Dynamic compensation, parameter identifiability, and equivariances

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Abstract

The recently proposed notion of dynamical compensation in biological circuits is reinterpreted in terms of two related notions in systems biology: system equivalence and parameter (un)identifiability. This recasting leads to effective tests for verifying the validity of the property.

1 Introduction

The recent paper [1] introduced the system property of *dynamical compensation (DC)* with respect to variations in a parameter p, meaning that the complete output dynamics $y(t)$ is exactly the same, independently of the precise value of p, for any time dependent input $u(t)$, and showed the biological significance of this notion. The authors argued that physiological control systems should ensure a precise dynamical response despite variations in certain parameters, lest pathological conditions arise. They provided a sufficient condition for DC to hold, and used this condition to prove the DC property for several biological systems such as a model of plasma glucose response in the face of changes in insulin sensitivity.

In this paper, we frame the notion of DC in the context of two related notions in systems biology: equivariances and parameter identifiability. We provide a necessary and sufficient condition for DC in the language of equivariances, for which the sufficient condition given in [1] becomes a particular case, as does the condition given in [2] for fold-change detection (FCD) or input symmetry invariance, a Weber-like law in psychophysics [3]. We also remark that DC is equivalent to (structural) non-identifiability, which leads to another necessary and sufficient condition for DC, using Lie derivatives.

2 Systems and equivalence

We formally state definitions in the language of dynamical systems with inputs and outputs, the standard paradigm in control systems theory [4]:

$$\dot{x} = f(x,u,p)\,, \quad y = h(x,u,p)\,, \quad x(0) = \xi_p\,, \tag{1}$$

or, more explicitly,

$$\frac{dx}{dt}(t) = f(x(t),u(t),p)\,, \quad y(t) = h(x(t),u(t),p)\,, \;\; t \geq 0\,, \quad x(0) = \xi_p.$$

The functions f, h describe respectively the dynamics and the read-out map; $u = u(t)$ is an input (stimulus, excitation) function, assumed to be piecewise continuous in time, $x(t)$ is an n-dimensional vector of state variables, $y(t)$ is the output (response, reporter) variable, and p is the parameter (or vector of parameters)

that we wish to focus our attention on. In typical applications, $y(t) = x_i(t)$ is a coordinate of x. Values of states, inputs, outputs, and parameters are constrained to lie in particular subsets $\mathbb{X}$, $\mathbb{U}$, $\mathbb{Y}$, $\mathbb{P}$ respectively, of Euclidean spaces $\mathbb{R}^n, \mathbb{R}^m, \mathbb{R}^q, \mathbb{R}^s$. Typically in biological applications, one picks $\mathbb{X}$ as the set of positive vectors in $\mathbb{R}^n$, $x = (x_1, x_2, \ldots, x_n)$ such that $x_i > 0$ for all i, and similarly for the remaining spaces. The state $\xi_p \in \mathbb{X}$ is an initial state, which could be different for different parameters; thus we view ξ_p as a function $p \to \mathbb{X}$. (We prefer the notation ξ_p instead of $\xi(p)$, so that we do not confuse p with the time variable.) For each input $u : [0, \infty) \to \mathbb{U}$, we write the solution of (1) with initial condition $x(0) = \xi_p$ as

$$x(t) \;=\; \varphi(t, \xi_p, u, p)$$

and the corresponding system response, which is obtained by evaluating the read-out map along trajectories, as

$$y(t) \;=\; h(\varphi(t, \xi_p, u, p), u(t), p) \;=\; \psi(t, \xi, u, p)\,.$$

We assume that for each input and initial state (and each fixed parameter p), there is a unique solution of the initial-value problem $\dot{x} = f(x, u, p)$, $x(0) = \xi_p$, so that the mapping φ is well-defined; see [4] for more discussion, regularity of f, properties of ODE's, global existence of solutions, etc. We refer to (1) as a *parametrized* (because of the explicit parameter) *initialized* (because of the specification of a given initial state for each parameter) family of systems.

