Symmetry Invariance for Adapting Biological Systems[*]

Oren Shoval[†], Uri Alon[†], and Eduardo Sontag[‡]

Abstract. For a general class of dynamical systems, this paper presents a necessary and sufficient characterization of invariance of transient responses to symmetries in inputs. A particular example of this property, scale-invariance or "fold-change detection" (FCD), has been shown to be exhibited in biological sensory systems ranging from bacterial chemotaxis pathways to signal transduction mechanisms in eukaryotes. The characterization is in terms of a notion of equivariance and amounts to the solvability of an associated partial differential equation. For several simple system motifs that are recurrent in biology, the solvability criterion may be checked explicitly.

Key words. input transformations, scale-invariance, fold-detection

AMS subject classifications. 93B15, 93B20, 92B05

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1. Introduction. We study in this paper certain properties of the responses of dynamical systems to external inputs. Our results are purely mathematical and thus of wide applicability, but our motivation arises from molecular systems biology. Indeed, the behavior, adaptability, and survival of organisms depend critically upon their capability to formulate appropriate responses to chemical and physical environmental cues. In particular, signal transduction and gene regulatory networks in individual cells mediate the processing of measured chemical concentrations and physical conditions, such as ligand concentrations or stresses, eventually leading to regulatory changes in metabolism and gene expression. Often, the ultimate goal of these changes is to maintain a narrow range of concentration levels of vital quantities (homeostasis, adaptation) while at the same time appropriately reacting to changes in the environment (signal detection). Much theoretical, modeling, and analysis effort has been devoted to the understanding of these questions, traditionally in the context of steady-state responses to constant or step-changing stimuli.

In this work, we are concerned with questions that complement the analysis of simple temporal inputs and steady-state responses, focusing on certain properties of *transient* behaviors, both for simple stimuli like step changes and for more complex time-varying input profiles. The study of transient responses is of central concern in cell biology, since behavior at the time-scale of signaling may have important consequences for cell survival. Moreover, typical signals encountered by cells in their natural environments may well exhibit interesting temporal information, and thus characterizing responses to fluctuating temporal patterns

may provide new insights regarding cell behavior. Such responses and the analysis of transient behavior can also help rule out postulated mechanisms when tested through modern experimental tools which allow for fine spatiotemporal resolution in measurements. This type of model falsification is of course routine, but the broader framework allows for testing of a richer class of "phenotypes" and may thus help guide searches for yet-unknown molecular mechanisms.

The immediate motivation for this work is the recent discovery of an important transient property related to Weber's law in psychophysics: *fold-change detection* (FCD) in adapting systems is the property that scale uncertainty does not affect responses. FCD appears to play an important role in key signaling transduction mechanisms in eukaryotes, including the ERK and Wnt pathways, as well as in *Escherichia ecoli* and possibly other prokaryotic chemotaxis pathways [8, 3, 32]. The mathematical analysis of FCD was started in [9, 32]. In this paper, we provide further theoretical results regarding this property. Far more generally, we develop a necessary and sufficient characterization of adapting systems whose transient behaviors are *invariant under the action of a set (often, a group) of symmetries in their sensory field.* A particular instance is FCD, which amounts to invariance under the action of the multiplicative group of positive real numbers. Our main result is framed in terms of a notion which considerably extends equivariant actions of compact Lie groups.

This paper is organized as follows. Section 2 introduces the main definitions and the statement of the main result of this paper. Section 3 illustrates how the main result can be used to check invariance in a number of simple examples. Section 4 has the proof of the main theorem, as well as a self-contained review of some key concepts needed from nonlinear control theory. Section 5 fills in a stability proof that is needed in order to justify that several of our simple examples are indeed adapting systems. Section 6 compares feedforward and feedback architectures in the context of the "internal model principle" of control theory. Section 7 provides a simple result showing that search strategies in sensory fields subject to symmetries is invariant, provided that the underlying system itself is invariant.

2. Notation, definitions, and statement of main theorem. We study dynamical systems with inputs and outputs:

$$(1) \qquad\qquad \dot{z} = F(z, u), \qquad y = h(z),$$

where F, h are functions which describe respectively the dynamics and the read-out map. Equation (1) is meant as shorthand for

$$\frac{dz}{dt}(t) = F(z(t), u(t)), \qquad y(t) = h(z(t)).$$

Here, $u = u(t)$ is a generally time-dependent input (also called, depending on the context, a "stimulus" or "excitation") function, $z(t)$ is an n-dimensional vector of state variables, and $y(t)$ is the output ("response" or "reporter" variable).

The paradigm of studying systems in the form (1) is standard in control systems theory [36].

Typically, $y(t)$ is just a read-out of one of the components, $z_i(t)$, of $z(t)$. However, it is also sometimes more natural to take a more complicated function $y(t) = h(z(t))$ of the

coordinates of z than to just pick an individual z_i. For instance, suppose that $z_1(t)$ represents the concentration of the free form of an enzyme E, that $z_2(t)$ is the concentration of E complexed with some substrate, and that these two species are indistinguishable by a Western blot assay measurement. Then the sum $y = h(z) = z_1 + z_2$ might be the reporter variable of interest. More generally, the theory does not change substantially if we allow the output variable $y(t)$ to be a function of the current input as well as on the current state, $y = h(z, u)$. It is notationally and technically more convenient to take $y = h(z)$, so we do that here. In any event, one could add a new variable z_{n+1} to $z = (z_1, \ldots, z_n)$ and a differential equation $\varepsilon \dot{z}_{n+1} = h(z, u) - z_{n+1}$ which (provided $0 < \varepsilon \ll 1$) quickly equilibrates to $y = z_{n+1} = h(z, u)$, and with this small modification, now y depends only on a single coordinate, z_{n+1}, of an extended state vector $(z_1, \ldots, z_{n+1})$ and does not directly depend on the current input.

In order to describe positivity of variables as well as other constraints, we introduce the following additional notation. States, inputs, and outputs are constrained to lie in particular subsets, which we call $\mathbb{Z}$, $\mathbb{U}$, and $\mathbb{Y}$, respectively, of Euclidean spaces $\mathbb{R}^n, \mathbb{R}^m, \mathbb{R}^q$. For example, $\mathbb{U} = \mathbb{R}_{>0}$ means that the input values must be scalar ($m = 1$, $\mathbb{U} \subset \mathbb{R}^1$) and positive. The functions F, h are differentiable. We will assume that for each piecewise-continuous input $u : [0, \infty) \to \mathbb{U}$, and each initial state $\xi \in \mathbb{Z}$, there is a (unique) solution $z : [0, \infty) \to \mathbb{Z}$ of (1) with initial condition $z(0) = \xi$, which we write as

$$\varphi(t, \xi, u),$$

and we denote the corresponding output $y : [0, \infty) \to \mathbb{Y}$, given by $h(\varphi(t, \xi, u))$, as
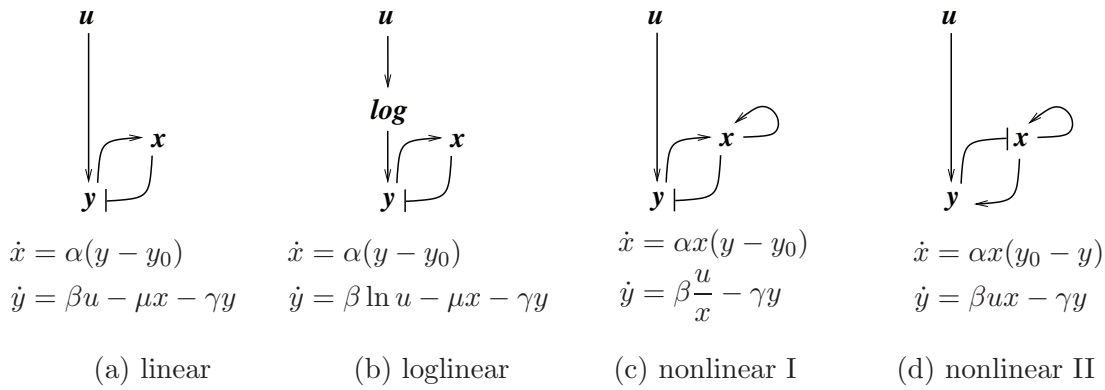
$$\psi(t, \xi, u)$$

(see [36] for more discussion, properties of ODEs, global existence of solutions, etc.).

Since we are interested in adapting systems, we will assume that for each constant input $u(t) \equiv \bar{u}$, there is a unique steady state of the system (which depends on the particular input). We denote this steady state by $\sigma(\bar{u})$. In other words, $\bar{z} = \sigma(\bar{u})$ is the unique solution of the algebraic equation $F(\bar{z}, \bar{u}) = 0$. Finally, we will assume that this steady state is *globally asymptotically stable* (GAS). This means that $\sigma(\bar{u})$ is Lyapunov stable and globally attracting for the system when the input is $u(t) \equiv \bar{u}$:
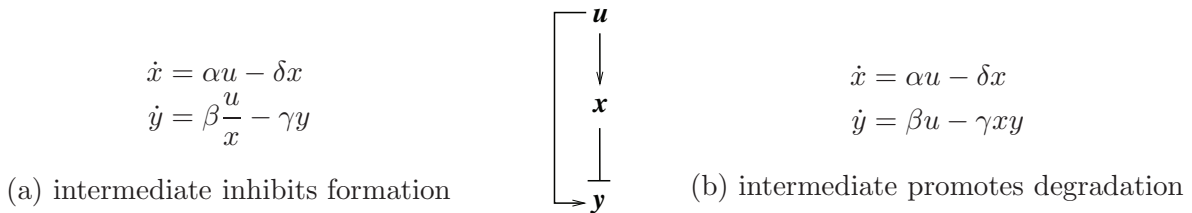
$$\lim_{t \to \infty} \varphi(t, \xi, u) = \sigma(\bar{u})$$

for every initial condition $\xi \in \mathbb{Z}$. Multistable systems may be considered as well, of course, but the definitions to follow become very cumbersome.

We will illustrate our results using the two sets of examples that are shown in Figures 1 and 2. In the diagrams shown in these figures, normal arrows indicate activation effects, and blunt edges denote inhibitions. In the respective equations, the vector $z = (z_1, z_2) = (x, y)$ has dimension $n = 2$, and the output is the second component, $h(z) = y$. In other words, in these examples, $F(z, u) = F(x, y, u)$ is a vector function with two components, which for $n = 2$ we write as $(f(x, y, u), g(x, y, u))$. We have that $f(x, y, u)$ is $\alpha(y - y_0)$ in Figure 1(a,b), $\alpha x(y - y_0)$ in Figure 1(c,d), and $\alpha u - \delta x$ in Figure 2, and $g(x, y, u)$ is $\beta u - \mu x - \gamma y$ in Figure 1(a), $\beta \ln u - \mu x - \gamma y$ in Figure 1(b), $\beta \frac{u}{x} - \gamma y$ in Figure 1(c) and Figure 2(a), $\beta u x - \gamma y$

$$\dot{x} = \alpha(y - y_0)$$
$$\dot{y} = \beta u - \mu x - \gamma y$$

(a) linear

$$\dot{x} = \alpha(y - y_0)$$
$$\dot{y} = \beta \ln u - \mu x - \gamma y$$

(b) loglinear

$$\dot{x} = \alpha x(y - y_0)$$
$$\dot{y} = \beta \frac{u}{x} - \gamma y$$

(c) nonlinear I

$$\dot{x} = \alpha x(y_0 - y)$$
$$\dot{y} = \beta u x - \gamma y$$

(d) nonlinear II

Figure 1. *Integral feedback systems (assuming $u > 0$ in (b) and $u, x > 0$ in (c,d)).*

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

(a) intermediate inhibits formation

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

(b) intermediate promotes degradation

Figure 2. *Incoherent feedforward loops (IFFLs) (assuming $u, x > 0$ in (a)).*

in Figure 1(d), and $\beta u - \gamma x y$ in Figure 2(b). The constants $\alpha, \beta, \dots$ are positive numbers. *We emphasize that our theory is valid for any dimension n;* these examples are picked only for illustration.

