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Scale-Invariant Systems Realize Nonlinear Differential Operators

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***Abstract*— In recent years, several biomolecular systems have been shown to be scale-invariant (SI), i.e. to show the same output dynamics when exposed to geometrically scaled input signals ($u \mapsto pu$, $p > 0$) after pre-adaptation to accordingly scaled constant inputs. In this article, we show that SI systems– as well as systems invariant with respect to other input transformations–can realize nonlinear differential operators: when excited by inputs obeying functional forms characteristic for a given class of invariant systems, the systems' outputs converge to constant values directly quantifying the speed of the input.**

I. INTRODUCTION

In this article, we analyze systems of ordinary differential equations (ODEs) whose outputs converge to constant values when excited by a class of characteristic inputs, with the value of the constant outputs directly quantifying the speed of the input. More precisely, consider a class of inputs given by $u_{k,t_0}(t) = g(kt + t_0)$, with $g : \mathbb{R} \to \mathbb{R}$ injective and $k, t_0 \in \mathbb{R}$. We are interested in systems having the property that when excited by such an input, their output $y(t)$ will converge to a constant value depending on k but not on t_0, i.e. $y(t) \to \bar{y}^* = \alpha_g(k)$, with $\alpha_g : \mathbb{R} \to \mathbb{R}$. Since we can write $\alpha_g(k) = \alpha_g(D_g u_{k,t_0})$, with $D_g = \frac{d}{dt} g^{-1}$, we refer to such systems as realizing the nonlinear differential operator D_g. Our focus lies on network architectures which can be implemented by biomolecular networks in single- or multi-cellular organisms.

As an introductory example, consider an asymptotically stable linear time-invariant system with zero DC-gain:

$$\frac{d}{dt} z(t) = Az(t) + bu(t),\ z(0) = \bar{z} \tag{1a}$$

$$y(t) = c^T z(t), \tag{1b}$$

with state vector $z(t) \in \mathbb{R}^n$, system matrix $A \in \mathbb{R}^{n \times n}$ being Hurwitz, input and output matrices $b, c \in \mathbb{R}^{n \times 1}$, and $u(t), y(t) \in \mathbb{R}$ the input, respectively output of the system. Zero DC-gain ($K_{DC} = -c^T A^{-1} b = \lim_{s \to 0} G(s) = 0$, with G the transfer function) implies that $y \to 0$ for constant inputs, corresponding to adaptation of a biomolecular network. In the following, we assume $c^T A^{-2} b \neq 0$.

When exciting (1) by a ramp input $u_{k,u_0}(t) = u_0 + kt$, with $k, u_0 \in \mathbb{R}$, the output of the system converges to a constant value $y \to \bar{y}^* = -c^T A^{-2} bk = -c^T A^{-2} b \frac{d}{dt} u_{k,u_0}$ proportional to the slope of the ramp k. In the context of biomolecular signaling networks, the sign of k can be interpreted as the type of an environmental change, e.g. if conditions are improving or degrading. Then, the value of k corresponds to the speed in which the environment changes. Thus, a (hypothetical) single- or multi-cellular organism implementing the system (1) could deduce from its output the speed in which the environment changes and orchestrate its cellular response accordingly, respectively "predict" future changes in order to pre-adapt and, thus, assure favorable conditions for survival and proliferation.

Now, consider the similar log-linear system

$$\frac{d}{dt} z(t) = Az(t) + b \log(u(t)),\ z(0) = \bar{z} \tag{2a}$$

$$y(t) = c^T z(t), \tag{2b}$$

with $u(t) > 0$ and all other variables as defined above. We can directly conclude that when exciting (2) by an exponential input $u_{k,u_0}(t) = u_0 e^{kt}$, with $k \in \mathbb{R}$ and $u_0 \in \mathbb{R}_{>0}$, the output of the system converges to a constant value only depending on k, but not on u_0: $y \to \bar{y}^* = -c^T A^{-2} bk = -c^T A^{-2} b \frac{d}{dt} \log(u_{k,u_0})$. Thus, the system (2) can detect the speed of environmanetal changes which can be approximated by exponential functions. It should be clear by now that one could replace the logarithm in (2) by other nonlinear functions to realize systems capable to detect the speed of other injective inputs.