Depending on the application, one might wish to impose additional restrictions on ξ_p. For example, in [1] an additional requirement is that $0 \in \mathbb{U}$ and $\xi_p \in \mathbb{X}$ is an equilibrium when $u(0) = 0$, which translates into $f(\xi_p, 0, p) = 0$, and a similar requirement is made in [2] (this latter reference imposes the requirement that for each constant input $u(t) \equiv \mu$ there should exist an equilibrium, in fact). One may also impose stability requirements on this equilibrium; nothing changes in the results to be stated.

3 I/O Equivalence, Equivariances, and Identifiability

The question that we wish to address is as follows: provide conditions on the functions f, h, and ξ so that

$$\psi(t, \xi_p, u, p) \;=\; \psi(t, \xi_q, u, q) \qquad \forall\, t \geq 0,\; u(\cdot),\; p,\; q\,. \tag{2}$$

This is the "dynamic compensation" property from [1]. We prefer to use the terminology $\mathbb{P}$-*invariance*. This property says that the parameters p are (structurally) *unidentifiable* from input/output data [5, 6].

In order to re-state this property in a more convenient form, let us fix from now on an arbitrary $p \in \mathbb{P}$, which we write as "$\underline{1}$" (for example, if $\mathbb{P}$ is the set of all positive vectors $(p_1, \ldots, p_s)$, $\underline{1}$ could naturally be taken as the vector $(1, 1, \ldots, 1)$). Let us write $f(x, u) := f(x, u, \underline{1})$, $h(x, u) := h(x, u, \underline{1})$, $\xi := \xi_{\underline{1}}$, $\varphi(t, \xi, u) := \varphi(t, \xi, u, \underline{1})$, and $\psi(t, \xi, u) := \psi(t, \xi, u, \underline{1})$. The following is a standard concept in control theory:

Definition 1 *For any given parameter p, the system* (1) *is said to be* input/output *(I/O)* equivalent *to the system*

$$\dot{x} = f(x, u)\,, \quad y = h(x, u)\,, \quad x(0) = \xi\,. \tag{3}$$

provided that

$$\psi(t, \xi_p, u, p) \;=\; \psi(t, \xi, u) \qquad \forall\, t \geq 0,\; u(\cdot)\,. \tag{4}$$

Obviously, (2) is equivalent to the property that, for every parameter p, (1) should be I/O equivalent to (3). Two approaches to testing I/O equivalence (or its lack) are described next.

3.1 Equivariances

Definition 2 *Given a parametrized initialized family of systems (1), a set of differentiable mappings*

$$\{\rho_p : \mathbb{X} \to \mathbb{X}\}_{p\in\mathbb{P}}$$

is an equivariance family *provided that:*

$$f(\rho_p(x), u, p) = (\rho_p)_*(x) f(x, u) \tag{5a}$$

$$h(\rho_p(x), u, p) = h(x, u) \tag{5b}$$

$$\rho_p(\xi) = \xi_p \tag{5c}$$

for all $x \in \mathbb{X}$, $u \in \mathbb{U}$, and $p \in \mathbb{P}$, where, in general ρ_* denotes the Jacobian matrix of a transformation ρ. □

An important observation is as follows.

Lemma 1 *If an equivariance family exists, then the parametrized family is $\mathbb{P}$-invariant.*

Observe that (5a) is a first order quasilinear partial differential equation on the components of the vector function ρ_p (for each constant value $u \in U$ and each parameter $p \in \mathbb{P}$), subject to the algebraic constraints given by (5b,c). Such equations are usually solved using the method of characteristics [7]. In principle, testing for existence of a solution through a "certificate" such as an equivariance is far simpler than testing all possible time-varying inputs $u(t)$ in the definition of equivalence, in a fashion analogous to the use of Lyapunov functions for testing stability or of value functions in the Hamilton-Jacobi-Bellman formulation of optimal control theory [4]. The paper [2] discusses the relation to classical equivariances in actions of Lie groups and symmetry analysis of nonlinear dynamical systems.