2.1. Perfect adaptation.

Definition 2.1. *The system* (1) perfectly adapts to constant inputs *provided that the steady-state output $h(\sigma(\bar{u}))$ equals some fixed $y_0 \in \mathbb{Y}$, independently of the particular input value $\bar{u} \in \mathbb{U}$.*

Adaptation (we will just say "adapt" instead of "perfectly adapt to constant inputs" in what follows) means that the steady-state output value is independent of the actual value of the input if the input is constant. This property may be achieved by differentiating the input signal before it is further processed by the system. However, differentiation is very sensitive to high-frequency noise, and in fact there is no need for differentiation to be explicitly performed: there are several alternative mechanisms, such as those represented in Figures 1 and 2, integral feedback and incoherent feedforward (IFFLs) loops, respectively, that are also capable of achieving adaptation.

In integral feedback systems, an internal "memory" variable keeps track of the accumulated (i.e., integrated) difference between the current value $y(t)$ of the response variable and its desired steady-state value y_0. A difference, or a nonlinear comparison such as a ratio, is performed between this memory variable and the current input, thus providing an "error" signal that is used to drive the feedback mechanism that brings the system back to its default value. Integral feedback is recognized as a key feature of perfectly adapting biological systems,

both at the physiological and cellular levels, such as, for example, in blood calcium homeostasis [5], in neuronal control of the prefrontal cortex [25], in the regulation of tryptophan in *E. coli* [43], and in *E. coli* chemotaxis [49].

Figure 1(a) shows the linear integral feedback configuration (PI, or proportional-integral, control) that is classically treated in control theory. When u is constant, the unique steady-state of this system is given by $\bar{x} = (\beta u - \gamma y_0)/\mu$ and $\bar{y} = y_0$. Thus, this system adapts: the steady-state value of y is independent of the input u. Moreover, since the eigenvalues of any matrix of the form

$$\begin{pmatrix} 0 & \alpha \\ -\mu & -\gamma \end{pmatrix}$$

are negative, it is clear that this system is globally asymptotically stable: $x(t) \to \bar{x}$ and $y(t) \to \bar{y} = y_0$ as $t \to \infty$. (Taking α and μ both negative instead of positive gives the same conclusions.) Two other integral feedback configurations, also perfectly adapting, are shown in Figure 1. In (b), a "loglinear system," the only difference from (a) is that the input is logarithmically preprocessed; this does not change the conclusions of adaptation and stability. In system (c), the memory variable feeds upon itself, and the ratio u/x, instead of a difference, is used to compare the current input and memory values. In system (d), the memory variable also feeds upon itself, and the product ux is used in the feedback term to y. Both (c) and (d) adapt (to $\bar{y} = y_0$), and $\bar{x} = \beta u/(\gamma \bar{y})$ in (c), $\bar{x} = \gamma \bar{y}/(\beta u)$ in (d). Stability is a bit more subtle and is based on a control-Lyapunov approach [36] that recasts (c) as a Hamiltonian system with added damping; see section 5. (The ratio "u/x" in (c) is not a natural choice for biological models; however, one may think of this term as an approximation of a Michaelis–Menten inhibition term $u/(K_m + x)$, with $K_m \ll 1$.)

A different type of architecture is based on *feedforward* as opposed to feedback interconnections. Feedforward circuits are ubiquitous in biology, as emphasized in [1], where they were shown to be overrepresented in *E. coli* gene transcription networks, compared to other "motifs" involving three nodes. Similar conclusions apply to certain control mechanisms in mammalian cells [20]. A large number of papers have been devoted to the signal-processing capabilities of the feedforward motif—notably [22], which looked into its properties as a "change detector" (essentially, sensitivity to changes in the magnitude of the input signal), and [4], which studied its optimality with respect to periodic inputs. Comparisons with other "three node" architectures with respect to the trade-off of sensitivity versus noise filtering are given in [12]. Other references on feedforward circuits include [31] (showing their overrepresentation at the interface of genetic and metabolic networks), [45] (classification of different subtypes of such circuits), and [15] (classification into "time-dependent" versus "dose-dependent" biphasic responses, which are in a sense the opposite of adapted responses).

In particular, in *incoherent feedforward loops* (IFFL), as in Figure 2, the input u directly helps promote formation of the reporter y and also acts as a delayed inhibitor, through an intermediate variable x. This "incoherent" counterbalance between a positive and a negative effect gives rise, under appropriate conditions, to adaptation. The reference [15] provides a large number of incoherent feedforward input-to-response circuits, which participate in EGF to ERK activation [30, 27], glucose to insulin release [24, 28], ATP to intracellular calcium release [21, 23], nitric oxide to NF-κB activation [29], microRNA regulation [40], and many others. Several varieties of IFFL circuits have been often proposed for perfect adaptation to
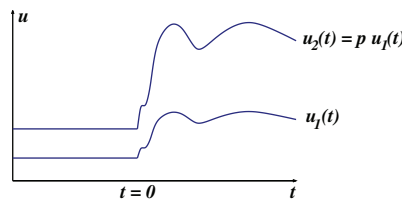
Figure 3. *Two scaled inputs.*

constant signals in biological systems. Notably, the IFFL shown in Figure 2(b), often called the "sniffer" [42, 38], appears in slightly modified forms in models for *Dictyostelium* chemotaxis and neutrophils [48, 18], microRNA-mediated loops [47], *E. coli* carbohydrate uptake via the carbohydrate phosphotransferase system [16], and other metabolic systems [44]. The work [2] shows experimentally and analytically that IFFLs are especially well suited to controlling protein expression under DNA copy variability. For both systems in Figure 2, the unique steady state, when the input u is constant, has coordinates $\bar{x} = \alpha u/\delta$ and $\bar{y} = y_0 = \beta\delta/(\alpha\gamma)$. Since $\bar{y}$ is independent of u, the system adapts. Global asymptotic stability for (a) follows from the fact that the x-subsystem is linear and stable, and the y-subsystem is a stable linear system driven by the converging signal u/x. For (b) (and several variations of this system), the GAS property is studied in [38].

2.2. Invariance. As mentioned in the introduction, we wish to study the invariance of outputs under input transformations. The original motivation was the study of the particular case of scale invariance, which is described through the following thought experiment.

2.2.1. A special case: Scale-invariance (FCD). Suppose that a system that adapts has had a chance to "preadapt" to a certain constant ("background") level $\bar{u}$ of the input, for $t < 0$, and that now we present the system with the new input $u(t)$, $t \geq 0$. Let $y_1(t)$ be the output function that results. Next imagine that we allowed the same system to preadapt, instead, to $p\bar{u}$ for $t < 0$, and we now present the system with $pu(t)$ for $t \geq 0$, where p is some positive scalar. Let $y_2(t)$ be the resulting output. Scale-invariance means that the outputs of the two experiments should be the same: $y_1(t) = y_2(t)$ for all $t > 0$. In other words, for any two inputs $u(t)$ and $pu(t)$, as in Figure 3, and no matter what positive number or "scale" p we picked, the *entire shape of the response*, including amplitude and duration, is identical. As an example, a step change in input from, say, a constant level 2 to a constant level 4 should result in precisely the same output as a step from constant level 5 to constant level 10 (we scaled everything by $p = 2.5$); see Figure 4(d). On the other hand, a change from, say, level 5 to 25 (which has a fold-change of 5 instead of 2) will typically lead to a different response. Thus, another way to describe this invariance property is to say that the only potentially detectable differences in response are due to fold changes, and this motivates the name *fold-change detection* (FCD) [9, 32]. FCD represents a particular type of adaptation in which there is with robustness to scale uncertainty, and it can be found at many levels of biological organization. A weak version is present in the Weber–Fechner law logarithmic sensing feature in psychophysics: many sensory systems (for weight, vision, hearing) produce responses whose maximal amplitude depends only on the *ratio* between the stimulus and a

(a) scaled inputs   (b) adapting system   (c) Weber-like   (d) FCD
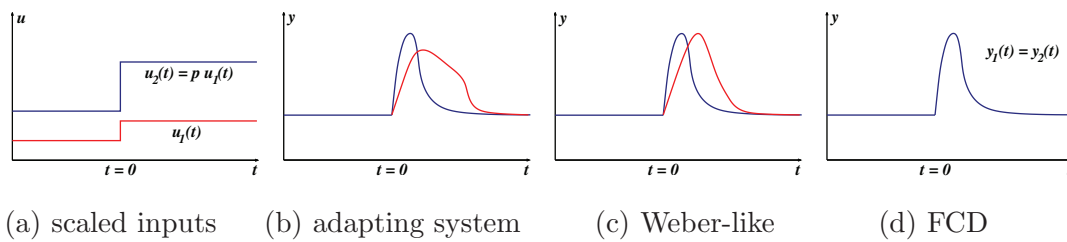
Figure 4. *In an adapting system, the response to scaled steps* (a) *returns to the same adapted value but may differ in time* (b) *or may produce the same maximal response* (c) *or even identical transients* (d)*).*

background or starting value, Figure 4(c). It was also recently discovered that the transient responses of several biological cellular signaling systems [3, 8] display FCD features.

We can formally define the FCD property as follows. Denoting by "πu" the input $t \mapsto pu(t)$ and by "$\pi \bar{u}$" the constant $p\bar{u}$, the equality of outputs

$$(2) \qquad\qquad \psi(t, \sigma(\bar{u}), u) \;=\; \psi(t, \sigma(\pi\bar{u}), \pi u)$$

should hold for all possible $p > 0$, times $t \geq 0$, and all constant inputs $\bar{u} \in \mathbb{U}$ and inputs $u = u(t)$ with values in $\mathbb{U}$. (Observe that the requirement that $\bar{u}$ and u take values in $\mathbb{U}$ serves to impose constraints such as, for example, positivity.)

Equipped with this formalism, we may study a far more general question, namely, invariance with respect to any set of transformations—not merely scalings but also far more general invariances to sensory field changes: translational, rotational, or reflection symmetries, anisotropic dilations, projective transformations, and so forth.

2.2.2. General case. Suppose we are given a set $\mathcal{P}$ of continuous and onto input transformations $\pi : \mathbb{U} \to \mathbb{U}$:

$$\{\pi : \mathbb{U} \to \mathbb{U} , \ \pi \in \mathcal{P}\} \ .$$

For an input $u(t)$, we denote by "πu" the function of time that equals $\pi(u(t))$ at time t. (For notational simplicity, we write "πu" rather than "$\pi(u)$" when there is no risk of confusion, but we emphasize that there is no requirement that the mapping π be linear.) The continuity assumption is only made in order to ensure that πu is a piecewise-continuous function of time if u is, as technically required when using it as an input to a differential equation. The ontoness assumption, that is, $\pi\mathbb{U} = \mathbb{U}$, is made for technical reasons in the proof of the main theorem.

Definition 2.2. The system (1) *has* response invariance to symmetries in $\mathcal{P}$ *or, for short, is* $\mathcal{P}$-invariant *if* (2) *holds for all* $t \geq 0$, *all inputs* $u = u(t)$, *all constants* $\bar{u}$, *and all transformations* $\pi \in \mathcal{P}$.

Under the assumption that the action of $\mathcal{P}$ is transitive, i.e., for any two $\bar{u}, \bar{v} \in \mathbb{U}$, there is some π such that $\bar{v} = \pi\bar{u}$, $\mathcal{P}$-invariance implies perfect adaptation, because the outputs in (2) must coincide at time zero, and any two inputs can be mapped to each other.

