Fold-change detection and scalar symmetry of sensory input fields

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Recent studies suggest that certain cellular sensory systems display fold-change detection (FCD): a response whose entire shape, including amplitude and duration, depends only on fold changes in input and not on absolute levels. Thus, a step change in input from, for example, level 1 to 2 gives precisely the same dynamical output as a step from level 2 to 4, because the steps have the same fold change. We ask what the benefit of FCD is and show that FCD is necessary and sufficient for sensory search to be independent of multiplying the input field by a scalar. Thus, the FCD search pattern depends only on the spatial profile of the input and not on its amplitude. Such scalar symmetry occurs in a wide range of sensory inputs, such as source strength multiplying diffusing/convecting chemical fields sensed in chemotaxis, ambient light multiplying the contrast field in vision, and protein concentrations multiplying the output in many cellular signaling systems. Furthermore, we show that FCD entails two features found across sensory systems, exact adaptation and Weber’s law, but that these two features are not sufficient for FCD. Finally, we present a wide class of mechanisms that have FCD, including certain nonlinear feedback and feed-forward loops. We find that bacterial chemotaxis displays feedback within the present class and hence, is expected to show FCD. This can explain experiments in which chemotaxis searches are insensitive to attractant source levels. This study, thus, suggests a connection between properties of biological sensory systems and scalar symmetry stemming from physical properties of their input fields.

Organisms and cells sense their environment using sensory systems. Certain sensory systems have been extensively studied, and their input–output relations are well-characterized, including human senses, such as vision (1, 2), touch, and hearing, and unicellular senses, such as bacterial chemotaxis (3). Many sensory systems have common features. One such feature is exact adaptation in which the output to a change in input to a new constant level gradually returns to a level independent of the input. A second common feature, called Weber’s law, states that the maximal response to a change in signal is inversely proportional to the background signal (4): \( \Delta Y = k \Delta u/u_0 \), where \( k \) is a constant, \( Y \) is the output, and \( \Delta u \) is the signal change over the background \( u_0 \). Weber’s law in vision, chemotaxis, and other sensory systems applies over a range of several orders of magnitude of background input levels. Note that this definition stems from current practice that generalizes Weber’s original measurements on psychophysical threshold sensitivity (4–7).

Recent studies of the input–output properties of certain cellular signaling systems (8, 9) suggest that these systems show a feature called fold-change detection (FCD): a response whose entire shape, including its amplitude and duration, depends only on fold changes in input and not on absolute levels (10) (Fig. 1A and B). For example, a step change in input from, for example, level 1 to 2 gives precisely the same output as a step from level 2 to 4, because the two steps have the same fold change. FCD is more general than Weber’s law and exact adaptation: Weber’s law concerns only the maximal initial response (Fig. 1D) and exact adaptation concerns only the steady state of the response (Fig. 1C), whereas FCD concerns the entire shape of the response.

Here, we ask what might be the biological function of FCD. We show that FCD is necessary and sufficient to make sensory searches in which an organism moves through a spatial sensory field invariant to the amplitude of the field. This may be useful, for example, to make sensory searches invariant to the source strength that multiplies the diffusing/convecting chemical fields sensed in chemotaxis, the ambient light that multiplies the contrast field in vision, and the stochastically varying protein concentrations that multiply the output in many cellular signaling systems.

Furthermore, we ask what molecular mechanisms might give rise to FCD. FCD places strong constraints on potential mechanisms. A recent study showed theoretically that many known models for biological regulation do not show FCD (10). That study identified one mechanism that can provide FCD based on the incoherent feed-forward loop (IFFL). The IFFL is one of the most common network motifs (recurring circuits in transcription networks) in which an activator activates both an output gene and a repressor of that gene (11–14). Here, we ask whether one can define a larger class of mechanisms for FCD. We present such a large class of FCD mechanisms. These include specific kinds of nonlinear integral-feedback loops. We show that one such loop is found in the bacterial chemotaxis sensory circuit.

Finally, we show that FCD entails both exact adaptation and Weber’s law but that these two features are not sufficient for FCD. This study suggests a relationship between symmetries of the physical world and the response and design of evolved sensors.

Results

Definition of FCD. Consider a system that has input \( u(t) \) and output \( y(t) \). The system is initially at steady state with \( y(t = 0) = y_0 \). FCD means that the output \( y(t) \) is exactly the same for any two inputs \( u_1(t) \) and \( u_2(t) \) that are proportional to each other, \( u_2(t) = pu_1(t) \), for any \( p > 0 \) and \( u_1(t) > 0 \). For example, consider two input steps with the same fold change but different absolute levels (Fig. 1A). A system with FCD displays precisely the same dynamical response to both steps (Fig. 1B), including equal amplitude and response times.

FCD Entails Exact Adaptation and Weber’s Law but Is Not Guaranteed by Having Both. Exact adaptation means that the steady-state output is independent on the steady-state level of input. FCD entails exact adaptation, because FCD by definition means that, for any two constant inputs \( u_1 \) and \( u_2 = pu_1 \), the steady-state output must be the same. However, exact adaptation does not entail FCD:

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Weber depend also on absolute input levels. depend on absolute changes. (with exact adaptation but no FCD, because peak response and dynamics change (note log scale). (signal. Two step changes with identical fold change and different absolute inputs, including amplitude and adaptation dynamics. (note log scale). We to scalar symmetry of the input constant (this can also be called amplitude symmetry). We that FCD is necessary and sufficient for spatial searches that are invariant to input source strength. This is consistent with the results of a classic experiment on bacterial chemotaxis. Mesibov et al. (24) measured the number of Escherichia coli that swim into a capillary containing attractant at concentration \( u_b \), when placed onto a glass slide with attractant concentration \( u_0 \) (Fig. 3B). They varied \( u_b \) and \( u_b \) across several orders of magnitude, keeping \( u_b = u_0/3.1 \). The number of bacteria that swim into the capillary after 1 h was nearly constant across two orders of magnitude of concentrations and varied by less than a factor of three across three orders of magnitude (7 ± 3 × 10^5 bacteria in the range from 10^-2 to 1 mM of α-methylaspartate) (Fig. 3C). This suggests that the mean bacterial search process in this spatiotemporal attractant field is independent of the source strength, a feature that may be provided by the FCD property of the chemotaxis system.

Fig. 1. Dynamics of sensory response to fold change in input. (A) Input signal. Two step changes with identical fold change and different absolute change (note log scale). (B) Output of FCD sensor is identical for the two inputs, including amplitude and adaptation dynamics. (C) Output of a sensor with exact adaptation but no FCD, because peak response and dynamics depend on absolute changes. (D) Output of a sensor with exact adaptation, Weber’s law, and no FCD. Weber’s law applies, because the peak response depends only on relative change and thus, is equal for both step inputs; however, FCD does not apply, because the temporal adaptation dynamics depend also on absolute input levels.

Fig. 2. Organisms with a spatial search dependent on FCD output feeding into the spatial movement of the agent.

FCD Allows Spatial Searches That Are Invariant to Input Source Strength. We now study the effects of FCD on organisms that use their sensory system to search in space. Consider an organism that searches by sensing an input field. The sensory-system output \( y \) guides the motion of the organism (Fig. 2), tending to bring it to a desired spatial location. We define sensory fields with scalar symmetry as fields that have the same pattern up to a multiplicative constant (this can also be called amplitude symmetry). We find that FCD is necessary and sufficient for the search to be invariant to scalar symmetry of the input field (invariant to the amplitude of the input field; proof shown in Materials and Methods). The intuitive reason for this invariance is that FCD cancels out the amplitude of the input field by facilitating a search that depends only on the relative changes in input that are generated as the sensing organism moves through space.