Proof of Lemma 1. Fix a parameter p and an input $u(\cdot)$; we must show that (4) is satisfied. Let $x(t) = \varphi(t, \xi, u)$, $t \geq 0$, be the solution of the initial-value problem $\dot{x} = f(x, u)$, $x(0) = \xi$, so that $\psi(t, \xi, u) = h(x(t), u(t))$. Viewing the mapping $x \mapsto \rho_p(x)$ as a change of variables, we define $z(t) := \rho_p(x(t))$. Differentiating with respect to t,

$$\dot{z}(t) = (\rho_p)_*(x(t))\dot{x}(t) = (\rho_p)_*(x(t)) f(x(t), u(t)) = f(\rho_p(x(t)), u(t), p) = f(z(t), u(t), p)$$

where we used (5a) applied with $x = x(t)$ and $u = u(t)$. Moreover, $z(0) = \rho_p(x(0)) = \rho_p(\xi) = \xi_p$, because of (5c). Thus, since the solution of the initial-value problem $\dot{x} = f(x, u, p)$, $x(0) = \xi_p$ is unique, it follows that $z(t) = \varphi(t, \xi_p, u, p)$. Now, by definition,

$$\psi(t, \xi_p, u, p) = h(\varphi(t, \xi_p, u, p), u(t), p) = h(z(t), u(t), p) = h(\rho_p(x(t)), u(t), p) = h(x(t), u(t))$$

where the last equality follows from (5b). On the other hand, since $\psi(t, \xi, u) = h(x(t), u(t))$, we conclude that (4) holds, as desired. ■

It is a deeper result that the existence of an equivariance is also *necessary* as well as sufficient, see Section 4 for a statement and proof. Necessity tells us that it is always worth searching for an equivariance, when attempting to prove that a system has $\mathbb{P}$-invariance. Often one can guess such functions by looking at the structure of the equations.

3.2 Identifiability and Lie derivatives

For simplicity, in this section of the paper we restrict attention to systems in which inputs appear linearly; that is, systems defined by differential equations of the following general form

$$\dot{x} = g_0(x, p) + u_1 g_1(x, p) + \ldots + u_m g_m(x, p)\,, \quad y = h(x, p)\,, \quad x(0) = \xi_p\,, \tag{6}$$

Linearity in inputs is not a serious restriction, nor is not having an explicit input in the read-out map, and it is easy to generalize to more general classes of systems, but the notations become far less elegant. We write the s coordinates of h as $h = (h_1, \ldots, h_s)$.

Consider the following set of functions ("elementary observables" of the system):

$$\mathcal{H} \;:=\; \left\{ L_{g_{i_1}} \ldots L_{g_{i_k}} h_j \;\middle|\; (i_1, \ldots, i_k) \in \{0, \ldots, m\}^k,\, k \geq 0,\, j \in \{1, \ldots, s\} \right\} .$$

We are using the notation

$$L_X H \;:=\; \nabla H \cdot X$$

for the directional or Lie derivative of the function H with respect to the vector field X, and an expression as $L_Y L_X H$ means an iteration $L_Y(L_X H)$. We include in particular the case in which $k = 0$, in which case the expression in the defining formula is simply h_j. For example, if the system is

$$\dot{x}_1 = \alpha u - \delta x_1 \,, \quad \dot{x}_2 = \beta u - \gamma x_1 x_2 \,, \quad y = x_2$$

(initial states do not matter at this point; the parameters or interest could be all or a subset of $\alpha, \beta, \gamma, \delta$), then

$$g_0 \;=\; \begin{pmatrix} -\delta x_1 \\ -\gamma x_1 x_2 \end{pmatrix} , \qquad g_1 \;=\; \begin{pmatrix} \alpha \\ \beta \end{pmatrix} , \qquad h(x) = x_2$$

and we compute, for example,

$$L_{g_0} h \;=\; (0 \;\; 1) \begin{pmatrix} -\delta x_1 \\ -\gamma x_1 x_2 \end{pmatrix} \;=\; -\gamma x_1 x_2 \,, \quad L_{g_1} L_{g_0} h \;=\; (-\gamma x_2 \;\; -\gamma x_1) \begin{pmatrix} \alpha \\ \beta \end{pmatrix} \;=\; -\alpha\gamma x_2 - \beta\gamma x_1 \,.$$

A necessary condition for invariance is as follows.