Some examples are as follows. In the special case of the transitive action with $\mathcal{P} = \mathbb{U} = \mathbb{R}_{>0}$ and $\pi u = pu$, we obtain the FCD property. Another example of a set of symmetries $\mathcal{P}$ is as follows. Suppose that $\mathbb{U} = \mathbb{R}^n$ and $\mathcal{P}$ consists of all the transformations $\pi_R(u) := Ru$ for $R \in SO(n)$, the special orthogonal group. That is, we transform inputs by multiplication

with a rotation matrix R. In dimension 2 or 3, this can be used to impose the requirement that a visual sensing system should react the same if the visual field is rotated. Another slightly different example would be that in which $\mathcal{R} \in O(n)$, the orthogonal group, meaning that we want invariance with respect to reflections as well as rotations.

2.3. Equivariances. We now introduce a concept that leads to an effective criterion for checking FCD, and more generally arbitrary $\mathcal{P}$-invariance, *without having to compute the solutions* $\psi(t, \sigma(\pi\bar{u}), \pi u)$. We make the definition for arbitrary systems as in (1), $\dot{z} = F(z, u)$, $y = h(z)$.

Definition 2.3. *Given a system* (1) *and a set of input transformations* $\mathcal{P}$, *a parametrized set of differentiable mappings* $\{\rho_\pi : \mathbb{Z} \to \mathbb{Z}\}_{\pi \in \mathcal{P}}$ *is a* $\mathcal{P}$-equivariance family *provided that, for each* π,

$$(3) \qquad F(\rho_\pi(z), \pi u) = \rho_\pi'(z)F(z, u) \quad and \quad h(\rho_\pi(z)) = h(z) \quad for\ all\ z \in \mathbb{Z},\ u \in \mathbb{U}$$

($\rho_\pi' = $ *Jacobian matrix of* ρ_π). *If* (3) *holds, we say that the system is* ρ_π-equivariant under the input transformation π.

The first part of (3) is a *first order quasilinear PDE* on the n components of the vector function ρ_π for each $u \in U$, and the second part is an additional algebraic constraint on these components.

We omit the subscript π when clear from the context. Quasi-linear first order PDEs appear in related questions in control theory, for instance [36], in the Hamilton–Jacobi–Bellman approach to optimal control and in feedback linearization based on Frobenius's theorem. They may in principle be solved using the method of characteristics [6].

Our notion of equivariance generalizes a mathematical concept fundamental in group theory, and specifically in the symmetry analysis of nonlinear dynamical systems [10, 11] with the same name. A parametrized vector field F is said to be ρ-equivariant, or ρ is a symmetry of F, if, for each solution $z(t)$ of $\dot{z} = F(z, u)$, $\rho(z(t))$ is also a solution. This property is equivalent to the PDE $F(\rho(z), u) = \rho'(z)F(z, u)$ [10] that is part of the equivariance definition when $\pi = $ identity. We are generalizing this concept in several ways. First, we must consider the far more general case $\pi \neq$ identity; in fact, in our context, $\pi = $ identity is not of any interest whatsoever, since we are precisely interested in the effect of the input transformations. Second, it is essential to our definition that we include the algebraic "boundary condition" $h(\rho_\pi(z)) = h(z)$, Finally, in dynamical systems one typically studies equivariances only with respect to Lie group actions. Moreover, since compact Lie groups acting on Euclidean space can be identified with subgroups of the orthogonal group $O(n)$, one finds in the classical definitions [10] only linear maps $\rho'(z) = \gamma z$ with $\gamma \in O(n)$ being considered (so $\rho'(z) = \gamma$).

2.4. Statement of main theorem. Our main result is as follows. It is proved in section 4.

Theorem 1. *An analytic and irreducible system is* $\mathcal{P}$-*invariant if and only if there exists a* $\mathcal{P}$-*equivariance family.*

An analytic system is one for which all the functions defining the system are real-analytic on the state coordinates. This means that they can be expanded into locally convergent power series around each point. Every function made up of elementary algebraic compositions of elementary functions is analytic; this includes all expressions involving polynomials and, more generally, any well-defined (no poles) rational functions (so mass-action kinetics and Hill-type models with any integer Hill coefficients are allowed) as well as trigonometric functions,

exponentials, and logarithms in any combination. All our examples are analytic as long as we restrict expressions such as u/x to $x > 0$ (or $x < 0$), so that there are no poles.

An irreducible system is one for which no conservation laws restrict motions to proper submanifolds (accessibility property) and no pairs of distinct states give rise to the same input/output behavior (observability property). We define precisely accessibility and observability in section 4. Irreducibility is a weak technical assumption; we will show that these two properties hold for all the systems in Figures 1 and 2. Irreducible systems, which are also called "minimal" or "canonical" in the control theory literature, are minimal in the sense that no lower-dimensional subsystem has an identical input/output behavior [39, 34, 35, 36]. Analogous, but simpler, notions of irreducibility also appear in areas such as group representations (Schur's lemma).

3. Examples of finding symmetries using the main theorem. We show here how Theorem 1 allows one to immediately determine invariance properties for large classes of two-dimensional systems, including the integral feedback and feedforward examples shown in Figures 1 and 2. In all these cases, the PDE for equivariances, if there is one, can be easily solved for in closed form. We consider two-dimensional systems with output equal to one of the coordinates. We write $z = (x, y)$, $F(z, u) = (f(x, y, u), g(x, y, u))$,

(4a) $$\dot{x} = f(x, y, u),$$

(4b) $$\dot{y} = g(x, y, u),$$

(4c) $$h(x, y) = y,$$

and we wish to determine for which possible input set mappings $\pi : \mathbb{U} \to \mathbb{U}$ there is an associated equivariance $\rho = \rho_\pi$. We drop the subscript and write $\rho = (\rho^x, \rho^y)$. Since $h(x, y) = y$, the condition $h(\rho(x)) = h(x)$ says that $\rho^y(x, y) = y$. Thus finding ρ is equivalent to finding its x-component, a function ρ^x that satisfies

$$f(\rho^x(x, y), y, \pi u) = \frac{\partial \rho^x}{\partial x}(x, y)\, f(x, y, u),$$
$$g(\rho^x(x, y), y, \pi u) = g(x, y, u)$$

(there is no derivative in the second equation because $\partial \rho^y / \partial y = 1$). This is a scalar first order quasi-linear PDE subject to a side algebraic "boundary condition."

We concentrate next on two special cases that cover many examples of interest. Particular instances of the first case are the systems in Figures 1(c), (d) and 2(a). A particular instance of the second case is the system in Figure 1(a). We assume that the systems in both of the next lemmas are irreducible. For all our examples, irreducibility is checked in section 4.

Lemma 3.1. *Suppose that*
$$g(x, y, u) \;=\; G(u^\beta x^\mu, y)$$

and $G(\cdot, y)$ is one-to-one for each fixed y (assuming $x > 0$ if $\mu < 0$ or $u > 0$ if $\beta < 0$). Then, the only possible symmetries are fold-changes $\pi u = pu$. Furthermore, the system is invariant under a set $\mathcal{P}$ of such symmetries if and only

$$p^{-\beta/\mu} f(x, y, u) \;=\; f(p^{-\beta/\mu} x, y, pu) \;\; for\ all\ x, y, u,$$

and each p in the set.

In the special case in which $\beta = 1$ and $\mu = -1$, that is, if g depends on the ratio u/x, this means that f must satisfy

$$p\,f(x, y, u) \;=\; f(px, y, pu),$$

and in the special case $\beta = \mu = 1$, f must satisfy $p^{-1}f(x, y, u) = f(p^{-1}x, y, pu)$. In either special case, if f is independent of u, then response-invariance to all scaling transformations $(\mathcal{P} = \mathbb{R}_{>0})$ is equivalent to the requirement that f be homogeneous of degree 1 in x.

Proof. Since G is one-to-one on y,

$$G\left((\pi u)^\beta (\rho^x(x,y))^\mu, y\right) \;=\; g(\rho^x(x,y), y, \pi u) \;=\; g(x, y, u) \;=\; G\left(u^\beta x^\mu, y\right) \quad \text{for all } x, y, u$$

implies that

$$(\pi u)^\beta (\rho^x(x,y))^\mu \;=\; u^\beta x^\mu \ \text{ for all } x, y, u$$

or, equivalently,

$$\left(\frac{\pi u}{u}\right)^\beta \;=\; \left(\frac{\rho^x(x,y)}{x}\right)^{-\mu} \ \text{ for all } x, y, u\,.$$

Define

$$p \;:=\; \left(\frac{\pi u_0}{u_0}\right)^{\frac{1}{\beta}}$$

for any fixed but arbitrary element $u_0 \in \mathbb{U}$. It follows that

$$\pi u = pu \ \text{ and } \ \rho^x(x,y) = p^{-\beta/\mu}x \ \text{ for all } x, y, u\,,$$

from which all the conclusions are immediate. ∎

Lemma 3.2. *Suppose that*

$$g(x, y, u) \;=\; G(\mu x + \beta u, y)$$

and $G(\cdot, y)$ is one-to-one for each fixed y. Then, the only possible symmetries are translations $\pi u = p + u$. Furthermore, the system is invariant under a set $\mathcal{P}$ of such symmetries if and only if

$$f(x, y, u) \;=\; f(-(\beta/\mu)p + x, y, p + u) \ \text{ for all } x, y, u\,,$$

and each p in the set.

Proof. Since G is one-to-one on y,

$$G\left(\mu\rho^x(x,y) + \beta\pi u, y\right) \;=\; g(\rho^x(x,y), y, \pi u) \;=\; g(x, y, u) \;=\; G\left(\mu x + \beta u, y\right)$$

implies that

$$\mu\rho^x(x,y) + \beta\pi u \;=\; \mu x + \beta u \ \text{ for all } x, y, u$$

or, equivalently,

$$\pi u - u \;=\; -\frac{\mu}{\beta}(\rho^x(x,y) - x) \ \text{ for all } x, y, u\,.$$

Define

$$p \;:=\; \pi u_0 \;-\; u_0$$

for any fixed but arbitrary element $u_0 \in \mathbb{U}$. It follows that

$$\pi u = p + u \text{ and } \rho^x(x, y) = -\frac{\beta p}{\mu} + x \text{ for all } x, y, u,$$

from which all the conclusions are immediate. ∎

We can now quickly classify the examples shown in Figures 1 and 2.

The linear integral feedback system in Figure 1(a) fits the form in Lemma 3.2, so it can only be $\mathcal{P}$-invariant with respect to transformations $u \mapsto p + u$, and the only possible equivariance is $\rho^x(x, y) = x + \beta p/\mu$. Since $f(x, y, u)$ is independent of x and u, this is indeed an equivariance. This system is $\mathcal{P}$-invariant with respect to translations.

The systems in Figure 1(c), (d) and Figure 2(a) all fit the form in Lemma 3.1, so they can only be $\mathcal{P}$-invariant with respect to scaling transformations $u \mapsto pu$, and the only invariance is equivalent to the condition

$$p^\varepsilon f(x, y, u) = f(p^\varepsilon x, y, pu),$$

where ε is $+1$ and -1 for the systems in Figure 1(c), (d), respectively, and is $+1$ for the system in Figure 2(a). In Figure 1(c), (d), the value of ε is irrelevant, because $f(x, y, u)$ is independent of u and is homogeneous of degree 1 in x, so the property holds. In Figure 2(a), f is homogeneous of degree 1 in x and u simultaneously, so again the property holds. In summary, all three systems are $\mathcal{P}$-invariant with respect to scalings $\mathcal{P}$.

The log-linear system in Figure 1(b) is also $\mathcal{P}$-invariant for the set of scalings. This may be shown with the equivariance $\rho^x(x, y) = x + \beta \ln p/\mu$.

We remark that, generalizing Figure 1(a) and Figure 2(a), any n-dimensional linear system $\dot{x} = Ax + bu$ with a stable A and $h(x) = cx$ such that $cA^{-1}b = 0$ (i.e., its DC gain is zero) is $\mathcal{P}$-invariant for $u \mapsto p + u$, with $\rho(x) = x - A^{-1}bp$. The corresponding log-linear system, in which $\dot{x} = Ax + b \ln u$, is invariant with respect to scalings.