Based on these two examples, we loosely define the linear system (1) to realize the "usual" differential operator $D_r = \frac{d}{dt}$ when excited by ramp inputs and after the decay of the effect of the initial conditions. Similarly, we loosely define the log-linear system (2) to realize the nonlinear differential operator $D_e = \frac{d}{dt} \log$ when excited by exponential inputs. We might ask if the two systems also perform the same differential operation for other inputs than ramps, respectively exponential functions. This is in general not the case, as can be easily verified when exciting the linear system (1) by sinusoidal inputs with fixed mean and amplitude, but increasing frequency. Due to the restriction of the differential operations on specific functional forms of the input, we will refer to the ramps, respectively exponential functions as the *characteristic inputs* for which the respective system realizes the nonlinear differential operator.

Our (yet only loosely defined) concept of systems realizing differential operators has notable similarities with the internal model principle (IMP, [1]) stating that a dynamic system should have an internal model of a class of environmental disturbances to be able to reject them, i.e. in order for the output to converge to a constant value independent of the specific disturbance. Note, that the linear (1) and the loglinear (2) systems would reject ramp or exponential inputs if $c^T A^{-2} b = 0$. The conceptual difference between our

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concept and the IMP is that the IMP concerns the question of how a system can *reject* inputs having certain functional forms, while we consider how it can *discriminate* between them. One might hypothesize a system should also possess (a set of) internal models of the environment to fulfill the latter. Due to subtle differences between the types of inputs analyzed in the IMP and in this article, this hypothesis will not be considered in the following.

In this article, we pose the question if there exist *structural* properties of (general nonlinear) systems rendering them able to realize nonlinear differential operators. We demonstrate that scale-invariant systems (also referred to as fold change detectors, see [2]) can realize nonlinear differential operators of the form $D_e = \frac{d}{dt}\log$, whereas systems being invariant with respect to different sets of input transformations [3] can realize other differential operators.

In the following, we briefly review the definition and known results for systems being invariant with respect to certain sets of input transformation. Then, we provide two examples of scale-invariant systems, an incoherent feed-forward loop and an integral feedback. Based on these examples, we derive a general mathematical definition of systems realizing nonlinear differential operators. Then, we derive the notion of *canonical models* for systems invariant with respect to Lie group input transformations and excited by characteristic inputs. This notion is in one-to-one relationship with the nonlinear differential operator realized by the invariant system. Finally, we provide an intuitive topological interpretation of our results. Our analysis shows that the differential operator an invariant system realizes is determined by the input invariance, and independent of other details of the specific system.

II. EQUIVARIANCE

Throughout this article, we consider dynamic systems of nonlinear ordinary differential equations (ODEs) of the form

$$\frac{d}{dt}z(t) = f(z(t), u(t)),\ \ z(0) = \bar{z} \tag{3a}$$

$$y(t) = h(z(t)), \tag{3b}$$

with state vector $z(t) \in Z \subseteq \mathbb{R}^n$, piecewise-continuous inputs $u : \mathbb{R}_{\geq 0} \to U \subseteq \mathbb{R}$, $u \in \mathcal{U} \subseteq \mathcal{PC}(\mathbb{R}_{\geq 0}, U)$, vector fields $f : Z \times U \to \mathbb{R}^n$, initial conditions $\bar{z} \in Z$, and outputs $y(t) \in \mathbb{R}$.