Note that FCD is also necessary for the search to be invariant to scalar symmetry of the input field. The putative system of Fig. 1D, for example, has no FCD, because its adaptation time depends on absolute input level. This would make the spatial search depend on the amplitude of the input field. Because input amplitudes in most sensory systems can vary by many orders of magnitude, such dependence could lead to long or inefficient searches and thus, limit the range of usefulness of the sensory system.

Note that at low signal levels, the cost of search might exceed its benefit. Furthermore, at very low and very high input levels, stochastic noise and saturation might affect the system. Thus, FCD is expected to be useful only in a finite range of input stimuli.

We now give three examples of input fields that have scalar symmetry: bacterial chemotaxis, vision, and protein-based signal-transduction system. In bacterial chemotaxis, bacteria perform a spatial walk through a chemo-attractant field: \( u(\mathbf{r}, t) \). Along this walk, they sense the concentration at their current position and compute the tumbling rate (rate of random direction changes) to climb up the gradient (Fig. 3) (15–22). The input field often results from diffusion or convection from a source of attractant (23), and bacteria attempt to accumulate at this source. Because the equations for diffusion or passive scalar convection are linear in the source strength \( u_0 \), the input field \( u(\mathbf{r}, t) \) is linear in the amplitude \( u_0 \). For example, diffusion from a pulse-like source at position \( r_0 \) results in \( u(\mathbf{r}, t) = u_b/(4\pi Dt)^{3/2} \exp \left(- (r^2 - r_0^2)/4Dt \right) \), which is linear in \( u_0 \). The information about the position of the source is, thus, encoded in the shape of the field, not in its amplitude. Therefore, it is reasonable for bacteria to evolve a search pattern that is independent of \( u_0 \).

Below, we show that recent models of bacterial chemotaxis (Fig. 3A) show FCD, predicting that bacterial chemotaxis should be invariant to source strength. This is consistent with the results of a classic experiment on bacterial chemotaxis. Mesibov et al. (24) measured the number of Escherichia coli that swim into a capillary containing attractant at concentration \( u_b \), when placed onto a glass slide with attractant concentration \( u_0 \) (Fig. 3B). They varied \( u_b \) and \( u_b \) across several orders of magnitude, keeping \( u_b = u_0/3.1 \). The number of bacteria that swim into the capillary after 1 h was nearly constant across two orders of magnitude of concentrations and varied by less than a factor of three across three orders of magnitude (7 ± 3 × 10^5 bacteria in the range from 10^-2 to 1 mM of α-methylaspartate) (Fig. 3C). This suggests that the mean bacterial search process in this spatiotemporal attractant field is independent of the source strength, a feature that may be provided by the FCD property of the chemotaxis system.
A bacterial example is vision. The reflectance of objects $R(r)$ is multiplied by the ambient light $I$ to provide the contrast field sensed by the eye, $u = IR(r)$ (4). The eyes make spatial patterns, for example, by means of rapid movements called fixational eye movements or saccades several times per second, which scan the visual field. The visual system shows exact adaptation, as evidenced by experiments that track the eyes and accordingly move the visual field to cancel out these rapid eye movements, rendering the viewer unable to discern contrast within seconds (25–27). Vision also shows Weber’s law to a good approximation across three decades of stimuli (28, 29). Because vision exhibits both exact adaptation and Weber’s law, it might also show FCD, a hypothesis that is experimentally testable. FCD in the visual system would allow visual searches to be independent on the strength of ambient light. Indeed, experiments suggest that spatial visual searches, in which the eyes search for specific objects within a visual field, are insensitive to ambient-light levels across several orders of magnitude (30, 31).

Scalar symmetry might also occur in a range of molecular sensing tasks, our third example. Consider signaling systems in a cell. A typical case involves a signaling protein $P$ whose concentration is $P_T$, which can be found in active or inactive forms, $P^*$ and $P_0$, respectively. The rates of transition between these forms are $v_1$ and $v_2$, respectively. The input signal $u$ (Eq. 1): 

$$P_0 \xrightarrow{v_2(u)} P^*$$

The resulting concentration of active protein (the input to downstream components) is a function of the input, multiplied by a scalar, $P_T$ (Eq. 2): 

$$P^* = \frac{v_1(u)}{v_1(u) + v_2(u)} P_T$$

The multiplicative factor $P_T$ is a protein concentration. Protein concentrations are known to vary stochastically from cell to cell and in the same cell over time, typically by tens of percent (32–36). An FCD system downstream of $P^*$ would allow response to changes in input $u$ and yet, cancel out stochastic variations in $P_T$ (9, 10).

**Class of Mechanisms That Show FCD.** Here, we provide conditions for the internal sensor structure that are sufficient for FCD. Consider a system described by a set of ordinary differential equations, with internal variables $x$, input $u$, and output $y$. The dynamics of these variables (Eqs. 3 and 4)

$$\dot{x} = f(x, y, u)$$

$$\dot{y} = g(x, y, u)$$

FCD holds if the system is stable (37, 38), shows exact adaptation, and $g$ and $f$ satisfy the following homogeneity conditions for any $p > 0$ (Eqs. 5 and 6):

$$f(px, y, pu) = pf(x, y, u)$$

$$g(px, y, pu) = g(x, y, u)$$

(proof shown in Materials and Methods). If $f$ is linear, then this condition is also necessary for FCD. A generalization of this condition, replacing $px$ by a function $\phi(p, x)$, is also provided in Materials and Methods. Note that, in a system that exhibits exact adaptation, the condition in Eq. 6 is sufficient to yield Weber’s law (Materials and Methods).

We now discuss examples of FCD mechanisms based on these conditions. The first example is the incoherent feed-forward loop presented in ref. 10. Here, an activator $u$ activates gene $y$ and represses $x$, which represses $y$. When $u$ is in its linear regime and $y$ is near saturation, one has (Eqs. 7 and 8)

$$\dot{x} = u - x$$

$$\dot{y} = \frac{u}{x} - y$$

where $x \neq 0$. These equations satisfy conditions in Eqs. 5 and 6 and show FCD (Fig. 4A). Note that here and in all of the examples that we consider, FCD holds only when the input $u$ and controller $x$ are far enough from 0. Generally, we expect FCD to hold only for a range of inputs: not too small so that ratio-based $(u/x)$ comparisons can be made without $x$ being too close to 0 and not too large to saturate the sensor.

Note that not all IFFL designs show FCD [we find that none of the list of feed-forward loop (FFL) designs compiled by ref. 39 show FCD]. For example, an incoherent FFL called a sniffer (40, 41), in which $x$ enhances $y$ degradation rather than repressing $y$ production, does not show FCD (in the sniffer, Eq. 8 is $\dot{y} = u - xy$, allowing exact adaptation but not FCD; the condition in Eq. 6 does not hold, except in a limit mentioned in ref. 10).

**Fig. 3.** Bacterial chemotaxis search patterns do not depend on chemoattractant source concentration. (A) Bacterial chemotaxis is comprised of runs and tumbles. When the bacteria sense an increase in attractant (i.e., movement in the right direction), they lower their tumbling frequency and tend to continue in that direction. (B) The experiment by Mesibov et al. (24). Bacteria are allowed to adapt to a background attractant concentration in the plate. After a period of time, a capillary with attractant concentration 3.1 times higher than the background was presented. This formed an attractant source concentration. (C) Bacterial chemotaxis is comprised of runs and tumbles. When the bacteria sense an increase in attractant (i.e., movement in the right direction), they lower their tumbling frequency and tend to continue in that direction. The eyes make spatial searches, for example, by means of rapid movements called fixational eye movements or saccades several times per second, which scan the visual field. The visual system shows exact adaptation, as evidenced by experiments that track the eyes and accordingly move the visual field to cancel out these rapid eye movements, rendering the viewer unable to discern contrast within seconds (25–27).
A well-known mechanism for exact adaptation, called integral feedback, does not provide FCD in its commonly used linear form (42, 43). Integral feedback involves feeding back on a controller \( x \), which integrates the error between \( y \) and its desired steady-state level \( y_0 \) (Eqs. 9 and 10):

\[
\dot{x} = y - y_0 \tag{9}
\]

\[
\dot{y} = u - x - y \tag{10}
\]

These equations do not meet either of the conditions in Eqs. 5 and 6, and FCD is not found (Fig. 1C). Indeed, because this is a linear system, it must show response amplitude that increases with absolute signal strength and cannot show FCD.