Finally, we study the "sniffer" IFFL shown in Figure 2(b). The equation $g(\rho^x(x, y), y, \pi u) = g(x, y, u)$ means that $\beta \pi u - \gamma \rho^x(x, y)y = \beta u - \gamma xy$ for all x, y, u, and thus evaluating at $y = 0$ it follows that $\pi u = u$ (assuming $\beta \neq 0$). So no nontrivial $\mathcal{P}$-equivariance exists. By the necessity part of Theorem 1, we conclude that this system is *not $\mathcal{P}$-invariant for any possible $\mathcal{P}$*.

Remark 3.3. Although derived as necessary and sufficient for two-dimensional systems, the conditions given in Lemmas 3.1 and 3.2 are sufficient for higher-dimensional systems as well. For example, consider a system of the form shown in (4), except that now x has dimension $n - 1$ (but the inputs and outputs u, y have dimension one). Suppose that

$$g(x, y, u) = G(u^\beta x_1^{\mu_1} x_2^{\mu_2} \dots x_{n-1}^{\mu_{n-1}}, y)$$

and pick $\beta_1, \dots, \beta_{n-1}$ such that $\sum \beta_i = \beta$. Consider the equivariance $\rho(x, y)$ with coordinates

$$\rho_i(x, y) = p^{-\frac{\beta_i}{\mu_i}} x_i, \quad i = 1, \dots, n - 1,$$

and $\rho_n(x, y) = y$. It is then easy to check that, if the coordinates f_i, $i = 1, \dots, n - 1$, of the vector field f satisfy the homogeneity property

$$p^{-\frac{\beta_i}{\mu_i}} f_i(x, y, u) = f_i\left(p^{-\frac{\beta_1}{\mu_i}} x_1, \dots, p^{-\frac{\beta_{n-1}}{\mu_{n-1}}} x_{n-1}, y, pu\right),$$

then the system has scale-invariance (FCD with respect to $\pi u = pu$).

Often, higher-dimensional systems can be simplified, using model reduction techniques such as singular perturbation, to lower dimensional systems. This is a standard procedure in molecular biology, for example, where different processes (such as signaling and transcription) operate at very separated time scales. If a symmetry invariance property holds for the reduced system, one may expect an approximate symmetry condition to hold for the original system. The next remark illustrates this principle.

Remark 3.4. Interestingly, although not invariant, the system in Figure 2(b), as well as many other examples from [38], satisfy an "approximate" invariance property in the following sense. Suppose that the y variable varies faster than the x variable, so that one may make a quasi–steady-state approximation $\beta u - \gamma xy = 0$. This allows one to reduce to a one-dimensional system $\dot{x} = \alpha u - \delta x$ with output $y = (\beta/\gamma)(u/x)$. Scalings $u \mapsto pu$ and $x \mapsto px$ preserve the equations, thus showing that the reduced system is $\mathcal{P}$-invariant with respect to scaling. (More generally, given a linear system with an output that depends on the ratio x_i/x_j of two variables x_i and x_j, one obtains scale-invariance.) This means that the original system is "close" to having the scale-invariance property. A precise statement can be made using singular perturbation theory. This observation was made several years ago in the context of models of *Dictyostelium* chemotaxis and neutrophils [13].

Remark 3.5. An example with vector inputs is as follows. Suppose that we consider a vector integral feedback system of the following form:

$$\dot{x} = (y - y_0)x,$$
$$\dot{y} = G(\langle u, x \rangle, y)$$

with output y. The state-space $\mathbb{Z}$ is $\mathbb{R}^{n+1}$: x and u are n-dimensional real vectors and y is scalar, and $\langle u, x \rangle$ denotes the inner (dot) product of x and u. We claim that this system is $\mathcal{P}$-invariant with respect to the rotation group $\mathcal{P} = SO(n)$. Indeed, for each $R \in SO(n)$ we may define the equivariance $\rho_R(x, y)$ by mapping (x, y) to the $n + 1$-vector with the first n components Rx and the last component y. Since ρ_R is linear, its partial derivative with respect to y is 1, and its Jacobian with respect to the x variables is R, we need only check that $R(y - y_0)x = (y - y_0)Rx$, which is true because $y - y_0$ is a scalar, and that $G(\langle Ru, Rx \rangle, y) = G(\langle u, x \rangle, y)$, which is true because R is a special orthogonal matrix. The exact same proof works for the larger orthogonal group (reflection/rotations) $O(n)$. We can also generalize to the case when $\mathcal{P}$ consists of completely arbitrary nonsingular transformations ($R \in GL(n)$). In that case, we would take $\rho_R(x) = (R^{\mathrm{T}})^{-1}x$ (inverse transpose) and use that $\langle Ru, (R^{\mathrm{T}})^{-1}x \rangle = \langle u, x \rangle$.

4. Details and proof of main theorem. The main theorem is stated for systems that are irreducible, meaning that both the accessibility and the observability properties must hold. We define precisely and discuss these two properties next.

4.1. The accessibility property and the accessibility Lie algebra. In order to define accessibility, we will need to employ the notion of the accessibility Lie algebra associated to a system (1), which we briefly review here; see [36] for further details and basic properties. Recall first the notion of the Lie bracket of two vector fields on a manifold, specialized here to open subsets of Euclidean space $\mathbb{R}^n$: for any two differentiable vector fields $f, g : \mathbb{Z} \to \mathbb{R}^n$

defined in an open set $\mathbb{Z} \subseteq \mathbb{R}^n$, their *Lie bracket* is the new vector field

$$[f, g] : \mathbb{Z} \to \mathbb{R}^n$$

defined by the formula

$$[f, g] := \frac{\partial g}{\partial x} f - \frac{\partial f}{\partial x} g.$$

When f, g are twice differentiable, $[f, g]$ is again differentiable, and one can take further brackets such as $[[f, g], g]$. More generally, if the vector fields are smooth (that is, infinitely differentiable), one may take any number of iterated brackets.

For any subset of smooth vector fields $\mathcal{F}$ on $\mathbb{Z}$, the Lie algebra generated by $\mathcal{F}$, denoted as $\mathcal{F}_{\mathrm{LA}}$, is defined as the intersection of all the Lie algebras of vector fields which contain $\mathcal{F}$. (The set of all such algebras is nonempty, since it includes the algebra of all vector fields on $\mathbb{Z}$.) Since the intersection of any family of Lie algebras is also a Lie algebra, it follows that $\mathcal{F}_{\mathrm{LA}}$ is the smallest Lie algebra of vector fields which contains the set $\mathcal{F}$, and it coincides with the set obtained as follows. Denote $\mathcal{F}_0 := \mathcal{F}$ and, recursively, $\mathcal{F}_{k+1} := \{[f, g] \,|\, f \in \mathcal{F}_k, g \in \mathcal{F}\}$, $k = 0, 1, 2, \ldots$, as well as $\mathcal{F}_\infty := \bigcup_{k \geq 0} \mathcal{F}_k$. Then, $\mathcal{F}_{\mathrm{LA}}$ is equal to the linear span of $\mathcal{F}_\infty$. (See [36, Lemma 4.1.4] for a proof of this equality.) In summary, every element in the Lie algebra generated by the set $\mathcal{F}$ can be expressed as a linear combination of iterated brackets of the form

$$[f_\ell, \ldots, [f_3, [f_2, f_1] \ldots]]$$

for some $f_i \in \mathcal{F}$.

If the system (1) is such that the state-space $\mathbb{Z}$ is an open subset of $\mathbb{R}^n$ and all the vector fields $\mathcal{F} = \{f(\cdot, u), u \in \mathbb{U}\}$ are smooth, we define its *accessibility Lie algebra* as $\mathcal{F}_{\mathrm{LA}}$. For each $z_0 \in \mathbb{Z}$, one may consider the subspace $\mathcal{F}_{\mathrm{LA}}(z_0) := \{X(z_0), X \in \mathcal{F}_{\mathrm{LA}}\}$ of $\mathbb{R}^n$. The *accessibility rank condition* is said to hold for the system if

$$\mathcal{F}_{\mathrm{LA}}(z_0) = \mathbb{R}^n \quad \text{for every } z_0 \in \mathbb{Z}.$$

For analytic systems, the accessibility condition is equivalent to the property that the set of points reachable from any given state z has a nonempty interior, as follows by a result of Sussmann [39] that generalizes Nagano's theorem [26] on integrability of involutive families of vector fields; see a proof and more details in the textbook [36].

In the special case of input-affine systems, i.e., those defined by differential equations

(5) $$\dot{z} = g_0(z) + u_1 g_1(z) + \cdots + u_m g_m(z),$$

where g_i, $i = 0, \ldots, m$ are $m + 1$ vector fields, it is not necessary to use all the vector fields in $\mathcal{F}$ when generating $\mathcal{F}_{\mathrm{LA}}$, since $\mathcal{F}_{\mathrm{LA}}(z_0) = \{g_0, \ldots, g_m\}_{\mathrm{LA}}(z_0)$ for all z_0. See [36, Lemma 4.3.3] for a proof. (The technical condition in that lemma that zero must belong to the input set $\mathbb{U}$ fails when inputs are asked to be strictly positive, as in many of our applications. However, the lemma also holds when $\mathbb{U}$ consists of positive inputs, since a continuity argument makes clear that one obtains the same spans if 0 is added to $\mathbb{U}$.)

For example, we show next that all the systems in Figures 1 and 2, which are all input-affine (with $m = 1$), satisfy the accessibility rank condition.

$\dot{x} = \alpha(y - y_0), \dot{y} = \beta u - \mu x - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha(y - y_0) \\ \mu x - \gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \beta \end{pmatrix}, \qquad [g_0, g_1] = \begin{pmatrix} -\alpha\beta \\ \gamma\beta \end{pmatrix}.$$

Since the determinant of $(g_1, [g_0, g_1])$ equals $\alpha\beta^2 \neq 0$ at every x, the accessibility rank condition holds.

$\dot{x} = \alpha(y - y_0), \dot{y} = \beta \ln u - \mu x - \gamma y$. This is the same as the previous case, in so far as the accessibility condition is concerned, because the set of vector fields $\mathcal{F}$ is identical to the previous one.

$\dot{x} = \alpha x(y - y_0), \dot{y} = \beta \frac{u}{x} - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha x(y - y_0) \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \frac{\beta}{x} \end{pmatrix}, \qquad [g_0, g_1] = \begin{pmatrix} -\alpha\beta \\ -\frac{\alpha\beta}{x}(y - y_0) + \frac{\beta\gamma}{x} \end{pmatrix}.$$

Since the determinant of $(g_1, [g_0, g_1])$ equals $\alpha\beta^2/x \neq 0$ at every x, the accessibility rank condition holds.

$\dot{x} = \alpha x(y_0 - y), \dot{y} = \beta u x - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha x(y - y_0) \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \beta x \end{pmatrix}, \qquad [g_0, g_1] = \begin{pmatrix} -\alpha\beta x^2 \\ \alpha\beta x(y - y_0) + \beta\gamma x \end{pmatrix}.$$

Since the determinant of $(g_1, [g_0, g_1])$ equals $\alpha\beta^2 x^3 \neq 0$ at every x, the accessibility rank condition holds.

$\dot{x} = \alpha u - \delta x, \dot{y} = \beta \frac{u}{x} - \gamma y$. Here

$$g_0 = \begin{pmatrix} -\delta x \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} \alpha \\ \frac{\beta}{x} \end{pmatrix}, \qquad [g_0, g_1] = \begin{pmatrix} \alpha\delta \\ \frac{\beta\delta}{x} + \frac{\beta\gamma}{x} \end{pmatrix}.$$

Since the determinant of $(g_1, [g_0, g_1])$ equals $\frac{\alpha\beta\gamma}{x} \neq 0$ at every x, the accessibility rank condition holds.