Lemma 2 *If a system is $\mathbb{P}$-invariant, then all elements in $\mathcal{H}$, when evaluated at the initial state, are independent of the values of parameters p.*

This condition is most useful when proving *non*-invariance. One simply finds one element of $\mathcal{H}$ which depends on parameters. This test can also be used as a test for identifiability, that is to say the possibility of recovering all parameters perfectly from outputs: if one can reconstruct the values of p from the elementary observables (evaluated at the initial state), that is to say if the map

$$p \;\mapsto\; \left(L_{g_{i_1}} \ldots L_{g_{i_k}} h_j(\xi_p) \right)_{(i_1,\ldots,i_k) \in \{0,\ldots,m\}^k \,, k \geq 0,\, j \in \{1,\ldots,s\}}$$

is one-to-one, then the parameters are identifiable. We discuss two examples in Section 3.3.

We sketch the proof of Lemma 2; see see [4], Remark 6.4.2 for more details and references. Consider a piecewise constant control which is equal to u^1 on $[0, t_1)$, equal to u^2 on $[t_1, t_1 + t_2)$, $\ldots$, and equal to u^k on $[t_1 + \ldots + t_{k-1}, t_1 + \ldots + t_k)$, starting from $x(0) = \xi_p$ By invariance, the resulting output at time $t = t_1 + \ldots + t_k$ is independent of the parameters. In general, let us denote the jth coordinate of this output value as

$$h_j(t_1, t_2, \ldots, t_k, u^1, u^2, \ldots, u^k)$$

It follows that the derivatives with respect to the t_i's of this output are also independent of parameters, for every such piecewise constant control. By induction, one has

$$\left. \frac{\partial^k}{\partial t_1 \ldots \partial t_k} \right|_{t_1 = t_2 = \ldots = 0} h_j(t_1, t_2, \ldots, t_k, u^1, u^2, \ldots, u^k) \;=\; L_{X_1} L_{X_2} \ldots L_{X_k} h_j(x)$$

where $X_l(x) = g_0(x) + \sum_{i=1}^m u_i^l g_i(x)$. This expression is a multilinear function of the u_i^l's, and a further derivation with respect to these control value coordinates gives the elementary observables, which therefore must also be independent of parameters. ∎

We remark that, assuming a certain technical condition, a converse statement holds: if the elementary observables give the same values for two parameters $p, q \in \mathbb{P}$, then the output for any possible inputs, whether step inputs or arbitrary inputs, is the same for these two parameters. The technical condition is that the vector fields g_i are real-analytic, that is, that they can be expanded into locally convergent power series. The expressions that commonly appear in systems biology models, such as mass action kinetics (polynomial functions) or Hill functions (rational functions) are real analytic, as are trigonometric, logarithmic, and exponential functions. The proof of this converse fact consists two parts: (1) showing that outputs coincide for piecewise constant inputs, which is true because $h_j(t_1, t_2, \ldots, t_k, u^1, u^2, \ldots, u^k)$ can be expressed as a power series in terms of the observables, followed by (2) an approximation of arbitrary inputs by step ones (see Proposition 6.1.11 in [4], and Section 4 in [8]).