The present conditions point the way to modifying linear integral feedback to achieve FCD. The following mechanism multiplies the error \( y - y_0 \) by \( x \) to satisfy the condition in Eq. 5 and uses a ratio-based controller \( u/x \) to satisfy the condition in Eq. 6 (Eqs. 11 and 12):

\[
\dot{x} = x(y - y_0) \tag{11}
\]

\[
\dot{y} = u/x - y \tag{12}
\]

This nonlinear feedback loop shows FCD (Fig. 4B). These equations are stable (SI Text) and reminiscent of certain forms of adaptive control (44). In addition, if the dynamics of \( y \) are very fast compared with \( x \), one can replace \( y \) with its steady-state value and still obtain FCD (Eqs. 13 and 14):

\[
\dot{x} = x(y - y_0) \tag{13}
\]

\[
y = g(u/x) \tag{14}
\]

for any function \( g \).

A third example is shown in Fig. 4C, where a linear integral feedback system is provided with a log-transformed input. This mechanism satisfies more general FCD conditions detailed in SI Text. In addition, relationships between the three mechanisms depicted in Fig. 4 can be found using variable transformations, as discussed in SI Text.

Model of Bacterial Chemotaxis Shows FCD. A recent study by Tu et al. (3) provides a model of bacterial chemotaxis that captures a wide range of experimental findings by the Berg lab, including small signal response, response to exponential ramps and sinusoidal perturbations, and large-step responses. The input of the system is the chemoeffector, the ligand concentration \( u \). The output \( y \) is the receptor activity that determines the rate of tumbles that guide the bacterium up chemoeffector gradients (Fig. 3A). The model is based on a Monod-Wyman-Changeux (MWC) description of receptor clusters that rapidly responds to attractant and generates a signal that affects the cells tumbling frequency. Exact adaptation is provided by a slow integral feedback loop, first described by Barkai and Leibler (45, 46), that adjusts receptor methylation level and affects its affinity to the attractant. The model in ref. 3, for a wide range of ligand input, can be written as (Methods) (Eqs. 15 and 16)

\[
\dot{x} = xF(y) \tag{15}
\]

\[
y = \frac{1}{1 + (u/x)^N} \tag{16}
\]

where \( F \) has a single stable fixed point \( F(y_0) = 0 \). Here, the variable \( x \) represents the effective \( K_d \) of the receptors for attractant, which depends on the methylation level of the receptor.

This approximation to the full model holds in the range \( K_f << u << K_d \), a range of more than two orders of magnitude for attractants such as \( \alpha \)-methylaspartate, for which \( K_f = 18 \mu M \) and \( K_d = 2.9 \mu M \). These equations satisfy the present conditions for FCD (Eqs. 5 and 6). Thus, we predict that the response to two steps with the same fold change would yield identical output. As discussed above, the experimental results of Mesibov et al. (24) support the FCD behavior of bacterial chemotaxis.

Discussion

This study considered mechanisms and functions of FCD, a property of sensory systems in which the complete dynamics of the output, including its amplitude and response time, depend only on fold changes in the input and not on absolute input level. We find that FCD is necessary and sufficient to allow organisms to search in a spatial input field in a way that is invariant to multiplying the field by a constant. This can explain experiments in which searches in bacterial chemotaxis and vision are independent of variations over several orders of magnitude in attractant source and ambient light, respectively.

FCD entails two commonly found features of sensory systems, exact adaptation and Weber’s law. However, we found that these features are not sufficient for FCD. Weber’s law concerns only response amplitude, whereas FCD includes the amplitude, adaptation time, and indeed, full temporal profile of the dynamics. Thus, one may view Weber’s law and exact adaptation observed in sensory systems as stemming from FCD.

The present study provides a range of mechanisms that can provide FCD. These mechanisms include certain nonlinear integral feedback loops, one of which seems to be found in the chemotaxis sensory circuit of \( E. \) coli.

Future work may investigate the possibility of FCD in other sensory systems and molecular signaling in cells. Examples include sensory modalities such as auditory searches for sound sources and olfactory searches for odorant sources (47–50). Experiments can investigate this on several levels: whether search movement is independent of signal source strength, whether the input–output relationship shows FCD, and whether the molecular mechanism follows the present conditions for FCD. Such studies can test the hypothesis that FCD evolved in response to the scalar symmetry of the sensory inputs found in nature to make searches independent of the amplitude of sensory fields.
Materials and Methods

Sufficient Conditions for FCD. Consider a system with $x = f(x, y, u)$ and $y = g(x, y, u)$ that shows exact adaptation to a steady-state output $y = y_0$. Here, we show that if $f(x, y, u) = p(x, y, u)$ and $g(x, y, u) = q(x, y, u)$, then FCD holds. Consider the coordinate transformation for the system to two different inputs: $u_1(t)$ and $u_2(t)$ with a constant ratio $P > 0$ between them, $u_2(t) = pu_1(t)$. At time 0, the system is adapted, $y(t) = y_0$ to constant input $u_1(0) = u_0$ and $u_2(0) = 0$. Thus, at time 0, $f = 0$ and $g = 0$, with corresponding $x = x_0$ and $y = y_0$. Using the condition of Eq. (5), we have that $x_0^\prime = p(x_0, y_0, u_1)$ because $f(x_0, y_0, u_1) = x_0^\prime = p(x_0, y_0, u_1)$ and there is only one value for $x$ that yields $F = 0$ at a given input $u_1$ at steady state.

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Conditions in Eqs. 5 and 6 have additional consequences. Setting the parameter $P$ in Eqs. 5 to $P = 1$ yields $\frac{x'}{y'} = f(1; y, x|y, x)$ for small perturbations around a steady state. Thus, $f(x, y, u) = x'\phi(u), x'\phi(u)$ is a function of the ratio $u$. Similarly, $g(x, y, u) = y\psi(u, y)$, for small perturbations around a steady state. A more general result is discussed in SI Text.

The sufficient conditions for FCD can be generalized: FCD holds if $f(x, y, u)$, $y = g(x, y, u)$, and $f(x, y, u)$ are measurable functions of $y$. The sufficient condition for having the output invariant under a function $\Phi(u)$ is transformation is having a function $f(x, y, u)$ that yields $F = 0$ at a given input $u_1$ at steady state.

Weber's Law and Adaptation. Weber's law states that a small perturbation in input yields a small perturbation in output. The response of inputs $x = \Delta x_1$ and $y = x_1$ is about the same, $x_1$ is a large input. Thus, $f(x, y, u) = x'\phi(u), x'\phi(u)$ is a function of the ratio $u$. Similarly, $g(x, y, u) = y\psi(u, y)$, for small perturbations around a steady state. A more general result is discussed in SI Text.

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Generalized Fold-Change Detection: Symmetry Invariance. We study general systems with inputs and outputs of the following form (Eq. S1 A and B):
\[
\begin{align*}
\frac{dx}{dt} &= f(x, u) \\
y &= h(x, u)
\end{align*}
\]  

where \( u = u(t) \) is a stimulus, excitation, or input function and \( y = y(t) \) is a response or output function. We are using here the standard control-theory formalism: typically, \( y \) represents a selection of one of the state variables \( x \), which quantifies the response of the system. This variable, which is one of the coordinates of \( x \), satisfies a differential equation, and the output map \( h \) is of the form \( y = h(x) = x \). Eqs. 3 and 4 are for this special case, which is also discussed in detail in Coordinate projection.