We assume that the functions f and h are differentiable, and that for each initial condition $\bar{z} \in Z$ and each input $u \in \mathcal{U}$ there exists a unique, piecewise differentiable and continuous solution of Eq. 3, which we denote by

$$\xi : \mathbb{R}_{\geq 0} \times Z \times \mathcal{U} \to Z, \quad \xi(t, \bar{z}, u) = z(t).$$

If the system (3) has a globally asymptotically stable (GAS) steady-state for constant inputs $u(t) = \bar{u} \in U$, we denote this steady-state by $\sigma(\bar{u}) \in Z$, i.e. $\xi(t, \bar{z}, \bar{u}) \to \sigma(\bar{u})$ for all $\bar{z} \in Z$. Then, the system (3) is *invariant* [3] with respect to a set of continuous and onto input transformations $\mathcal{P} = \{\pi : U \to U\}$ (in short, is $\mathcal{P}$-invariant), if

$$h(\xi(t, \sigma(\bar{u}), u)) = h(\xi(t, \sigma(\pi(\bar{u})), \pi \circ u)),$$

for all $\bar{u} \in U$, $u \in \mathcal{U}$, $\pi \in \mathcal{P}$ and $t \geq 0$, with $\circ$ the function composition.

Conversely, the system (3) is *equivariant* [3] with respect to $\mathcal{P}$ (in short, is $\mathcal{P}$-equivariant), if there exists an indexed family of differentiable state transformations $\mathcal{R}_{\mathcal{P}} = \{\rho_\pi : Z \to Z\}_{\pi \in \mathcal{P}}$ such that

$$f(\rho_\pi(z), \pi(\bar{u})) = \rho'_\pi(z) f(z, \bar{u}), \text{ and}$$
$$h(\rho_\pi(z)) = h(z)$$

for all $z \in Z, \bar{u} \in U$, and $\pi \in \mathcal{P}$, with ρ'_π the Jacobian matrix of ρ_π.

In [3], it was shown that an analytic and irreducible system having a GAS steady-state for each constant input is $\mathcal{P}$-invariant if and only if it is $\mathcal{P}$-equivariant. Furthermore, it was shown [3] that if the action is transitive, i.e. $\forall \bar{u}_1, \bar{u}_2 \in U, \exists \pi \in \mathcal{P} : \pi(\bar{u}_1) = \bar{u}_2$, $\mathcal{P}$-invariance implies perfect adaptation to constant inputs. Note, that–different to $\mathcal{P}$-invariance–the concept of $\mathcal{P}$-equivariance does not require the system (3) to possess a GAS steady-state, or any steady-state at all. We refer to [3] for details of the definitions and the proofs.

Two important classes of $\mathcal{P}$-invariant systems are scale-invariant systems, i.e. systems invariant with respect to geometric scaling $\mathcal{P} = \{\pi : U \to U, (\pi \circ u)(t) = pu(t), p \geq 0\}$ of the input by positive constants, and translational-invariant systems, i.e. systems invariant with respect to $\mathcal{P} = \{\pi : U \to U, (\pi \circ u)(t) = u(t) + p, p \in \mathbb{R}\}$.

A. EXAMPLES OF SCALE-INVARIANT INTEGRAL FEEDBACKS AND INCOHERENT FEEDFORWARD LOOPS

Before providing a mathematical definition of when a given nonlinear system (3) realizes a nonlinear differential operator, we analyze two scale-invariant systems realizing (i) an integral feedback and (ii) an incoherent feedforward loop to provide intuition about the details of our definition.

The first system (see [3], Figure 1c) is given by the ODEs

$$\frac{d}{dt}x(t) = ax(y(t) - y_0) \tag{4a}$$

$$\frac{d}{dt}y(t) = b\frac{u(t)}{x(t)} - dy(t), \tag{4b}$$

with $a, b, d, y_0 \in \mathbb{R}_{>0}$, $x(t) > 0$, $y(t) \geq 0$, $u(t) \geq 0$, and output $h(x(t), y(t)) = y(t)$. As shown in [3], the system is asymptotically stable for constant inputs and scale-invariant, with $(\pi_p \circ u)(t) = pu(t)$, $p > 0$, and $\rho_p(x, y) = (px, y)^T$.