3.3 Examples from the paper [1]

In its Supplement, the paper [1] presents the following class of systems that have $\mathbb{P}$-invariance (called there "dynamic compensation"), and the main text specializes to $n = 1$:

$$\begin{aligned}
\dot{x}_1 &= g(p_2 x_{n+1}, x_{n+2}) - \mu_1 x_1 && \text{(7a)}\\
\dot{x}_i &= \eta_{i-1} x_{i-1} - \mu_i x_i\,, \quad i \in \{2, \ldots, n\} && \text{(7b)}\\
\dot{x}_{n+1} &= x_{n+1}\ell(x_{n+2}) && \text{(7c)}\\
\dot{x}_{n+2} &= k(p_1 x_1, p_1 x_2, \ldots, p_1 x_n, x_{n+2}, u) && \text{(7d)}\\
y &= x_{n+2}\,. && \text{(7e)}
\end{aligned}$$

The state variables are positive, that is, $\mathbb{X} = \mathbb{R}_{>0}^{n+2}$, inputs and outputs are scalar and positive, $\mathbb{U} = \mathbb{R}_{>0}$, $\mathbb{Y} = \mathbb{R}_{>0}$, and the parameters for which we desire invariance are two positive numbers, $p = (p_1, p_2) \in \mathbb{P} = \mathbb{R}_{>0}^2$. The additional parameters η_i and μ_i are fixed, and g, k, ℓ are three scalar (differentiable) functions, with the following positive homogeneity property for g:

$$g(r x_{n+1}, x_{n+2}) \;=\; r g(x_{n+1}, x_{n+2}) \quad \forall\, r > 0,\, x_{n+1} > 0,\, x_{n+2} > 0\,. \tag{8}$$

The initial state is not explicitly specified in [1], but it is assumed that, given any specified parameters $p = (p_1, p_2)$, there is a unique steady state when $u = 0$, and we call this state ξ_p. We take the reference parameter set to be $\underline{1} = (1, 1)$.

In the paper [1], when n=1 this system is motivated as a mechanism for a hormonal circuit in which the output y is a regulated variable, x_1 is a hormone that regulates $y = x_3$, and the variable $x_{n+1} = x_2$ represents the functional mass of the tissue that secretes the hormone x_1. There is feedback on the regulated variable y, with a gain p_1, and a growth rate in x_{n+1} that is controlled by y, for instance through increase of proliferation. The parameter p_2 quantifies the magnitude of the effect of the mass on the hormone production rate. In one of the examples in [1], the input $u(t)$ is the meal intake of glucose, x_{n+1} represents β cells, x_1 is insulin, and y is plasma glucose concentration, the coefficients η_i correspond to transport rates, and the μ_i combine degradation rate and transport rates. The more general case n>1 represents the various physiological compartments that the hormone may circulate through.

To show $\mathbb{P}$-invariance, we exhibit an equivariance. In fact, the proof of dynamical compensation in [1] is based (without using that terminology) on showing that the following mapping is an equivariance family:

$$\rho_p(x_1, x_2, \ldots, x_n, x_{n+1}, x_{n+2}) \;:=\; (p_1^{-1} x_1, p_1^{-1} x_2, \ldots, p_1^{-1} x_n, p_1^{-1} p_2^{-1} x_{n+1}, x_{n+2})\,.$$

Since $h(x,u,p) = x_{n+2}$ is not changed by ρ_p, we have that $h(\rho_p(x),u,p) = h(x,u)$, and since as equivariances always map steady states into steady states, and steady states are assumed to be unique, there is no need to test the condition $\rho_p(\xi) = \xi_p$. So we only need to check that:

$$f(\rho_p(x),u,p) \;=\; (\rho_p)_*(x)f(x,u)$$

for all p,x,u. The map ρ_p is linear, and its Jacobian matrix is diag $(p_1^{-1},p_1^{-1},\ldots,p_1^{-1},p_1^{-1}p_2^{-1},1)$, thus we need to verify:

$$\begin{array}{rcl} g(p_2(p_1^{-1}p_2^{-1}x_{n+1}),x_{n+2}) - \mu_1(p_1^{-1}x_1) & = & p_1^{-1}\left[g(x_{n+1},x_{n+2}) - \mu_1 x_1\right] \\ \eta_{i-1}(p_1^{-1}x_{i-1}) - \mu_i(p_1^{-1}x_i) & = & p_1^{-1}\left[\eta_{i-1}x_{i-1} - \mu_i x_i\right]\,, \quad i\in\{2,\ldots,n\} \\ (p_1^{-1}p_2^{-1}x_{n+1})\ell(x_{n+2}) & = & p_1^{-1}p_2^{-1}\left[x_{n+1}\ell(x_{n+2})\right] \\ k(p_1(p_1^{-1}x_1),p_1(p_1^{-1}x_2),\ldots,p_1(p_1^{-1}x_n),x_{n+2},u) & = & k(x_1,x_2,\ldots,x_n,x_{n+2},u)\,, \end{array}$$

the last $n+1$ of which are trivial, and the first one requires $g(p_1^{-1}x_{n+1},x_{n+2}) = p_1^{-1}g(x_{n+1},x_{n+2})$, which holds because of the homogeneity property (8).

We next discuss the "linear integral feedback" and "linear proportional integral feedback" examples in the paper [1], which are given as examples of systems that are not $\mathbb{P}$-invariant (the paper does this by simulation). The first system is:

$$\begin{array}{rcl} \dot{x}_1 & = & x_2 - b \\ \dot{x}_2 & = & a - p_1x_1 - p_2x_2 + u \\ y & = & x_2 \end{array}$$

with the unique steady state $\xi_p = ((a-p_2b)/p_1,b)$ for $u(0)=0$. Let us show that there is no possible equivariance $\rho_p(x_1,x_2) = (\alpha_p(x_1,x_2),\beta_p(x_1,x_2))$. The requirement that $h(\rho_p(x),u,p) = h(x,u)$ means that $\beta_p(x_1,x_2) = x_2$, so $\rho_p(x_1,x_2) = (\alpha_p(x_1,x_2),x_2)$. The PDE $f(\rho_p(x),u,p)) = (\rho_p)_*(x)f(x,u)$ translates into:

$$\left(\begin{array}{c} x_2 - b \\ a - p_1\alpha_p(x_1,x_2) - p_2x_2 + u \end{array}\right) = \left(\begin{array}{c} \frac{\partial\alpha_p}{\partial x_1}(x_1,x_2)(x_2-b) + \frac{\partial\alpha_p}{\partial x_2}(x_1,x_2)(a - x_1 - x_2 + u) \\ a - x_1 - x_2 + u \end{array}\right).$$

Comparing coefficients of u in the first component, we have that $\frac{\partial\alpha_p}{\partial x_2} \equiv 0$, and this in turn implies that $\frac{\partial\alpha_p}{\partial x_1}(x_1,x_2) \equiv 1$. Thus the only possible choice is a linear function $\alpha_p(x_1,x_2) = c + x_1$. On the other hand, comparing second components, we have

$$\alpha_p(x_1,x_2) \;=\; \frac{1}{p_1}x_1 + \frac{1-p_2}{p_1}x_2\,,$$

contradicting this formula. Thus, no possible equivariance exists, even if we only ask one of the parameters to vary. Combined with the necessity result to be shown below, this implies no invariance.

Another way to analyze this example is as follows. Let us compute the derivatives $d_i := y^{(i)}(0^+)$ when applying an input $u(t)$ that is differentiable for $t>0$. We have that $m_0 = b$, $m_1 = u_0$, $m_2 = -p_2u_0 + u_1$, $m_3 = (p_2^2 - p_1)u_0 - p_2u_1 + u_2$, where $u_i := u^{(i)}(0^+)$. Therefore, from the output y (and in particular from its derivatives at time zero) we can reconstruct p_2 and p_1, for example using a step function $u\equiv 1$. This means that the parameter vector p is identifiable, which is the same as saying that the system is not invariant.