As usual, Eq. S1 is meant as shorthand for
\[
\begin{align*}
\frac{dx}{dt} &= f(x(t), u(t)) \\
y &= h(x(t), u(t))
\end{align*}
\]

The spaces of states, input values, and output values, \( X, U \), and \( Y \), respectively, are subsets of Euclidean spaces \( \mathbb{R}^n \), \( \mathbb{R}^m \), and \( \mathbb{R}^q \), respectively, and \( u : [0, \infty) \rightarrow U, x : [0, \infty) \rightarrow X, y : [0, \infty) \rightarrow Y \).

Our central question is as follows. Suppose that we are interested in understanding how a certain set of transformations \( P \) or symmetries (Eq. S2) acting on the space \( U \) of input values affects the response of the system. The set \( \pi \in P \) might constitute, for example, a group of rotations, translations, and/or dilations in an image-recognition system.

Specifically, we are interested in what one might call response invariance to symmetries in \( P \): the system response that is observed after a jump from some constant value of \( u \) to a new input \( v(t) \) will be the same as if we started instead with the constant value \( \pi(u) \) and then jumped to \( \pi(v(t)) \). For example, suppose that we are watching a distant static image, and suddenly, a target appears in the visual field. Our response should be identical (if response invariance to translations is valid) when we observe the image from a displaced location.

One particular example of interest is \( P = U = \mathbb{R}_{>0} \) (positive real numbers) and \( \pi u = \) multiplication. The requirement that the response should be the same when jumping from \( u \) to \( v \) as when jumping from \( pu \) to \( pv \), for any \( p > 0 \) means that the response only depends on the fold change or ratio \( v/u \). We use the terminology fold-change detection (FCD) because of this motivation.

Technical assumptions. We take the functions \( f, h \) to be differentiable and make the assumption that, for each input \( u : [0, \infty) \rightarrow U \) and each initial state \( \xi \in X \), there is a (unique) solution of the initial value problem (Eq. S1) with initial condition \( x(0) = \xi \). We denote this solution as:

\[
\phi(t, \xi, u)
\]

and the corresponding output as:

\[
\psi(t, \xi, u) = h(\phi(t, \xi, u), u(t))
\]

We also make the assumption that, for each constant input \( u \), there is a unique steady state, which we denote as \( \sigma(u) \). That is to say, there is a unique solution of \( f(x, u) = 0 \) given by \( x = \sigma(u) \) (Eq. S3):

\[
f(\sigma(u), u) = 0
\]

We will say that the system is stable\(^*\) if, in addition, it holds that every trajectory approaches \( \sigma(u) \) when the constant input \( u(t) = u \) is used, which is to say:

\[
\lim_{t \rightarrow \infty} \psi(t, \xi, u) = \sigma(u) \quad \text{for all } \xi \in X, u \in U.
\]

Here and later, we make the abuse of notation of viewing an element \( u \in U \) both as an input value \( u(t) \in \mathbb{R} \) and as a constant input function \( u : [0, \infty) \rightarrow U \); the meaning should be clear from the context. Main definitions. Suppose a system (Eq. S1) and a set of symmetries \( \pi \in P \) as in Eq. S2.\(^5\)

Definition: property FCD is satisfied if the equality

\[
\psi(t, \sigma(u), v) = \psi(t, \sigma(u), \pi v)
\]  

holds for all constants \( u \in U \), all input functions \( v : [0, \infty) \rightarrow U \), all \( \pi \in P \), and all \( t \geq 0 \).\(^4\)

A consequence of FCD is as follows. Suppose that we use \( v(t) = v(\text{constant function}) \) in the definition of FCD. Then, evaluating at \( t = 0 \) and using that, by definition, \( \psi(0, \sigma(u), v) = h(\sigma(u), v) \) and \( v(0) = h(\sigma(u), v) \) in (Eq. S4):

\[
h(\sigma(u), v) = h(\sigma(u), \pi v) \quad \text{for all } u \in U, v \in U, \pi \in \pi.
\]

Definition: the system perfectly adapts to constant inputs if there exists some value \( \psi_0 \in Y \) so that:

\[
h(\sigma(u), u) = \psi_0 \quad \text{for all } u \in U.
\]

Remark: suppose that a system perfectly adapts to constant inputs and also, that it is stable in the sense previously defined. This means that, given any initial state \( \xi \in X \) and any constant input \( u, \phi(t, \xi, u) \rightarrow \sigma(u) \) as \( t \rightarrow \infty \). It then follows that:

\[
\psi(t, \xi, u) = h(\phi(t, \xi, u), u) \rightarrow h(\sigma(u), u) = \psi_0.
\]

This stronger property of output convergence to the same value \( \psi_0 \), independent of initial state, is often taken as the definition of perfect adaptation.

\[^*\]A more proper mathematical term is attracting, because this weak definition of stability does not rule homoclinic phenomena.

\[^{\text{4}}\]\(To be precise, we should require that \( v(t) \) be a piecewise-continuous function (or more generally, Lebesgue-measurable) whenever \( v(t) \) is a piecewise-continuous function. Asking that every \( v(t) \) be continuous is enough to guarantee this requirement.

\[^{\text{5}}\]The expression \( \pi v \) on the right side of FCD means the input \( v(t) = \pi v(t) \). We could just require the property to hold only for \( t > 0 \), but the property would be equivalent, taking limits as \( t \rightarrow 0^+ \).
**FCD Implies Perfect Adaptation and Weber’s Law.** 2.1 Perfect adaptation. We say that the action is transitive on inputs if the following property holds: for each pair of distinct \( u, v \in \mathbb{U} \), there is some \( \pi = \pi_{uv} \) such that \( v = u\pi \).

The most interesting example of transitive action in our context is as follows: \( \mathbb{U} = \mathbb{P} = \mathbb{R}_{>0}^m \) (\( m \) vectors consisting of positive entries) and \( \pi(u) = (p_1u_1, \ldots, p_mu_m)^T \), which we write as \( pu \), if \( \pi = (p_1, \ldots, p_m) \). Clearly, \( \pi_{uv} = (v/u_1, \ldots, v/u_m) \) achieves \( uu = v \).

Lemma 1: suppose that the action of \( \pi \) is transitive on inputs. Then, FCD implies perfect adaptation.

Proof: pick an arbitrary element \( u_0 \in \mathbb{U} \) and define \( y_0^\pi = h(\sigma(u_0), u_0) \). Now, pick an arbitrary \( w \in \mathbb{U} \). By transitivity, there exists some \( \pi \in \mathbb{P} \) such that \( \pi u_0 = w \). We now apply Eq. S4 with \( u = u_0 \) and also \( v = u_0 \). \( h(\sigma(w), w) = h(\sigma(u_0), u_0) \). \( h(\sigma(u_0), u_0) = h(\sigma(u_0), u_0), u_0 = u \), as required for adaptation.

2.2 Weber’s law. We now discuss connections between the FCD property, relative to the symmetries \( u \rightarrow pu \) (\( \mathbb{U} = \mathbb{P} = \mathbb{R}_{>0}^n \)) and the Weber or Weber-Fechner law of perception.

There are several versions of Weber’s law. The textbook (1) provides two relevant definitions (a third one, based on steady-state sensitivity, is irrelevant to systems that perfectly adapt). The main definition used in ref. 1 can be phrased, using our notation, as follows.