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

$$g_0 = \begin{pmatrix} -\delta x \\ -\gamma x y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} \alpha \\ \beta \end{pmatrix},$$

$$[g_0, g_1] = \begin{pmatrix} \alpha\delta, \\ \alpha\gamma y + \beta\gamma x \end{pmatrix}, \qquad [g_1, [g_0, g_1]] = \begin{pmatrix} 0 \\ 2\alpha\beta\gamma \end{pmatrix}.$$

Since the determinant of $(g_1, [g_1, [g_0, g_1]])$ equals $2\alpha^2\beta\gamma \neq 0$ at every x, the accessibility rank condition holds.

4.2. The observability property. A system (1) is said to be observable, or to have the *observability property*, if no two distinct states can give rise to an identical temporal response to all possible inputs. Formally,

$$\psi(t, z_0, u) = \psi(t, \tilde{z}_0, u) \text{ for all } u, t \quad \Rightarrow \quad z_0 = \tilde{z}_0.$$

For analytic input-affine systems (5) with output $h = (h_1, \ldots, h_p)$, one can restate the observability property as follows. The *observation space* $\mathcal{O}$ associated to the system is the vector space spanned by the set of all functions of the type

$$(6) \qquad\qquad\qquad\qquad\qquad L_{g_{i_1}} \ldots L_{g_{i_k}} h_j$$

(called the elementary observables of the system) over all possible sequences $i_1, \ldots, i_k$, $k \geq 0$, out of $\{0, \ldots, m\}$ and all $j = 1, \ldots, p$, where $L_X H = \nabla H \cdot X$ is the directional or Lie derivative of the function H with respect to the vector field X and one understands $L_Y L_X H$ as the iteration $L_Y(L_X H)$. We include the case in which $k = 0$, in which case the expression in (6) is simply h_j. Two states z_1 and z_2 are said to be *separated by* $\mathcal{O}$ if there exists some $H \in \mathcal{O}$ such that $H(z_1) \neq H(z_2)$. Observability is equivalent to the property that any distinct two states can be separated by the observation space. See [36, Remark 6.4.2] for a proof and discussion.

For example, it is very easy to see that all the systems in Figures 1 and 2, which are all input-affine (with $m = 1$ and $p = 1$), satisfy the observability condition. We must prove that if $H(z_1) = H(z_2)$ for every elementary observable (6), then $z_1 = z_2$. Since already with $k = 0$ we have that $y_1 = h(z_1) = h(z_2) = y_2$, it remains only to show that some linear combination of observables gives a one-to-one function of x. Note that $\nabla h = (0, 1)$, so the dot product $L_g H = \nabla H.g$ simply picks out the second coordinate of g.

$\dot{x} = \alpha(y - y_0), \dot{y} = \beta u - \mu x - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha(y - y_0) \\ \mu x - \gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \beta \end{pmatrix}, \qquad L_{g_0} h = \mu x - \gamma y.$$

Since $L_{g_0} h + \gamma h = \mu x$ is one-to-one on x, the observability condition holds.

$\dot{x} = \alpha(y - y_0), \dot{y} = \beta \ln u - \mu x - \gamma y$. This is the same as the previous case, in so far as the observability condition is concerned, because $\psi(t, z_0, u)$ is the same as $\psi(t, z_0, \log u)$ for the previous system.

$\dot{x} = \alpha x(y - y_0), \dot{y} = \beta \frac{u}{x} - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha x(y - y_0) \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \frac{\beta}{x} \end{pmatrix}, \qquad L_{g_1} h = \frac{\beta}{x}.$$

Since $L_{g_1} h$ is one-to-one on x, the observability condition holds.

$\dot{x} = \alpha x(y_0 - y), \dot{y} = \beta u x - \gamma y$. Here

$$g_0 = \begin{pmatrix} \alpha x(y - y_0) \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} 0 \\ \beta x \end{pmatrix}, \qquad L_{g_1} h = \beta x.$$

Since $L_{g_1} h$ is one-to-one on x, the observability condition holds.

$\dot{x} = \alpha u - \delta x, \dot{y} = \beta \frac{u}{x} - \gamma y$. Here

$$g_0 = \begin{pmatrix} -\delta x \\ -\gamma y \end{pmatrix}, \qquad g_1 = \begin{pmatrix} \alpha \\ \frac{\beta}{x} \end{pmatrix}, \qquad L_{g_1} h = \frac{\beta}{x}.$$

Since $L_{g_1} h$ is one-to-one on x, the observability condition holds.

$\dot{x} = \alpha u - \delta x, \dot{y} = \beta u - \gamma xy$. Here

$$g_0 = \begin{pmatrix} -\delta x \\ -\gamma xy \end{pmatrix}, \qquad g_1 = \begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \qquad L_{g_0} h = -\gamma xy, \qquad L_{g_1} L_{g_0} h = -\alpha \gamma y - \beta \gamma x.$$

Since $L_{g_1} L_{g_0} h + \alpha \gamma h y = -\beta \gamma x$ is one-to-one on x, the observability condition holds. (Observe that we cannot argue simply with $L_{g_0} h$, because the function $-\gamma xy$ is not one-to-one on x in the special case $y = 0$.)

4.3. Proof of Theorem 1. We must prove that, for analytic and irreducible systems, existence of a $\mathcal{P}$-equivariance family is sufficient as well as necessary for $\mathcal{P}$-invariance.

Sufficiency. Suppose we are given a $\pi \in \mathcal{P}$ and an associated equivariance $\rho = \rho_\pi$. We claim that the steady-state mapping σ interlaces π and its associated $\rho = \rho_\pi$ in the sense that

$$\rho(\sigma(\bar{u})) = \sigma(\pi(\bar{u}))$$

for every $\bar{u} \in \mathbb{U}$. Indeed, from the property $F(\rho(z), \pi u) = \rho'(z) F(z, u)$, applied with any constant input $u(t) \equiv \bar{u}$, and $z = \sigma(\bar{u})$, it follows in particular that $F(\rho(\sigma(\bar{u})), \pi \bar{u}) = \rho'(\sigma(\bar{u})) F(\sigma(\bar{u}), \bar{u})$. Now, $F(\sigma(\bar{u}), \bar{u}) = 0$, by definition of $\sigma(\bar{u})$, so also $F(\rho(\sigma(\bar{u})), \pi \bar{u}) = 0$, which means that $\rho(\sigma(\bar{u}))$ is the steady state $\sigma(\pi \bar{u})$ corresponding to the constant input $\pi \bar{u}$, as we claimed.

Now suppose that $z(t) = \varphi(t, \sigma(\bar{u}), u)$ solves $\dot{z} = F(z, u)$ with initial condition $z(0) = \sigma(\bar{u})$. Consider $z_*(t) = \rho_\pi(z(t))$. Computing the derivative $\dot{z}_*(t)$ and using the chain rule,

$$\dot{z}_*(t) = \rho_\pi'(z(t)) \dot{z}(t) = \rho_\pi'(z(t)) F(z(t), u(t)) = F(\rho_\pi(z(t)), \pi u(t)) = F(z_*(t), \pi u(t)).$$

Moreover, $z_*(0) = \rho_\pi(\sigma(\bar{u})) = \sigma(\pi \bar{u})$ by the interlacing property. It follows that z_* is the solution with initial condition corresponding to the "preadapted" value $\sigma(\pi \bar{u})$ and the input $\pi(u(t))$, i.e., $z_*(t) = \varphi(t, \sigma(\pi \bar{u}), \pi u)$. We conclude that

$$\psi(t, \sigma(\bar{u}), u) = h(z(t)) = h(\rho_\pi(z(t))) = \psi(t, \sigma(\pi \bar{u}), \pi u).$$

Necessity. Suppose we are given an analytic and irreducible system that is $\mathcal{P}$-invariant. Fix any $\pi \in \mathcal{P}$. We must find a differentiable mapping $\rho = \rho_\pi : \mathbb{Z} \to \mathbb{Z}$ such that (3) holds: $F(\rho(z), \pi u) = \rho'(z) F(z, u)$ and $h(\rho(z)) = h(z)$. Let us consider a modified system in which $G(z, u) = F(z, \pi u)$ and with the same output $k(z) = h(z)$. Then (3) asks that

$$(7) \qquad \rho'(z) F(z, u) = G(\rho(z), u), \quad k(\rho(z)) = h(z) \qquad \text{for all } z \in \mathbb{Z}, \; u \in \mathbb{U}.$$

In the language of [39], property (7) says that ρ should be an isomorphism between the two systems

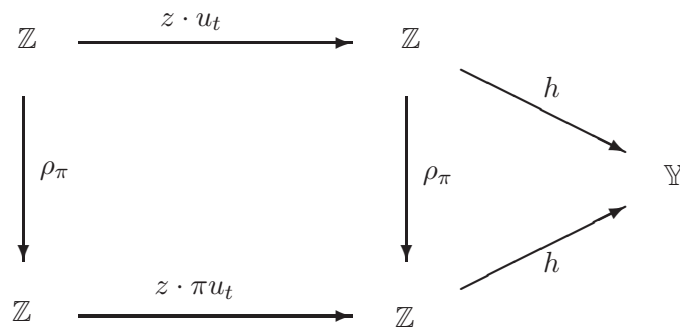$$(8) \qquad \qquad \qquad \dot{z} = F(z, u), \quad y = h(z)$$

Figure 5. *Equivariance as commutative diagram.*

and

$$(9) \qquad\qquad \dot{z} = G(z, u), \quad y = k(z)$$

or, equivalently, that the diagram in Figure 5 should be commutative, where we write "$z \cdot u_t$" and "$z \cdot \pi u_t$" to denote the states $\phi(t, z, u)$ and $\phi(t, z, \pi u)$, respectively.

Paraphrased in our language, Theorem 5 in [39] asserts the following. Suppose we are given any two analytic and irreducible systems (8) and (9), and two initial states z_0 and $\widetilde{z}_0$, respectively, with the property that the input/output behaviors are the same:

$$\psi(t, z_o, u) = \widetilde{\psi}(t, \widetilde{z}_o, u)$$

for all t and all inputs u (where we use tildes for the ψ map of the second system). Then, there exists an isomorphism ρ (that is, (7) holds) such that also $\rho(z_o) = \widetilde{z}_0$. To apply this theorem to our case, we need to show that the modified system, with $G(z, u) = F(z, \pi u)$, is irreducible (it is clearly analytic, since the original system is), and we must find, for our original system and for $G(z, u) = F(z, \pi u)$, two respective initial states z_0 and $\widetilde{z}_0$ that lead to the same input/output behavior. This latter requirement is achieved by taking $z_0 = \sigma(u)$ for any fixed u, and $\widetilde{z}_0 = \sigma(\pi u)$ for the same u. The definition of $\mathcal{P}$-symmetry is precisely the statement that the two input/output behaviors are identical. We next verify that the modified system with $G(z, u) = F(z, \pi u)$ is irreducible.

Accessibility. Since π is onto, the set of vector fields $\{F(\cdot, u), u \in \mathbb{U}\}$ is included in the set of vector fields $\{F(\cdot, \pi u), u \in \mathbb{U}\}$. Thus, the accessibility Lie algebra of the modified system can only be larger, and hence the accessibility property for the original system guarantees that of the modified system.

Observability. Suppose that two different states z_1, z_2 give rise to different outputs in the original system, when the input is $u(t)$. Since π is onto, there is an input v such that $u(t) = \pi(v(t))$ for all t. This means that the outputs corresponding to the initial states z_1 and z_2 in the modified system, under the input v, will be different. This argument can be applied for any two distinct states. Thus, the observability property for the original system guarantees that of the modified system.