We have not yet given a mathematical definition stating when we consider a system to realize a (nonlinear) differential operator, nor provided any framework to determine which differential operator a system realizes–if any. Nevertheless, based on the observation that both the integral feedback (4) as well as the log-linear system (2) are scale-invariant, we can hypothesize that the output of both systems should

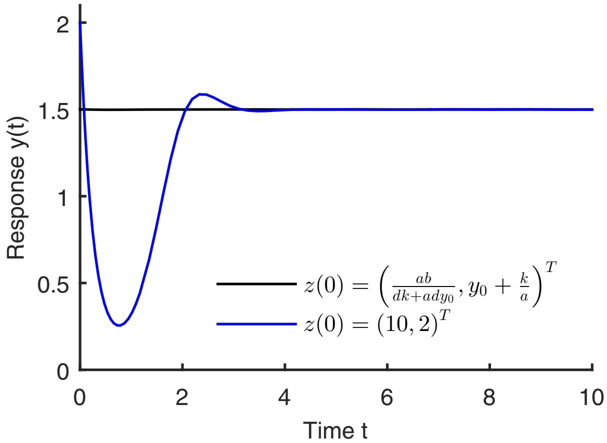

Fig. 1: Simulation results for the integral feedback system (4) for the exponential input $u(t) = e^{kt}$. The black curve represents the system initialized at $(\bar{x}^*, \bar{y}^*)^T$, while the blue curve is initialized at $(10,2)^T$. The parameters were set to $k = 1$, $T = 6$, $a = 2$, $b = 3$, $d = 4$, and $y_0 = 1$.

somewhat behave similarly when the system is excited by an exponential input $u_{k,u_0}(t) = u_0 e^{kt}$. Specifically, we expect the output y of (4) also to converge to a constant value $\bar{y}^*$ depending on k, but not on u_0. To verify this hypothesis, we directly plug $u_{k,u_0}(t)$, $y(t) = \bar{y}^*$ and $\frac{d}{dt}y(t) = 0$ into (4b) and obtain that $x(t) = \frac{bu_0}{d\bar{y}^*}e^{kt}$ for $\bar{y}^* > 0$. Plugging $x(t)$ and its time derivative $\frac{d}{dt}x(t)$ in (4a) results in $\bar{y}^* = y_0 + \frac{k}{a}$. We conclude that the system (4) excited by inputs of the form u_{k,u_0} and initialized at $(\bar{x}^*, \bar{y}^*)^T = (\frac{abu_0}{dk+ady_0}, y_0 + \frac{k}{a})^T$ has a constant output (see Fig. 1), i.e. $y(t) = \bar{y}^* = y_0 + \frac{1}{a}\frac{d}{dt}\log(u_{k,u_0})$ if $k > K_L$, with $K_L = -ay_0$.

Since $\bar{y}^*$ only depends on the input transformed by the nonlinear differential operator $D_e = \frac{d}{dt} \circ \log$, we also loosely define the integral feedback system (4) to realize D_e, similar to the log-linear system (2). Due to the differences between these two systems (and the analysis we performed on them), this has important implications for the general mathematical definition yet to come: (i) the constant output $\bar{y}^*$ might not be proportional to k, but have some other (injective) dependence; (ii) a system might realize a differential operator only for a certain range of inputs of a given functional form; (iii) the existence of an initial condition such that the output is constant does in general not guarantee that the output for other initial conditions converges to this constant, and our definition should account for that.