Consider the maximum deviation of the output in response to a step from an input value \( u \) to an input value \( v \):
\[
\Psi(v, u) = \max_{t \geq 0} |y(t, \sigma(u), v) - y_0|,
\]
where \( y_0 = h(\sigma(u), u) \) is the adapted value of the output. Suppose that \( \Psi \) is differentiable and introduce the sensitivity of the response
\[
S(u) := \frac{\partial \Psi(v, u)}{\partial v} \bigg|_{v = u}.
\]

With these concepts, ref. 1 defines the Weber law as asserting that \( S(u) \) is (approximately) inversely proportional to \( u \), which formalize as there exists a constant \( \kappa \) such that
\[
S(u) = \frac{k}{u}.
\]

**FCD implies Weber’s law.** FCD implies that \( \Psi(v, u) = f(v/u) \), for some function \( f \), which we assume is differentiable, and therefore,
\[
S(u) = \frac{\partial f(v/u)}{\partial v} \bigg|_{v = u} = f'(1) u,
\]
and Weber’s law is indeed satisfied with \( k = f'(1) \).

An intuitive way to restate this property is as follows. We expand \( \Psi \) to first order around \( v = u \), and therefore,
\[
\Psi(v, u) = \Psi(u, u) + S(u)(v - u) + o(v - u).
\]
If the system perfectly adapts, then \( \Psi(u, u) = 0 \), and therefore, Weber’s law amounts to the property \( \Psi(v, u) \approx \frac{k(v - u)}{u} \). If we write \( \Delta v = \Psi(v, u) \) to represent a maximal response change in output and \( \Delta u = v - u \), we can write
\[
\Delta y \approx \frac{\Delta u}{u}.
\]

More generally, one can prove that the entire response has the same proportionality property. Take any two constant input values \( u \) and \( v \). Picking \( p = 1/u \) in the FCD condition \( \Psi(t, \sigma(u), v) = \psi(t, \sigma(mu), \pi v) \), we conclude that \( \psi(t, \sigma(u), v) = \psi(t, \sigma(u), v) \).

\[\sigma(1, w) = Q(t, w) \] where \( w = v/u \). We expand \( Q(t, w) = Q(t, 1) + M(t)(w - 1) + o(w - 1) \) to first order, where \( M(t) = \frac{\partial}{\partial u} Q(t, 1) \), and observe that \( Q(t, 1) = \psi(t, \sigma(1), v_0) \) for all \( t \), where \( v_0 = h(\sigma(1), 1) \) is the adapted value of the output. Note that \( y(t) = \psi(t, \sigma(u), v) \) is the output that results after the input jumps from \( u \) to \( v \). Writing \( \Delta u = v - u \), we conclude:
\[
\Delta y(t) = \psi(t) - y_0 = M(t)\frac{\Delta u}{u} + o\left(\frac{\Delta u}{u}\right),
\]
which is one way to formalize \( \Delta y \approx k\frac{\Delta u}{u} \) for all \( t \). The function \( M(t) \) can be computed explicitly, as follows:
\[
M(t) = c\exp(-t)A^{-1}b + d
\]
where
\[
A = \frac{\partial f}{\partial x}(\xi, 1), B = \frac{\partial f}{\partial t}(\xi, 1), c = \frac{\partial h}{\partial x}(\xi, 1), d = \frac{\partial h}{\partial t}(\xi, 1)
\]
is a matrix and vectors of sizes \( n \times n \), \( n \times 1 \), \( q \times n \), and \( q \times 1 \), respectively, and \( \xi = \sigma(1) \). This follows from the fact that the derivative is computed by solving the variational differential equation \( \dot{z} = Az + Bu \) with output \( c\exp(-t)z + d\Delta u \) (see the proof of theorem 1 in ref. 1). Observe that, when \( M(t) = 0 \), one can expand to higher order, in which case \( \Delta y(t) \) becomes proportional to a power \( \left(\Delta u/\Delta t\right)^k \).

**Psychophysical sensitivity.** There is a second possible definition of Weber’s law, also discussed in ref. 1, based on psychophysical sensitivity and defined as follows. We let \( r \) be the smallest possible observable response (in a subjective sense of an individual responding to a stimulus or of a given physical measurement) and let \( R(u) \) be the smallest value of the constant input \( v \) for which \( \Psi(v, u) = r \). Thus, \( v \) represents the smallest input that elicits an observable response. Now, the sensitivity \( S(u) \) is defined as \( 1/R(u) \), and Weber’s law is once again the property that \( S(u) = \frac{k}{2} \) for some \( k \). We prove that FCD implies this version of Weber’s law as well.

Indeed, let \( f \) be as defined, and therefore, \( R(u) = \inf_{v} (f(v/u) = r) \). We assume that \( f \) is monotonic before reaching its global maximum or minimum (which is satisfied when there is a unimodal response) and introduce the function \( g \) as the inverse of \( f \) in its initially monotonic interval. Thus,
\[
R(u) = \inf_{v} \{v/u \geq g(r)\} = ug(r) = \frac{u}{k}
\]
with \( k = 1/g(r) \). Therefore, Weber’s law in this psychophysical sensitivity sense holds true, because \( \Delta y(t) = 1/R(u) = \frac{k}{2} \).

**Sufficient Conditions for FCD.** We discuss here a technique for verifying the FCD property.

We will call a mapping \( \phi : \mathbb{X} \rightarrow \mathbb{X} \) an equivariance associated to a given symmetry \( \pi \in \mathbb{P} \) if it is differentiable and satisfies the following properties (Eq. S5):
\[
f(\phi(x), \pi u) = \rho_{\pi}(x)f(x, u)
\]
and (Eq. S6)
\[
\rho_{\pi}(x, \pi u) = h(x, u)
\]
for all \( x \in \mathbb{X} \) and \( u \in \mathbb{U} \), where \( \rho_{\pi} \) denotes the Jacobian matrix of \( \rho \).

Note that we are using a slightly more compact notation than in the paper: we write \( \rho(x) \) instead of \( \phi(\rho, x) \) if \( \rho \) is the equivariance associated to a symmetry parametrized by \( p \). Thus, \( \rho(x) \) is the same as \( \partial \phi(\rho, x) \).

Lemma 2: the steady-state mapping \( \sigma \) interlaces \( \pi \) and its associated \( \rho \) as follows (Eq. S7):

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\[ \rho(\sigma(u)) = \sigma(x(u)) \text{ for all } u \in U. \]  \[ S7 \]

Proof: indeed, we use Eq. S5 with any \( u \) and \( x = \sigma(u) \):

\[ f(\rho(\sigma(u)), \pi u) = \rho_u(x)f(\sigma(u), u) = 0, \]

because \( f(\sigma(u), u) = 0 \), by definition of \( \sigma(u) \); this means that \( \rho(\sigma(u)) \) is the steady state \( \sigma(\pi u) \) corresponding to the constant input \( \pi u \), which is what Eq. S7 asserts.

Lemma 3: suppose that for each \( \pi \in \mathbb{P} \), there is an associated equivalence \( \rho \). Then, FCD holds.

Proof: pick any \( \pi \in \mathbb{X} \), any constant \( u \in U \), and any input function \( v : [0, \infty) \rightarrow \mathbb{U} \). Consider the two solutions \( x(t) = \psi(t, \sigma(u), v) \) and \( z(t) = \psi(t, \sigma(u), \pi v) \). We need to show that (Eq. S8)

\[ h(x(t), v(t)) = \psi(t, \sigma(u), v) = \psi(t, \sigma(\pi u), \pi v) = h(z(t), \pi v(t)) \]  \[ S8 \]

for every \( t \geq 0 \).

Take an equivalence \( \rho \) associated to \( \pi \) and define \( \tilde{x}(t) := \rho(x(t)) \). Because

\[ \tilde{x}(0) = \rho(x(0)) = \rho(\sigma(u)) = \sigma(\pi(u)) \]  \[ \text{using Eq. S7 and} \]

\[ \left( \frac{d}{dt} \right) \tilde{x}(t) = \rho_u(x(t))f(\sigma(u), v(t)) = f(\tilde{x}(t), \pi v(t)) \]  \[ \text{using the chain rule and then Eq. S5}, \]

it follows, by definition of \( \psi \), that

\[ z(t) = \tilde{x}(t) = \rho(x(t)). \]

Therefore, Eq. S8 becomes:

\[ h(x(t), v(t)) = h(\rho(x(t)), \pi v(t)). \]

This property is the second equivalence condition (Eq. S6). For controllable and observable systems, the condition in Lemma 3 is necessary as well as sufficient, as follows from uniqueness results in minimal realization theory in control theory [3].

