested to govern optimal cell growth upon nutrient uptake [67]. Roles of FCD circuits were suggested also in engineering and control theory. An FCD circuit can be considered as nonlinear differential operator [68], and can implement the least mean square (LMS) algorithm [69]. More theoretical work is needed to understand how an FCD module can provide useful functions as a component inside larger circuits.

Input−output relations in FCD systems. (A) The response amplitude R of the I1FFL increases approximately logarithmically with fold-change in the input F, and approximately linearly in the NLIFL. (B) FCD adaptation and response times mildly decrease with F. (C) In response to ramps with different slopes ($u(t) = u_0 + at$), both the I1FFL and NLIFL show exact adaptation. (D) Exponential ramps ($u(t) = u_0 e^{\alpha t}$) break exact adaptation, with steady-state output that depends on the growth rate of the input (α). Note that damped oscillations in the NLIFL occur except when the timescale ratio ρ is very large, and never occur in the I1FFL. (E) Steps in two inputs to an FCD system with fold-changes F_1, F_2, yield the same response as a step of $F_1 F_2$ in one input when the other doesn't change. (F) Therefore, a step increase of two-fold in one input and a decrease of two-fold in the second input should yield no response. (G) FCD allows robustness by removing multiplicative variation in input signals.

It is challenging to devise experimental tests to explore such functional benefits of FCD (or of any other biological circuit), and in particular the differential benefits of different FCD mechanisms. In comparing circuit designs, one needs to be mindful of making a fair (mathematically controlled) comparison [40,70] — making the circuits as equal as possible in terms of their internal parameters (e.g. basal concentration of x) and external features (e.g. baseline output level). An important avenue for the future are evolutionary experiments that compare different circuits in well-defined situations. It will be fascinating to see what functions new experimental and theoretical approaches will discover for FCD.

Acknowledgments

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