This completes the proof of the main theorem. ∎

Remark 4.1. The intuitive idea of the construction of ρ is not difficult to understand and is standard in control theory [39, 34, 35, 36]: given an initial state $x^0 = \sigma(\bar{u})$, input u,

and time $t > 0$, we look at the state $z = \varphi(t, x^0, u)$ and the state $\widetilde{z} = \varphi(t, x^0, \pi u)$, and define $\rho(z) = \widetilde{z}$. The accessibility property says that this map is defined on an open subset of the state space. The interlacing property represented by Figure 5 is checked by seeing that the states $\rho(z) \cdot u_t$ and $z \cdot \pi u_t$ are not distinguishable by any input/output experiments, and hence by observability must be the same. The technical difficulties arise in proving the differentiability of ρ and its definition on the entire state space, not merely a subset, and this was one of the main contributions of [39].

Remark 4.2. In the proof of the theorem, we only needed to know the existence of some two initial states z_0 and $\widetilde{z}_0$ that lead to identical behaviors. This means that, if we define a "weakly invariant" system as one for which there exists *some* constant $\bar{u}$ such that (2) holds, $\psi(t, \sigma(\bar{u}), u) = \psi(t, \sigma(\pi\bar{u}), \pi u)$ for all inputs u and all $t \geq 0$ (instead of asking that this holds for every $\bar{u}$), then weak invariance implies the existence of an equivariance, and hence also invariance. (The irreducibility property plays a subtle role in this argument.)

5. Stability result for nonlinear integral feedback systems. We wish to show the global asymptotic stability (GAS) of the unique steady states $(\beta u/(\gamma y_0), y_0)$ and $(\gamma y_0/(\beta u), y_0)$, respectively, of the two nonlinear integral feedback systems in Figure 1:

$$\dot{x} = \alpha x(y - y_0),$$
$$\dot{y} = \beta \frac{u}{x} - \gamma y$$

$$\dot{x} = \alpha x(y_0 - y),$$
$$\dot{y} = \beta u x - \gamma y$$

for any constant input u, where we assume that $x(t) > 0$ and $u > 0$.

Lemma 5.1. *Consider any two-dimensional system evolving on $\mathbb{R}^2$ having the following "nonlinear damping" form:*

$$\dot{x} = g(y),$$
$$\dot{y} = -f(x) - k(y),$$

where f, g, k are functions that have positive derivatives. Suppose that (x_0, y_0) is a steady state. Then this is the unique steady state of the system, and it is globally asymptotically stable.

Corollary 5.2. *Consider any two-dimensional system evolving on $\mathbb{R}_{>0} \times \mathbb{R}$ and having the following form:*

$$\dot{x} = x g(y),$$
$$\dot{y} = -f(x) - k(y),$$

where k has positive derivatives and either (a) *both f and g have positive derivatives or* (b) *both f and g have negative derivatives. Suppose that (x_0, y_0) is a steady state. Then this is the unique steady state of the system, and it is globally asymptotically stable.*

Proof. Suppose first that both f and g have positive derivatives. We transform the system into one in $\mathbb{R}^2$, using variables y and $z = \ln x$:

$$\dot{z} = \widetilde{g}(y),$$
$$\dot{y} = -\widetilde{f}(z) - k(y),$$

where $\widetilde{g}(y) = g(y)$ and $\widetilde{f}(z) := f(e^z)$. This functions defining this system have positive derivatives, as required in Lemma 5.1. Moreover, the transformed system has the steady state

$(\ln x_0, y_0)$, which is therefore globally asymptotically stable (and unique). Transforming back to the original coordinates, we proved our claim. Now suppose that case (b) holds instead: both f and g have negative derivatives. We pick $z := -\ln x$. The equations transform as above, except that now $\widetilde{g}(y) = -g(y)$ and $\widetilde{f}(z) := f(e^{-z})$. Since these now have positive derivatives, the same argument as in case (a) applies. ∎

The nonlinear integral feedback systems discussed earlier are particular cases of the above form. The linear function $k(y) = \gamma y$ is increasing. When $g(y) = \alpha x(y - y_0)$, g is increasing, and when $g(y) = \alpha x(y_0 - y)$, g is decreasing. The function $f(x) = -\beta u/x$ (where u is any positive constant) is increasing, while $f(x) = -\beta ux$ is decreasing.

Proof of Lemma 5.1. Uniqueness: since g is strictly increasing, y_0 is uniquely determined, and it then follows that x_0 is also uniquely determined (because f is increasing) as the solution of $f(x) = -k(y_0)$.

At the steady state (x_0, y_0), we may assume without loss of generality that $f(x_0) = 0$ and $k(y_0) = 0$ (as well as $g(y_0) = 0$). Indeed, let $c := f(x_0) = -k(y_0)$. Redefining $\widetilde{f}(x) := f(x) - c$ and $\widetilde{k}(y) := k(y) + c$, we have that $\widetilde{f}(x_0) = 0$ and $\widetilde{k}(y_0) = 0$, and the differential equations have not changed, since $-\widetilde{f}(x) - \widetilde{k}(y) = -(f(x) - c) - (k(y) + c) = -f(x) - k(y)$. Since f is strictly increasing, its values are positive when $x > x_0$ and negative otherwise, and similarly for g, k with respect to y_0. Let us define

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

By definition, $V(x_0, y_0) = 0$ and $V(x, y) > 0$ for all $(x, y) \neq (x_0, y_0)$. As $\frac{\partial^2 V}{\partial^2 x} = f'(x) > 0$, $\frac{\partial^2 V}{\partial^2 y} = g'(y) > 0$, and mixed second derivatives are zero, it follows that the Hessian matrix of V is positive definite everywhere. Thus, V is strictly convex, and it follows that V is a proper function: $V(x, y) \to \infty$ as $\|(x, y)\| \to \infty$. In conclusion, V is a Lyapunov function candidate function. To conclude global stability based on the LaSalle invariance principle [36], we must show that the derivative of V along trajectories,

$$\dot{V}(x, y) := \frac{\partial V}{\partial x}(x, y)g(y) + \frac{\partial V}{\partial y}(x, y)\left[-f(x) - k(y)\right],$$

has the properties that $\dot{V}(x, y) \leq 0$ for all (x, y) and that $(x(t), y(t)) \equiv (x_0, y_0)$ is the only solution with $\dot{V}(x(t), y(t)) \equiv 0$. Now,

$$\dot{V}(x, y) = f(x)g(y) + g(y)\left[-f(x) - k(y)\right] = -g(y)k(y) \leq 0$$

because g and k have everywhere the same sign (positive if $y > y_0$ and negative if $y < y_0$). Suppose that a solution satisfies that $\dot{V}(x(t), y(t)) \equiv 0$. Then $y(t) \equiv y_0$, so that also $\dot{y}(t) \equiv 0$, which substituted into the second equation gives $0 = -f(x(t)) - 0$, which implies that $x(t) \equiv x_0$. ∎

Observe that the only place where k appears in the proof is in the statement that g and k have everywhere the same sign; thus the same proof works if instead of assuming that k has everywhere positive derivatives, we assume that $f(x_0) = 0$ and $(y - y_0)k(y) > 0$ for all $y \neq y_0$. Note that V would be a Hamiltonian for the system if $k \equiv 0$, so the system can be thought of simply as adding damping to a conservative system.

6. Comparing feedforward and feedback structures. We make several remarks in this section concerning the relations and comparisons between adapting feedforward and feedback architectures.

6.1. Internal model principle. The "internal model principle" (IMP) in control theory states that one should be able to recast any system which adapts to steps as a system which integrates an "adaptation error" signal (integral feedback). For example, it should be possible to rewrite the feedforward system in Figure 2(a) in such a manner. In this section, we review one precise statement of the IMP and apply it to this example.

Adaptation is called "disturbance rejection" in control theory [36] (not to be confused with a different topic, "adaptive control"). A key mathematical idea, the IMP states that, to be able to adapt to all signals in a given class of inputs $\mathcal{U}$, the system *must* include an "internal model": a subsystem which is driven by the "error" in adaptation, and whose solutions when the error is zero (that is, when the system has perfectly adapted) are the possible signals in $\mathcal{U}$. Intuitively, an internal representation of the external signal is memorized, and adaptation performance is constantly evaluated; any error in adaptation is used to form a better estimate of this external signal. For example, for adaptation to constant signals, the IMP requires integral feedback, as in Figure 1: $\mathcal{U} =$ all constant signals, the error is $y - y_0$, and solutions of $\dot{x} = 0$ are precisely the constant signals. In systems biology, the IMP suggests biochemical structures, thus guiding modeling and experiments as well as interpretation of the role of various regulatory and signal processing motifs. For instance, the relevance of the IMP to *E. coli* chemotaxis was remarked on in [49]: the methylation state can be viewed as a memory (integrator), and the "error" is the average kinase activity relative to its basal value. The IMP encompasses adaptation also with respect to richer classes of signals $\mathcal{U}$— not just constant ones. For example, one might speculate [37] that circadian rhythms might have evolved as an IMP mechanism to allow adaptation to day/night light and temperature cycles: a harmonic oscillator with period T is predicted by the IMP when a system adapts to $\mathcal{U} =$ all signals of the form $A \sin(2\pi t/T + \varphi)$. The IMP was proved as a theorem for linear dynamics by Francis and Wonham in the mid 1970s [7, 46]. It remains an open problem to find ultimate nonlinear generalizations, but there are some partial extensions known. For example, using "zero dynamics" ideas from [14], a theorem was given in [37] that shows, under appropriate technical assumptions, the existence of coordinate changes, generally nonlinear, that exhibit an internal model. Using this theorem, one should expect to find coordinate changes transforming IFFL circuits into integral feedback form, and this is indeed true. We first describe the comparatively trivial case of linear systems and then discuss how to obtain an analogous result for nonlinear IFFL systems.

As a simple first illustration, consider the following feedforward linear system:

$$\dot{x} = -x + u, \quad \dot{y} = -x - y + u,$$

which perfectly adapts to $y = y_0 = 0$ but is not in integral feedback form. We may perform a simple change of coordinates, representing the system using the state variables $(x = x - y, y)$ instead of the original (x, y). In this new set of coordinates, we have

$$\dot{x} = y, \quad \dot{y} = -x - 2y + u, \tag{10}$$

which is now an integral feedback system (the variable z integrates the "error" y). We next review the main theorem from [37] and then work out the application to the nonlinear feed-forward system in Figure 2(a).

The general setup in [37] is as follows. The systems studied are scalar-input scalar-output n-dimensional systems for which the input appears to first order:

$$(11) \qquad \dot{z} = f(z) + ug(z), \qquad y = h(z).$$

The vector fields f and g are smooth, and h is a smooth function. We assume that $z = 0$ is a steady state when $u = 0$, $f(0) = 0$.

We will say that the system (11) *adapts to inputs in a class* $\mathcal{U}$ if for each $u \in \mathcal{U}$ and each initial state $x^0 \in \mathbb{R}^n$, the solution of (11) with initial condition $x(0) = x^0$ exists for all $t \geq 0$ and is bounded, and the corresponding output $y(t) = h(x(t))$ converges to a fixed value $y_0 \in \mathbb{Y}$ (which does not depend on the particular input $u \in \mathcal{U}$) as $t \to \infty$.