A Subset of Conditions That Is Sufficient for Weber’s law. We consider now the very special case of systems with two variables in which the second variable is the output:

\[ \dot{x}_1 = f_1(x_1, x_2, u) \]  \[ S9A \]

\[ \dot{x}_2 = f_2(x_1, x_2, u) \]  \[ S9B \]

\[ y = x_2. \]  \[ S9C \]

We assume that the system adapts \( h(\sigma(u), u) = y_0 \) for all \( u \), which translates in this special case to the following property:

\[ \sigma_2(u) = y_0 \text{ for the second component of the steady-state map } \sigma. \]

We impose the following property for the second component \( f_2 \) of \( f \), but no assumptions are made for \( f_1 \):

\[ f_2(p x_1, y_0, pu) = f_2(x_1, y_0, u) \]  \[ S10 \]

for all \( u \in \mathbb{R}_{>0} \) (as with the other Weber’s Law results, we are restricting attention to the special symmetries \( u \rightarrow pu \) with \( U = \mathbb{P} \)).

We claim that, for small times \( t \) and small \( \Delta u = v - u \), there holds the approximate Weber’s Law:

\[ \Delta y(t) \approx c \frac{\Delta u}{u} \]

where \( \Delta y(t) = \psi(t, \sigma(u), v) - y_0 \), for an appropriate constant \( c \) (which is linearly dependent on \( t: c = kt \)). Note that \( y(t) = \psi(t, \sigma(u), v) \) can be expanded to first order as \( y(t) = y_0 + y(0)t + o(t) \), and that \( y(0) = f_2(\sigma_1(u), y_0, v) \). Thus, we now give the precise statement:

Proposition 1: Suppose that Eq. S10 holds, that \( f_2 \) is a differentiable function, and that \( \sigma \) is a continuous function. Then, there is a constant \( k \) such that

\[ f_2(\sigma_1(u), y_0, v) = \frac{k}{u} \frac{v - u}{u} + o\left(\frac{v - u}{u}\right) \]

for all \( u, v \).

Proof: Eq. S10 applied with \( p = 1/u \), means that \( f_2(x_1, y_0, u) = f(x_1/u) = f_2(x_1/u, y_0, 1) \) for all \( x_1, u \). Thus, our objective is to show that, for some constant \( k \):

\[ F\left(\frac{\sigma_1(u)}{u}\right) = \frac{k}{u} \frac{v - u}{u} + o\left(\frac{v - u}{u}\right) \]  \[ S11 \]

for all \( v, u \). Since \( \sigma \) is by definition the steady state map, we have that \( f_2(\sigma_1(u), y_0, u) = 0 \) for all \( u \in \mathbb{R}_{>0} \) that is,

\[ F\left(\frac{\sigma_1(u)}{u}\right) = 0 \]  \[ S12 \]

for all \( y \). So Eq. S11 can be restated as:

\[ \frac{\partial}{\partial v} F\left(\frac{\sigma_1(u)}{v}\right) = \frac{k}{u} \]

for all \( u \). Because of the chain rule, we need to show that:

\[ -F\left(\frac{\sigma_1(u)}{u}\right) \frac{\sigma_1(u)}{u^2} = \frac{k}{u} \]

or, equivalently, that:

\[ F\left(\frac{\sigma_1(u)}{u}\right) \frac{\sigma_1(u)}{u^2} \text{ is constant}. \]

Let us write \( \sigma(u) := \sigma_1(u)/u \) (this is a continuous function defined on the positive reals). We need to show that \( F(\sigma(u))/u \) is constant, knowing (from Eq. S12) that \( F(\sigma(u))/u \) is constant.

It is a general fact that \( F(\sigma(u))/u \) constant implies \( F(\sigma(u))/u \) is constant, for any differentiable function \( F \) and any continuous function \( \alpha \). To prove this general fact, let us call \( J \) the range \{\( \sigma(u), u \in \mathbb{R}_{>0} \)\} of \( \alpha \). Since \( \sigma \) is continuous, \( J \) is an interval. There are two possibilities: (a) \( J \) has only one point or (b) \( J \) has interior.

Case (a) means that \( \alpha \) is a constant function, which obviously implies that \( F(\sigma(u))/u \) is constant. If, instead, case (b) holds, then \( F \) must vanish identically on the interval \( J \), which implies that \( F(\sigma(u))/u \) is 0 for all \( u \), and thus again this expression is constant.

Examples of Generalized FCD Systems. Log-linear systems. FCD properties for example shown in Fig. 4C. The system depicted in Fig. 4C satisfies the general FCD conditions (Eqs. S13 and S14)

\[ f(\psi(p, x), y, pu) = \partial_x \psi(p, x)f(x, u, y) \]  \[ S13 \]

\[ g(\psi(p, x), y, pu) = g(x, u, y) \]  \[ S14 \]

using the transformation (Eq. S15)

\[ \psi(p, x) = \log(p) + x. \]  \[ S15 \]

The above conditions are a slight generalization of the basic conditions (Eqs. 5 and 6) in Text. One can prove them directly using the same methodology. In addition, they are a subset of the generalized conditions discussed in Sufficient conditions for FCD.
An interesting class of functions holds, where \( A, B, C, \) and \( D \) are matrices of sizes \( n \times n, n \times m, q \times n, \) and \( q \times m, \) respectively, and \( F \) and \( G \) are differentiable maps, possibly nonlinear, that vanish only at \( 0. \) For example, \( F \) and \( G \) might be the identity mappings. We interpret \( \log \) as independent of \( u = (u_1, \ldots, u_m)^T \) and that the system perfectly adapts. Then, the system has the FCD property.

Proof: given a constant input \( u, \) the corresponding steady states \( x \) satisfy \( F(Ax + B \log u) = 0, \) which, because of the property that \( F \) vanishes only at \( 0, \) means that \( Ax + B \log u = 0. \) Thus, uniqueness of steady-states property is equivalent to the assumption that \( A \) is invertible, and

\[
\sigma(u) = -A^{-1}B\log u.
\]

Because \( h(u, u) = G(C(eu) + D \log u) = G((D - CA^{-1}B) \log u), \) perfect adaptation, the property that this expression must be independent of \( u, \) amounts to the following condition (Eq. [S16]):

\[
D - CA^{-1}B = 0. \tag{S16}
\]

Given any \( \rho = (\rho_1, \ldots, \rho_k) \in \mathcal{P}, \) we define the equivariance \( \rho(x) = x - A^{-1}B \log p. \) We must verify (Eq. [S5]):

\[
F(A\rho(x) + B \log pu) = F(A(x - A^{-1}B \log p) + B \log pu)
\]

\[
= F(Ax + B \log u)
\]

\[
= \rho(x) \cdot F(Ax + B \log u)
\]

(because \( \log pu = \log p + \log u \) and \( \rho(x) \) is the identity matrix) and also need to have (Eq. [S6]):

\[
G(C(x - A^{-1}B \log p) + D \log pu) = G(Cx + D \log u),
\]

which holds because of Eq. [S16].