As a second example, consider an incoherent feed-forward loop (compare [4], Figure 3) given by the ODEs

$$\frac{d}{dt}x(t) = -ax(t) + bu(t) \tag{5a}$$

$$\frac{d}{dt}y(t) = c\frac{u(t)}{x(t) + u(t)} - dy(t), \tag{5b}$$

with parameters $a, b, c, d \in \mathbb{R}_{>0}$, states $x(t), y(t) \in \mathbb{R}_{\geq 0}$, positive inputs $u(t) \in \mathbb{R}_{>0}$, and output $h(x(t), y(t)) = y(t)$. It is easy to verify that the system has a GAS steady-state $\sigma(\bar{u}) = \left(\frac{b}{a}\bar{u}, \frac{ac}{d(a+b)}\right)^T$ for constant inputs $u(t) = \bar{u} \in \mathbb{R}_{>0}$ and is scale-invariant, with $(\pi_p \circ u)(t) = pu(t)$, $p > 0$, and $\rho_p(x, y) = (px, y)$.

When performing the same analysis as for the integral feedback system (4), we find that the output of the system (5) initialized at $(\bar{x}^*, \bar{y}^*) = (\frac{bu_0}{a+k}, \frac{c}{d}\frac{a+k}{a+b+k})^T$ and excited by $u_{k,u_0}(t) = u_0 e^{kt}$ is constant with $y(t) = \frac{c}{d}\frac{a+k}{a+b+k} = \frac{c}{d}\frac{a+\frac{d}{dt}\log(u_{k,u_0})}{a+b+\frac{d}{dt}\log(u_{k,u_0})}$, if $k > K_L = -a$. Given that these results are in agreement with the conclusions obtained for the integral feedback system (4), we are now confident enough to give a general mathematical definition of when a nonlinear system realizes a given nonlinear differential operator.

III. SYSTEMS REALIZING NONLINEAR DIFFERENTIAL OPERATORS

Definition 1: Consider a general nonlinear system of the form (3) and an indexed family of inputs $\mathcal{U}_g = \{u_{k,t_0} : [0,\infty) \to \mathbb{R} | u_{k,t_0}(t) = g(kt + t_0)\}_{k,t_0 \in \mathbb{R}}$ defined by a non-constant piecewise-continuous "prototype" function $g : \mathbb{R} \to \mathbb{R}$. Then, the system *realizes* the (nonlinear) differential operator $D_g : \mathcal{U}_g \to \mathbb{R}$, if there exists a set $KT = K \times T \subseteq \mathbb{R}^2$ with non-empty interior, such that for all inputs $u_{k,t_0} \in \mathcal{U}_g$ with $(k, t_0) \in KT$ there exists an initial condition $\bar{z}_u^* \in Z$ for which the output is constant and independent of t_0, i.e. $\bar{y}_u^* = h(\xi(t, \bar{z}_u^*, u_{k,t_0})) = \alpha_g(k) = \alpha_g(D_g u_{k,t_0})$ for all $t \geq 0$, with $\alpha_g : K \to \mathbb{R}$ a function which might depend on the specific system.

If a system realizes the differential operator D_g, we denote the inputs $\mathcal{U}_g$ as its *characteristic inputs*, and the inputs $\bar{\mathcal{U}}_g = \{u_{k,t_0} \in \mathcal{U}_g | (k, t_0) \in KT\}$ as its *proper characteristic inputs*. For a given characteristic input $u_{k,t_0} \in \bar{\mathcal{U}}_g$, if there exists a neighborhood $\bar{Z} \subseteq Z$ of $\bar{z}_u^*$ such that the output of the system initialized at every $\bar{z} \in \bar{Z}$ converges to $\bar{y}_u^*$, we say that the system is *convergent* with respect to the input, and if $\bar{Z} = Z$ that it is *globally convergent*. If there does not exist a set KT for which α_g is injective, the system is a *degenerated* realization of D_g.

We do not provide an explicit definition of the differential operator D_g. If there exists an inverse g^{-1} for g, then $D_g = \frac{d}{dt} \circ g^{-1}$. However, the definition in principle also allows for non-injective prototype functions like $g(t) = \sin(t)$ and similar. Note, that in general, g, D_g, and α_g are not unique. Interestingly, an important class of degenerated realizations of differential operators are systems for which $\alpha_g(k) = \text{const}$, i.e. systems rejecting inputs/disturbances of class $\bar{\mathcal{U}}_g$ (compare with the IMP, [1]).