Alternatively, using the formalism of Lie derivatives, with

$$g_0 \;=\; \left(\begin{array}{c} x_2 - b \\ a - p_1x_1 - p_2x_2 \end{array}\right), \quad g_1 \;=\; \left(\begin{array}{c} 0 \\ 0 \\ 1 \end{array}\right), \quad h(x) = x_2$$

we can compute

$$L_{g_1} L_{g_0} h(x) = -p_2 \,, \quad L_{g_1} L_{g_0}^2 h = -p_1 + p_2^2 \,,$$

and we again see that we can recover the parameters, giving identifiability and hence non-invariance.

The second example of a system that fails invariance in the paper [1] is the "linear proportional integral feedback" given by:

$$\begin{aligned} \dot{x}_1 &= x_3 - x_1 \\ \dot{x}_2 &= x_3 - b \\ \dot{x}_3 &= a - p_2 x_1 - p_1 x_2 + u \\ y &= x_3 \end{aligned}$$

with the unique steady state $\xi_p = (b, (a - p_2 b)/p_1, b)$ for $u(0) = 0$. The non-existence of equivariances is shown similarly to the previous example and is not shown. For simplicity, we only perform the Lie derivative test. One can find

$$L_{g_1} L_{g_0}^2 h(x) = -p_2 - p_1 \,, \quad L_{g_1} L_{g_0}^3 h = p_2 \,,$$

so once more we can recover the parameters, giving identifiability and hence non-invariance.

3.4 Relations to FCD

The papers [2,3] studied a notion of scale invariance, or more generally invariance to input-field symmetries. We restrict attention here to linear scalings

$$u = (u_1, u_2, \ldots, u_m) \;\mapsto\; p \odot u = (p_1 u_1, p_2 u_2, \ldots, p_m u_m) \,,$$

although the same ideas apply to more general symmetries as well. The property being studied is the invariance of the response of the following parametrized family of systems:

$$\dot{x} = f(x, p \odot u) \,, \quad y = h(x, p \odot u) \,, \quad x(0) = \xi_p \,,$$

where the initial states ξ_p are the (assumed unique) steady states associated to $p \odot u(0)$. This property is also called "fold change detection" (FCD), because the only changes that are detectable are possibly "fold" changes in u, not simply scalings such as changes of units. It is clear that this is merely a special case of the general setup in this paper,

4 Converses of the criteria

As pointed out earlier, the criterion in Lemma 2 admits a converse, provided that the system is defined by real-analytic functions: if all elements of $\mathcal{H}$ are independent of the values of the parameters, then the system is $\mathbb{P}$-invariant. A similar result holds for identifiability: if one can recover all parameters as functions (perhaps nonlinear) of the elementary observables, then there is complete parameter identifiability (two different parameters give two different outputs, for some input).

The converse of Lemma 1 is also true, provided again that the maps f and h are real-analytic. An additional technical assumption, verified by all reasonable models including all examples in this paper, is that the systems are *irreducible*, meaning that it is accessible and observable. An accessible system is one for which the accessibility rank condition holds: $\mathcal{F}_{\mathrm{LA}}(x_0) = \mathbb{R}^n$ for every $x_0 \in \mathbb{X}$, where $\mathcal{F}_{\mathrm{LA}}$ is the accessibility Lie algebra of the system. Intuitively, this means that no conservation laws restrict motions to proper submanifolds. For analytic systems, accessibility is equivalent to the property that the set of points reachable from

any given state x has a nonempty interior; see a proof and more details in the textbook [4]. An observable system (for a fixed parameter $p \in \mathbb{P}$, not shown in the notation) is one for which $\psi(t, x_0, u) = \psi(t, \widetilde{x_0}, u)$ for all u, t implies $x_0 = \widetilde{x_0}$. Intuitively, observability means that no pairs of distinct states can give rise to an identical temporal response to all possible inputs. For analytic input-affine systems, observability is equivalent to the property that any distinct two states can be separated by the observation space ([4], Remark 6.4.2). The proof of necessity is totally analogous to that of the main theorem in [2] and is not repeated here.

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