Recasting of log-linear systems. Log-linear systems can be recast in the following way, after a change of variables. Let us introduce variables \( \bar{z}_1 = e^z. \) Then, \( \dot{z} = \text{diag}(z)F(A\log z + B\log u), \) where \( \text{diag}(z) \) is the diagonal matrix whose diagonal entries are \( z_1, \ldots, z_n. \)

The \( r \)th row of \( A \) log \( z + B \log u \) is:

\[
\sum_{j=1}^k a_{rj} \log z_j + \sum_{j=1}^m b_{ij} \log u_j = \log z^u_{rj},
\]

where the notation \( z^u_r \) means \( z_1^{u_1} \cdots z_m^{u_m} \) (analogously for \( u \)). A similar rewriting may be done for the output function. Let us define \( M(z) = F(\log z) \) and \( N(z) = G(\log z). \) We have shown that a log-linear system can also be written as

\[
\dot{z} = \text{diag}(z)M(z^u)
\]

\[
\dot{y} = N(z^u)
\]

where the variables \( x_i \) are positive. The monomials appearing in the above expression represent the entries \( z_1^{u_1} \cdots z_m^{u_m} \) (analogously for outputs). Furthermore, if \( N \) is invertible, one may redefine the output as \( N^{-1}(y) \), so that no \( N \) is required.

For example, consider this 1D log-linear system:

\[
\dot{x} = F(-x + \log u)
\]

\[
y = G(-x + \log u)
\]

\( F \) and \( G \) are two scalar nonlinear maps. We let \( z = e^x. \) Then, with \( M = F(\log z) \) and \( N(z) = G(\log z), \)

\[
\dot{z} = zM(z)
\]

\[
y = N(u/z).
\]

Let us redefine the output to be \( w = N^{-1}(y) \) (assuming that \( N \) is invertible). We arrive to the following system:

\[
\dot{z} = zM(w)
\]

\[
w = u/z.
\]

Coordinate projection. Another interesting general subclass is that in which the output \( y(t) \) is one coordinate (or, more generally, a subset of coordinates). That is to say, the state space can be written as a Cartesian product \( \mathcal{X} = \mathcal{X}_1 \times \mathcal{X}_2, \) and using the obvious block notation \( x = (x_1, x_2) \) (Eq. [S17 A–C]):

\[
\dot{x}_2 = f_2(x_1, x_2, u)
\]

\[
\dot{x}_1 = f_1(x_1, x_2, u)
\]

\[
y = x_2.
\]

Lemma 5: FCD holds for the system (Eq. [S17]), provided that (Eq. [S18]) holds.

Proof: we observe that the map \( \rho(x_1, x_2) = (\rho_1(x_1), x_2) \) is an equivariance. Indeed, its Jacobian has the block form diag \( [(r_1(x_1), I)], \) therefore, Eq. [S18] is equivalent to Eq. [S5], and Eq. [S6] is true because \( h(x, u) = x_2 \) is independent of \( x_1 \) and \( u. \)

A special case of this setup is when the \( x_1 \) subsystem is linear and independent of \( x_2 \) (feed-forward connection), \( U = \mathbb{R}_{>0}^m \) (scalar positive inputs), and \( \mathcal{P} = \mathbb{R}_{>0} \) acts by scalings \( u \to pu. \) We write (Eq. [S19])

\[
\dot{f}_1(x_1, u) = Ax_1 + bu
\]

(because \( u \) is scalar, \( B = b \) is a column vector). Let us suppose that the following property is satisfied (Eq. [S20]):

\[
f_2(pu_1, x_2, pu) = f_2(x_1, x_2, u) \quad \text{for all } x_1, x_2, u, p.
\]

Then, FCD holds, because we may use \( \rho_1(x_1) = pu_1 \) for \( \pi = p, \) in which case \( (\rho_1\mid_{x_1}) = p \) and therefore,

\[
f_1(p\rho_1, x_2, pu) = A(p\rho_1) + bu = p(Ax_1 + bu)
\]

and

\[
f_2(p\rho_1, x_2, pu) = f_2(px_1, x_2, pu) = f_2(x_1, x_2, u)
\]

Therefore, Eq. [S18] holds.

For these special systems for which Eq. [S19] holds, Eq. [S20] is not merely sufficient, but it is also necessary for FCD to hold (still assuming \( U = \mathcal{P} = \mathbb{R}_{>0}, \) and an action by scalings \( u \to pu. \)) We prove this next.
More precisely, we will assume that the system (Eq. S1) is controllable from steady states, meaning that for each state \( \xi \in \mathbb{R} \), there is some steady state \( \bar{\xi} = \sigma(u) \) (for some constant input \( u \)), some input \( \nu(t) \), and some finite time \( T \geq 0 \) such that \( \xi = \phi(T, \xi, \nu) \). There are control theory tools for checking controllability of linear and nonlinear systems (1). Without loss of generality, one may assume that \( \nu \) is continuous at \( T \) and has an arbitrary prespecified value \( \nu_0 \) there. Proof: For any desired value \( \nu_0 \), consider a solution \( z(t) \) of Eq. S1 backward in time, starting from \( \xi \) and using the constant input \( \nu_0 \). Let us pick some \( \zeta' = z(-\tau_0) \), \( \tau_0 > 0 \). Now, find a \( \nu(t) \) that sends \( \zeta' \) to \( \xi \) in time \( T \). The concatenation of \( \nu \) and the constant \( \nu_0 \) is an input so that at time \( T = T_1 + \tau_0 \), the state \( \xi \) is reached and its value is \( \nu_0 \) at time \( T \).

Lemma 6: Suppose that the system (Eq. S1) is controllable from steady states and has the form (Eq. S17) with Eq. S19. Then, the system satisfies FCD for the scaling action \( u \mapsto pu \) if and only if Eq. S20 holds.

Proof: Sufficiency was already proved, and therefore, we show necessity. Pick some \( \xi = (\xi_1, \xi_2) \in \mathbb{R} \) and \( p, \nu_0 \in \mathbb{R}_{>0} \). We need to show that Eq. S20 holds (Eq. S21) (i.e., that

\[
f_2(p\xi_1, \xi_2, \nu_0) = f_2(\xi_1, \xi_2, \nu_0).
\]

Pick a constant input \( u \) and some input \( v(t) \) such that \( \xi = \phi(T, \sigma(u), v) \) and \( v(T) = \nu_0 \). The assumption is that FCD holds, which means, in particular, that \( x_1(t) = \bar{x}_2(t) \) for all \( t \geq 0 \), where \( x_1(t) = \phi(t, \sigma(u), v) \) and \( \bar{x}_2(t) = \phi(t, \sigma(pu), \nu_0) \). Because also the derivatives of \( x_2 \) and \( \bar{x}_2 \) must coincide (at the points of differentiability of these functions), it follows, in particular, that

\[
f_2(\xi_1, \xi_2, \nu_0) = f_2(x_1(T), x_2(T), v(T)) = f_2(\bar{x}_1(T), x_2(T), \nu_0(T)) = f_2(\bar{x}_2(T), x_2(T), \nu_0(T)) = f_2(\bar{x}_2(T), \xi_2, \nu_0).
\]

(The last equality because \( \bar{x}_2(t) = x_2(t) \), again using FCD). To conclude, observe that \( x_1(t) = px_1(t) \) (by linearity of the equation for \( x_1 \)) and therefore, evaluating at \( t = T \), \( \bar{x}_1(T) = p\xi_1 \); thus, we have proven that Eq. S21 is satisfied.

Relationship between the incoherent feed-forward loop and integral feedback. Here, we show the relationship between the incoherent feed-forward loop and integral feedback.

A system is said to be affine in inputs if the vector field has degree 1 on \( u \). Using control-theory notations, one writes the differential equations for the system as follows (assuming, for notational simplicity, that the input \( u \) is scalar):

\[
\dot{x} = f(x) + ug(x)
\]

where \( f \) and \( g \) are two vector fields. That is, the \( f(x, u) \) in the general form \( \dot{x} = f(x, u) \) is written as \( \dot{x} = f(x) + ug(x) \).