In control theory, it is standard to describe the class of inputs $\mathcal{U}$ with respect to which adaptation holds through the specification of an "exosystem" that produces these inputs. An exosystem is simply any autonomous system Γ,

$$(12) \qquad \dot{w} = Q(w), \quad u = \theta(w),$$

with the following property: the input class $\mathcal{U}$ consists exactly of the functions $u(t) = \theta(w(t))$, $t \geq 0$, for each possible initial condition $w(0)$. For example, if we are interested in step responses, we pick $\dot{w} = 0$, $u = w$. This means that the possible signals are the solutions of $\dot{w} = 0$, i.e., the constant functions of time; that is, $\mathcal{U}$ is the set of functions $u(t)$ for which $u(t) = \bar{u}$ for all t for some $\bar{u} \in \mathbb{U}$. On the other hand, if we are interested in sinusoidals with frequency ω, then we use $\dot{x}_1 = x_2$, $\dot{x}_2 = -\omega^2 x_1$, $u = x_1$. A technical assumption is that the signals in $\mathcal{U}$ do not grow without bound. Specifically, one assumes that the exosystem is *Poisson-stable*, meaning that for every state w^0, the solution $w(\cdot)$ of $\dot{w} = Q(w)$, $w(0) = w^0$ is defined for all $t > 0$ and it satisfies that w^0 is in the omega-limit set of w (recall that this means that there is a sequence of times $t_i \to \infty$ such that the sequence $w(t_i)$ converges to w^0 as $t \to \infty$). In other words, the exosystem is almost periodic in the sense that trajectories keep returning to neighborhoods of the initial state. Both the constant and sinusoidal examples mentioned above are generated by Poisson-stable systems. In contrast, ramps (linearly growing signals) are not generated by Poisson-stable systems, since they require an unstable second-order system $\dot{w}_2 = 0$, $\dot{w}_1 = w_2$, $u = w_1$ to generate them. Thus, the phenomenon of adaptation to ramps is not included in the scope of the theorem to be stated. The exosystem is assumed to have states that evolve on some differentiable manifold, Q is a smooth vector field, and θ is a real-valued smooth function.

The IMP claims that a copy of this exosystem must be embedded in the system (11). More precisely, one says that the system *contains an output-driven internal model of* $\mathcal{U}$ if there is a change of coordinates which brings (11) into the block form

$$(13) \qquad \begin{aligned} \dot{z}_1 &= f_1(z_1, z_2) + ug_1(z_1, z_2), \\ \dot{z}_2 &= f_2(y, z_2), \\ y &= \kappa(z_1), \end{aligned}$$

so that the subsystem with state variables z_2 is capable of generating all the possible functions in $\mathcal{U}$: for some function $\varphi(z_2)$, and for each possible $u \in \mathcal{U}$, there is some solution of

$$(14) \qquad \dot{z}_2 = f_2(y_0, z_2)$$

which satisfies $\varphi(z_2(t)) \equiv u(t)$. "Change of coordinates" means that there is some integer $r \leq n$ and two differentiable manifolds Z_1 and Z_2 of dimensions r and $n - r$, respectively, as well as a smooth function $\kappa : Z_1 \to \mathbb{R}$ and two vector fields F and G on $Z_1 \times Z_2$ which take the partitioned form

$$F = \begin{pmatrix} f_1(z_1, z_2) \\ f_2(\kappa(z_1), z_2) \end{pmatrix}, \quad G = \begin{pmatrix} g_1(z_1, z_2) \\ 0 \end{pmatrix}$$

and a diffeomorphism $\Phi : \mathbb{R}^n \to Z_1 \times Z_2$, such that

$$\Phi'(x)f(x) = F(\Phi(x)), \quad \Phi'(x)g(x) = G(\Phi(x)), \quad \kappa(\Phi_1(x)) = h(x)$$

for all $x \in \mathbb{R}^n$, where Φ_1 is the Z_1-component of Φ and prime indicates Jacobian. Intuitively, the signal z_2 computes an integral of a function of the output $y(t)$, and when $y(t) \equiv y_0$, z_2 is (up to the mapping φ, which may be interpreted as a sort of rescaling) a signal in $\mathcal{U}$. For example, if $\mathcal{U}$ consists of constant functions (adaptation to steps), then for $y \equiv y_0$ one obtains (for different initial conditions) the possible constant signals.

In order to prove a theorem justifying the IMP, several technical conditions are imposed in [37]. The first is a signal detection or "sensitivity" property: (1) for some positive integer r, called in control theory a finite uniform relative degree,

$$L_g L_f^k h \equiv 0, \; k = 0, \ldots, r - 2, \qquad \text{and} \qquad L_g L_f^{r-1} h(x) \neq 0 \quad \text{for all } x \in \mathbb{Z}.$$

As in the section on observability, generally, $L_X H$ denotes the directional or Lie derivative of a function H along the direction of a vector field X, $(L_X H)(x) = \nabla H(x) \cdot X(x)$, and one understands $L_Y L_X H$ as the iteration $L_Y(L_x H)$. (In the special case that $L_g h(x) \neq 0$ for all x, the relative degree is $r = 1$, since the condition for $k < r - 1$ is vacuous.) Given that the relative degree is r, one may consider the following vector fields:

$$\widetilde{g}(x) \; = \; \frac{1}{L_g L_f^{r-1} h(x)} g(x), \quad \widetilde{f}(x) \; = \; f(x) - \left(L_f^r h(x) \right) \widetilde{g}(x), \quad \tau_i := \text{ad}_{\widetilde{f}}^{i-1} \widetilde{g}, \; i = 1, \ldots r,$$

where ad_X is the operator $\text{ad}_X Y = [X, Y] =$ Lie bracket of the vector fields X and Y, and $\text{ad}_{\widetilde{f}}^{i-1}$ is the iteration of this operator $i - 1$ times (when $i = 1$, $\tau_i = \widetilde{g}$). One says that a vector field X is complete if the solution of the initial value problem $\dot{x} = X(x)$, $x(0) = x^0$ is defined for all t and for any initial state x^0. Two vector fields X and Y are said to commute if $[X, Y] = 0$. The final assumptions, then, are that (2) τ_i is complete for $i = 1, \ldots, r$ and (3) the vector fields τ_i commute with each other. (In the special case $r = 1$, condition (3) is automatic, since every vector field commutes with itself.) These assumptions are satisfied for linear systems. They are also satisfied, for example, for the feedforward system in Figure 2(a):

$$(15) \qquad \dot{x} = \alpha u - \delta x, \qquad \dot{y} = \beta \frac{u}{x} - \gamma y$$

with $h(x, y) = y$. In vector form, this is $\dot{z} = f(z) + ug(z)$, where the vector fields are

(16)
$$f(x, y) = \begin{pmatrix} -\delta x \\ -\gamma y \end{pmatrix} \qquad \text{and} \qquad g(x, y) = \begin{pmatrix} \alpha \\ \beta/x \end{pmatrix}.$$

Since $L_g h = (0, 1) \cdot (\alpha, \beta/x)^{\mathrm{T}} = \beta/x$ is everywhere nonzero, we have that $r = 1$. Thus we need only check that

$$\tau_1 = \widetilde{g} = \frac{1}{L_g h(x)} g(x) = \frac{x}{\beta} g(x) = \begin{pmatrix} \frac{\alpha}{\beta} x \\ 1 \end{pmatrix}$$

is complete, which is true because $\widetilde{g}$ is a linear vector field.

The main theorem in [37] says the following: *Suppose that assumptions* (1)–(3) *hold for the system* (11). *If* (11) *adapts to inputs in a class $\mathcal{U}$ generated by a Poisson-stable exosystem, then it contains an output-driven internal model of $\mathcal{U}$.*

The proof of the theorem consists of showing that there is, under the stated conditions, a change of variables as claimed. The map producing the change of variables is obtained by solving a first-order PDE.

6.2. Illustration of IMP for the feedforward system in Figure 2(a). We consider the system (15), or (16) in vector form. We already checked properties (1)–(3), and the system adapts to steps (constant inputs), so the theorem says that it should be possible to recast it in integral feedback form. The proof in [37] asserts the existence of a mapping $\varphi(x, y)$ whose Lie-derivative along g solves the following first order linear PDE:

$$L_g \varphi = \nabla \varphi \cdot g = \alpha \varphi_x(x, y) + \frac{\beta}{x} \varphi_y(x, y) = 0.$$

Generally, such an equation may be solved using the method of characteristics. However, in our example the solution is immediate: $\varphi(x, y) = \alpha y - \beta \log x$. The map

$$(x, y) \mapsto (z_1, z_2) = (y, \varphi(x, y)) = (y, \alpha y - \beta \log x)$$

is a diffeomorphism whose inverse is $y = z_1$ and $x = e^{(\alpha z_1 - z_2)/\beta}$. We obtain the following equations in the new coordinates (z_1, z_2):

$$\dot{z}_1 = \beta u e^{(z_2 - \alpha z_1)/\beta} - \gamma z_1,$$
$$\dot{z}_2 = \beta \delta - \alpha \gamma z_1$$

with output $y = z_1$. This has the desired internal model form $\dot{z}_1 = f_1(z_1, z_2) + u g_1(z_1, z_2)$, $\dot{z}_2 = f_2(y, z_2)$, $y = \kappa(z_1)$, if we define $f_1(z_1, z_2) = -\gamma z_1$, $g_1(z_1, z_2) = \beta e^{(z_2 - \alpha z_1)/\beta}$, $f_2(y, z_2) = f_2(y) = \beta \delta - \alpha \gamma y$, and $\kappa = $ identity. Thus z_2 is the variable that integrates the error: when $y = y_0 = 1$, the equation for z_2 becomes $\dot{z}_2 = 0$, whose solutions are all the possible constant signals. We can also write this system in terms of the coordinates $x = e^{z_2/\beta}$, $y = z_1$ as

(17)
$$\dot{x} = x\left(\delta - \frac{\alpha\gamma}{\beta} y\right), \qquad \dot{y} = \beta u x e^{-\frac{\alpha}{\beta} y} - \gamma y,$$

which has the generic form $\dot{x} = xF(y)$, $\dot{y} = G(ux, y)$ of nonlinear integral feedback systems considered in Lemma 3.1.

6.3. What are the relative advantages of different architectures? Both integral feedback and IFFL circuits allow adaptation, as well as, for appropriate models, symmetry invariance to scalings. Thus, it is natural to ask what the relative merits of each of these architectures are: what fitness-conferring signal processing and control properties are special for them? We view this as a question for further research and limit ourselves here to a few remarks.

In a certain sense, the question is meaningless, since feedforward networks can often be simulated by feedback networks, as just shown. Nonetheless, the variable $\widetilde{x} = x - y$ may well be merely a mathematical construct with no biological meaning. In addition, any (linearized) system obtained by such a transformation from an IFFL is special: it can have *only real eigenvalues*, while the more general integral feedback form may have damped oscillatory behavior (depending on parameters).

This means that the feedback systems have a wider range of possible dynamical behaviors and thus might be selected when it is desirable to meet specific performance objectives. In addition, feedback confers a certain robustness to uncertainty. We illustrate this point by comparing the feedforward system in Figure 2(a),

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

with its recasting in feedback form,

$$\dot{x} = x \left(\delta - \frac{\alpha\gamma}{\beta} y \right) \,, \qquad \dot{y} = \beta u x e^{-\frac{\alpha}{\beta} y} - \gamma y \,.$$

Both systems adapt $(y(t) \to \frac{\beta\delta}{\alpha\gamma})$. However, while in the feedback form, any perturbation of the right-hand side $\dot{y} = \beta u x e^{-\frac{\alpha}{\beta} y} - \gamma y + \Delta(x, y)$ does not alter the property that the steady state must have $y = \frac{\beta\delta}{\alpha\gamma}$, no analogous simple statement can be made for the feedforward form.

Conversely, one may also speculate that biological or evolutionary factors could constrain the value of feedback structures. As an example, the stability of feedback (but not feedforward) systems is fragile to delays. Delays could arise from slower time scales for processes such as transcription and translation, compared to protein modifications. As an illustration, Figure 6 shows oscillations arising from a delay from y to x in the linear integral feedback system (10), and Figure 7 shows oscillations arising from a delay from y to x in the nonlinear integral feedback system (17).

7. Invariant steering. As remarked in [32], motile systems that measure a field in order to determine their velocity of movement have the property that their entire search patterns, as a function of time, are invariant to scale, if their sensory systems have the FCD property. We now discuss a precise formulation of this fact for arbitrary systems and symmetries.