A theorem is given in ref. 2 showing that, under appropriate efficiency was already proved, and therefore, we show

\[
f(x, y) = \begin{pmatrix} -x \\ -y \end{pmatrix}, \quad g(x, y) = \begin{pmatrix} 1/y \\ 1/x \end{pmatrix}.
\]

The relative degree of this system \( r = 1 \). One can verify the assumptions of the main theorem in ref. 2 for this system. The recipe for coordinate changes in ref. 2 (see also the Feedback Linearization Theorem, Theorem 15 in ref. 3) is to use \( z_1 = y \) and \( z_2 = \phi(x, y) \) with the following conditions on the differentiable map \( \phi \):

1. The map \( (x, y) \mapsto (y, \phi(x, y)) \) has a differentiable inverse (technically, is a diffeomorphism).
2. The Lie-derivative \( L_\phi \) vanishes everywhere, which means \( V_\phi g = 0 \) (\( Vg \) is the gradient of \( \phi \)).

The condition \( V_\phi g = 0 \) says, more explicitly, for this example:

\[
\phi_x(x, y) - \frac{1}{y} \phi_y(x, y) = 0
\]

where \( \phi_x, \phi_y \) are partial derivatives. This linear first-order partial differential equation on \( \phi \) may be solved by the method of characteristics, but a solution can be seen by inspection:

\[
\phi(x, y) = y - \log x.
\]

Observe that \( (x, y) \mapsto (y, y - \log x) = (z_1, z_2) \) is clearly invertible, with inverse \( y = z_1 \) and \( x = e^{z_2} - z_2 \). In the new coordinates \( z_1, z_2 \), we have:

\[
\begin{align*}
z_1 &= y \left( e^{z_2} - z_2 \right) - z_1 \\
z_2 &= 1 - z_1.
\end{align*}
\]

Up to a change of coordinates \( z_1 \mapsto 1 - z_1 \), to bring the system into the form in ref. 2 (which normalized the adaptation value to 0; it is 1 in this example), we have that the variable \( z_2 \) implements the integral feedback ensured by theorem 1 in ref. 2.

The form in \((z_1, z_2)\) coordinates is known in control theory as the feedback linearization normal form (3) and is a special case of a normal form for affine nonlinear systems.

Stability Result. We wish to show the global asymptotic stability (GAS) of the unique steady state \((x_0, y_0) = (\frac{u_0}{\beta}, \gamma)\) of the nonlinear integral feedback system (Eq. S22A and B):

\[
\begin{align*}
\dot{x} &= \alpha x(y - y_0) & \text{[S22A]} \\
\dot{y} &= \frac{u_0}{x} - \beta y & \text{[S22B]}
\end{align*}
\]

where \( \alpha, \beta, \gamma, u_0, \) and \( y_0 \) are positive constants and the integrator variable \( x(t) \) is positive. We prove this as a consequence of a more general result.

Lemma 7: Consider a 2D system of the following general form (Eq. S23A and B):

\[
\begin{align*}
\dot{x} &= g(y) & \text{[S23A]} \\
\dot{y} &= -f(x) - ky & \text{[S23B]}
\end{align*}
\]

where \( f \) and \( g \) are functions with positive derivatives, \((y - y_0)k(y) > 0 \) whenever \( y \neq y_0 \). Let \((x_0, y_0)\) be so that \( f(x_0) = g(y_0) = k(v_0) = 0 \), which means that \((x_0, y_0)\) is the unique steady state of the system. Then, \((x_0, y_0)\) is a globally asymptotically stable state.

We provide a proof below but first remark how the stability of Eq. S22 is a consequence of this Lemma.

Corollary: Consider a 2D system of the following general form (Eq. S24A and B):

\[
\begin{align*}
\dot{x} &= g(y) & \text{[S24A]} \\
\dot{y} &= -f(x) - ky & \text{[S24B]}
\end{align*}
\]

where \( f \) and \( g \) are functions with positive derivatives, \((y - y_0)k(y) > 0 \) whenever \( y \neq y_0 \). Let \((x_0, y_0)\) be so that \( f(x_0) = g(y_0) = k(v_0) = 0 \), which means that \((x_0, y_0)\) is the unique steady state of the system. Then, \((x_0, y_0)\) is a globally asymptotically stable state.
\[ \dot{x} = xg(y) \]  
\[ \dot{y} = -f(x) - k(y) \]

where \( f \) and \( g \) are functions with positive derivatives, \( g(y_0)k(y) > 0 \) whenever \( y \neq y_0 \), the variable \( x(t) \) is positive, and \( (x_0, y_0) \) is so that \( f(x_0) = g(y_0) = k(y_0) = 0 \), which means that \( (x_0, y_0) \) is the unique steady state of the system. Then, \( (x_0, y_0) \) is a globally asymptotically stable state.

This corollary is proved as follows. We let \( z = \ln x \) and express the system in the variables \( (z, y) \). We have that (Eq. S25 A and B):

\[ \dot{z} = g(y) \]  
\[ \dot{y} = -\bar{f}(z) - k(y) \]

where \( \bar{f}(z) := f(e^z) \) again has a positive derivative. Now the unique steady state is \( (z_0, y_0) \), where \( z_0 = \ln x_0 \). By the Lemma, this state is globally asymptotically stable, which implies that the system in original coordinates (Eq. S24) is also stable.

The system (Eq. S22) is the particular case of Eq. S24 with \( f(x) = \beta y_0 - \frac{1}{\gamma_0}, g(y) = \gamma(y - y_0), \) and \( k(y) = \beta(y - y_0) \).

We now prove Lemma 7. The proof is based on the LaSalle Invariance Principle (3). We must produce a function \( V(x, y) \) of two variables with the following properties:

1. \( V(x_0, y_0) = 0 \).
2. \( V(x, y) > 0 \) for all \( (x, y) \neq (x_0, y_0) \).
3. \( \dot{V}(x, y)\to\infty \) as \( \| (x, y) \| \to\infty \) (properness or radial unboundedness).
4. \( \dot{V}(x, y) := \frac{\partial}{\partial x}(x, y)g(y) + \frac{\partial}{\partial y}(x, y)[-f(x) - k(y)] \) is so that \( (i) \) \( \dot{V}(x, y) \leq 0 \) for all \( (x, y) \) and \( (ii) \) if a solution satisfies that \( \dot{V}(x(t), y(t)) \equiv 0 \), then \( (x(t), y(t)) \equiv (x_0, y_0) \).

We define:**

\[ V(x, y) := \int_{x_0}^x f(r)dr + \int_{y_0}^y g(r)dr. \]

Observe that properties 1 and 2 (positive definiteness) are satisfied by definition. Regarding property 3, we note that \( \frac{\partial V}{\partial x} = f'(x) > 0, \frac{\partial V}{\partial y} = g'(y) > 0 \) and mixed second derivatives are 0, and therefore, the Hessian matrix of \( V \) is positive definite everywhere. This implies that \( V \) is strictly convex, and principle 3 follows. Finally, we prove principle 4. Observe that

\[ \dot{V}(x, y) = f(x)g(y) + g(y)[-f(x) - k(y)] = -g(y)k(y) \]

from which it follows that \( i \) holds, and moreover, \( \dot{V}(x, y) = 0 \) implies that \( y = y_0 \). Suppose that a solution satisfies that \( V(x(t), y(t)) \equiv 0 \). Then, \( y(t) \equiv y_0 \), and therefore, \( \dot{y}(t) \equiv 0 \). Substituted into the second equation of Eq. S23, we have that \( 0 = -f(x(t)) \) - 0, which implies that \( x(t) \equiv x_0 \); therefore, \( ii \) is true.

**This construction is based on the following idea: when \( k(y) \) is omitted, the vector field is Hamiltonian, with Hamiltonian function \( V \); this provides an energy-conservation constraint, but \( k(y) \) then adds damping to the system.


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