We think of a system that, through its output $y(t)$, drives a steering mechanism ("motor complex"), resulting in a new position $r(t)$. We model this by a system with inputs, which is a way of saying that the position is computed by a dynamical system that keeps track of the past history of y:
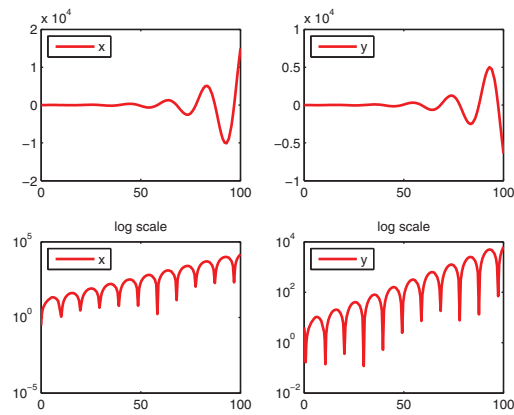
$$\dot{q} = Q(q, y) \,, \quad r = R(q) \,,$$

Figure 6. *Oscillations in $\dot{x}(t) = y(t-h)$, $\dot{y}(t) = -x(t) - 2y(t) + u(t)$ using $u \equiv 0$ and $h = 5$.*
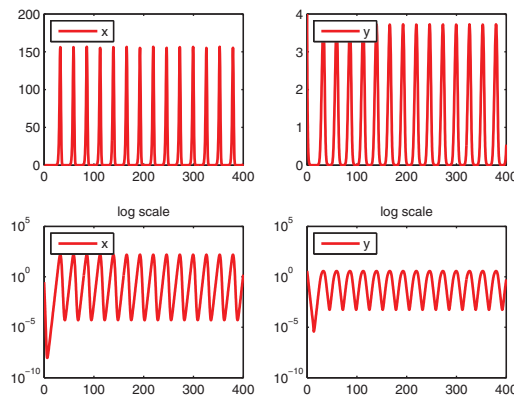

Figure 7. *Oscillations in $\dot{x}(t) = x(1 - y(t-h))$, $\dot{y}(t) = x(t)u(t)e^{-y(t)} - y(t)$ using $u \equiv 0$ and $h = 5$.*
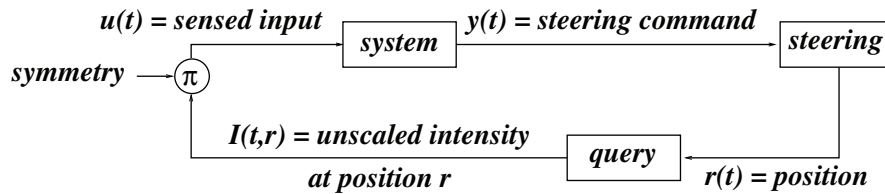

Figure 8. *Closed-loop diagram for search under symmetry uncertainty for inputs.*

where $q(t)$ is the internal state of the steering mechanism. At position $r(t)$ in space, an "intensity" (e.g., light or nutrient concentration) is queried, and the result is a sensed input $I(t, r(t))$. The intensity field $I(t, r)$ could well be time- as well as space-dependent. Finally, the loop is closed by the system measuring $I(t, r(t))$, except that we are interested in understanding how the system behaves if it measures $\pi I(t, r(t))$ instead of $I(t, r(t))$, where $\pi \in \mathcal{P}$ is a symmetry. See Figure 8 for an illustration. We want to study the invariance of behavior of this system, and in particular of its position $r(t)$ as a function of time, under the assumption that the system had preadapted to a constant environment $I(t, r) \equiv I_0$ when $t < 0$ before being placed in the current environment.

Formally, we start with a system that adapts and is invariant with respect to a set of symmetries $\mathcal{P}$, and we consider the following extended system:

$$\dot{z} = F(z, u), \qquad u = I(t, r),$$
$$\dot{q} = Q(q, y), \qquad y = h(z), \ r = R(q).$$

We let (z, q) be the solution with initial conditions $z(0) = \sigma(I_0)$ and $q(0) = q_0$, where $Q(q_0, y_0) = 0$, that is, q_0 is a steady state that corresponds to the adaptation value y_0 of the original system. Also, for any given $\pi \in \mathcal{P}$, we consider the solution $(\widetilde{z}, \widetilde{q})$ of the system with initial conditions $z(0) = \sigma(\pi I_0)$ and $q(0) = q_0$ and intensity field $\pi I(t, r)$:

$$\dot{\widetilde{z}} = F(\widetilde{z}, \widetilde{u}), \qquad \widetilde{u} = \pi I(t, \widetilde{r}),$$
$$\dot{\widetilde{q}} = Q(\widetilde{q}, \widetilde{y}), \qquad \widetilde{y} = h(\widetilde{z}), \ \widetilde{r} = R(\widetilde{q}).$$

We claim that $\widetilde{y}(t) = y(t)$, $\widetilde{u}(t) = \pi u(t)$, $\widetilde{r}(t) = r(t)$, and $\widetilde{q}(t) = q(t)$ for all $t \geq 0$.

To prove the claim, we consider the solution of the system

$$\dot{x} = F(x, \pi u(t)),$$
$$\dot{s} = Q(s, h(x))$$

with initial conditions $x(0) = \sigma(\pi I_0)$ and $s(0) = q_0$. By definition of $\mathcal{P}$-invariance, we know that $h(x(t)) = h(z(t))$ for all $t \geq 0$. Thus, since the initial conditions on q and s are the same, it follows that also $s(t) = q(t)$ for all $t \geq 0$. Therefore, $u(t) = I(t, r(t)) = I(t, R(q(t))) = I(t, R(s(t)))$ for all $t \geq 0$. It follows that $\dot{x} = F(x, \pi I(t, r))$. We conclude that (x, s) and $(\widetilde{z}, \widetilde{q})$ solve the same initial-value problem, and thus $x(t) = \widetilde{z}(t)$ and $s(t) = \widetilde{q}(t)$ for $t \geq 0$, from which $y(t) = h(z(t)) = h(x(t)) = h(\widetilde{z}(t)) = \widetilde{y}(t)$, and the claim is proved.

A converse of this result holds as well, and it is described next. In combination with the main theorem in this paper, we have a complete characterization of those systems for which search patterns are identical under symmetries in spatial sensory fields.

Remark 7.1. Suppose that, for every possible field I, the above system results in the same $r(t)$ when started from $z(0) = \sigma(I_0)$ as when starting from $z(0) = \sigma(\pi I_0)$ but using input $\pi I(t, r)$. This property then holds, in particular, when the field $I(t, r)$ is independent of position r, that is, I is merely an arbitrary open-loop input. We would like to conclude that $y(t) = \widetilde{y}(t)$ from $r(t) = \rho(t)$, which means, since the input is arbitrary, that the original system must be invariant under π. This conclusion will hold provided that the steering system has the following property: if we solve $\dot{q} = Q(q, y)$ with initial condition $q(0) = q_0$ and two inputs y_1 and y_2, and the resulting solutions satisfy $R(q_1(t)) = R(q_2(T))$ for $t \geq 0$, then $y_1(t) = y_2(t)$ for $t \geq 0$. In control-theoretic terms, this input reconstruction property is stated as the requirement that the system $\dot{q} = Q(q, y)$ with output $R(q)$ be *input-observable*, which is a property closely related to right-invertibility, inverse dynamics, and "output to input observability" [14, 19]. Observability is almost enough to guarantee input-observability: if the system is observable, then $q_1(t) = q_2(t)$ for $t \geq 0$, so it is only needed that $Q(q(t), y_1(t)) = Q(q(t), y_2(t))$ imply $y_1(t) = y_2(t)$, which is a weak nondegeneracy property.

Remark 7.2. In many applications, the system output $y(t)$ drives a *stochastic* steering mechanism: the system producing the location $r(t)$ is subject to randomness, For example,

in bacterial chemotaxis, $y(t)$ may represent a signal, such as the level of phosphorylated protein CheY, which serves to bias the random switches between tumbling and swimming behavior. One way to represent this probabilistic behavior is to model the dynamical system that computes the position from the history of $y(t)$ as

$$\dot{q} = Q(q, y, X), \quad r = R(q),$$

where X is a random process: $X = \{X_t(\omega), t \geq 0\}$ is defined on a probability space $(\Omega, \mathcal{F}, P)$, where Ω is a sample space, $\mathcal{F}$ is a σ-algebra of events, and P is a probability measure; $P(X{=}v(t))$ is the probability of a given outcome (sample path) of this process. Under such a formalization, and assuming appropriate technical conditions, all the variables

$$z(t), u(t), r(t), q(t), y(t)$$

are themselves stochastic processes defined on the same probability space Ω. (Technical conditions need to be imposed to ensure the existence of solutions of the differential equations. We proceed intuitively, assuming that X has piecewise continuous sample paths, thus avoiding complications of Itô calculus.) Now, given any fixed $\omega \in \Omega$, we may view $\dot{q} = Q(q, y, X)$ as a time-varying system $\dot{q}(t) = Q(q(t), y(t), t)$, where we have substituted $X = X_t(\omega)$ along this sample path. The previous proof extends, with no changes, to such a time-varying system. It follows that identical $r(t)$ (as well as $y(t)$ and $q(t)$) are obtained, whether using the field I or using the changed field πI, so long as the initial condition $z(0)$ has also been modified by π. This holds for each $\omega \in \Omega$. Thus, as a random variable, $r(t)$ is invariant under $\mathcal{P}$. In particular, all statistics of r remain invariant.

We may apply this result to the Tu–Shimizu–Berg *E. coli* chemotaxis model [41]. This model (see [32] for more details) may be formulated as

$$\dot{m} = F_0(y),$$
$$\dot{y} = G\left(\frac{u}{e^{\alpha m}}\right) - y,$$
$$h(x, y) = y,$$

where F_0 is a decreasing function which crosses zero at some value $y = y_0$. (More commonly, one considers the singularly perturbed version in which the output is at equilibrium: $y = G(u/e^{\alpha m})$.) Letting $x := e^{\alpha m}$, we may transform to (another) integral feedback form:

$$\dot{x} = x\, F(y),$$
$$\dot{y} = G\left(\frac{u}{x}\right) - y,$$
$$h(x, y) = y.$$

This is homogeneous, and the unique solution of the equivariance PDE is

$$\rho(x, y) \;=\; \begin{pmatrix} px \\ y \end{pmatrix}.$$

(Global asymptotic stability is easy to show by a LaSalle invariance argument.)

One can then predict scale-invariance behavior. Indeed, the groups of Roman Stocker (MIT) and Tom Shimizu (AMOLF, The Netherlands) have now confirmed this prediction [17], using both molecular level analysis of intracellular signaling (FRET experiments) and measurements of swimming behavior at the level of individual cells and populations (in microfluidic environments).

8. Conclusions. Motivated by the recent discovery of the important transient property of fold-change detection (FCD) in certain signaling transduction mechanisms, this paper studied the more general problem of invariance under symmetries in inputs. A necessary and sufficient characterization was provided of those adapting and irreducible systems whose behaviors are invariant. This characterization is through equivariances that solve a certain PDE and can be explicitly tested on several system motifs that are recurrent in biology. These motifs can be broadly classified into feedforward and feedback systems. Transformations that help connect these two types of systems, and their relative merits, were briefly analyzed. Finally, it was shown that invariance to symmetries in inputs is closely related to the invariance of search patters for motile systems under sensory field transformations.

We conclude that testing for invariance is feasible for several important classes of models of biological systems. A challenging question for further research is to better understand situations in which invariance holds mathematically in only an approximate sense. We showed an example of systems that exhibit approximate invariance, and a similar approach was recently taken [33] to classify those three-node enzymatic networks that exhibit FCD (scale-invariance).

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