Based on Definition 1, it is easy to validate that all three examples of scale-invariant systems (2,4,5) discussed so far are non-degenerate realizations of the differential operator $D_e = \frac{d}{dt} \circ \log$, with the characteristic functions defined by the prototype $e(t) = e^t$. On the other hand, the translational invariant linear system (1) realizes the differential operator $D_r = \frac{d}{dt}$ with prototype $r(t) = t$. For both systems from the Introduction (1,2), we have shown that $\bar{\mathcal{U}}_g = \mathcal{U}_g$, and that the systems are globally convergent with respect to the inputs in $\mathcal{U}_g$. Conversely, we have not shown this for the integral feedback (4) and the incoherent feedforward (5), yet, and will do so later in this article.

IV. LIE GROUP INVARIANCES AND CANONICAL MODELS

In this section, we analyze the relationship between the input transformations $\mathcal{P}$ a system is invariant to, and the set of characteristic functions $\mathcal{U}_g$ for which it realizes the nonlinear differential operator D_g.

In the following, we restrict ourselves to input and state transformations $\mathcal{P}\times\mathcal{R}_{\mathcal{P}}$ forming a one-parameter Lie group [5] under function composition $\circ$. This restricts the class of systems under consideration to the ones invariant with respect to continuous groups of input transformations (e.g. scale or translational-invariant systems). Systems having only discrete invariances, e.g. systems only invariant with respect to a change of the sign of the input, are not considered. Then, we can parametrize the input and state transformations by some parameter $p \in \mathbb{R}$, such that the functional composition is additive in p, i.e. $\pi_{p_1} \circ \pi_{p_2} = \pi_{p_1+p_2}$ and $\rho_{p_1} \circ \rho_{p_2} = \rho_{p_1+p_2}$, with ρ_p shorthand for ρ_{π_p}, and $\pi_0(\bar{u}) = \bar{u}$ and $\rho_0(z) = z$ the trivial input and state transformations.

We now consider the evolution of the states of a $\mathcal{P}$-equivariant system excited by the input $u(t) = \pi_{kt+t_0}(u_0)$, with $k \in \mathbb{R}$ and $u_0 \in U$, i.e. by an input directly defined by the additive parametrization of the input transformations. The system (3) can then be written as

$$\frac{d}{dt}z(t) = f(z(t), \pi_{kt+t_0}(u_0)),\ z(0) = \bar{z} \tag{6a}$$

$$y(t) = h(z(t)). \tag{6b}$$

Since (3) is time-invariant and equivariant with respect to $\mathcal{P}$, it directly follows that the solutions of (6) has symmetries $(t, z(t)) \mapsto (t+T, \rho_{kT}(z(t)))$, with $T \in \mathbb{R}$, i.e. a simultaneous transformation of the *time* and the states maps solutions of (6) into one another.

This suggests that there exist a change of coordinates $(t, z) \mapsto (\hat{t}, \hat{z})$ such that in the *canonical coordinates* $(\hat{t}, \hat{z})$ the system (6) is separable [5]. Indeed, when setting $(\hat{t}, \hat{z}) = (t, \rho_{-kt-t_0}(z))$, we obtain

$$\begin{aligned}\frac{d}{dt}\hat{z} =& \frac{d}{dt}\rho_{-kt-t_0}(z)\\ =& \frac{\partial}{\partial z}\rho_{-kt-t_0}(z)\frac{d}{dt}z + \frac{\partial}{\partial t}\rho_{-kt-t_0}(z)\\ =& \rho'_{-kt-t_0}(z) f(z(t), \pi_{kt+t_0}(u_0))\\ & + k\left(\frac{\partial}{\partial p}\rho_{-p}\right)\circ\rho_p(\hat{z})\Big|_{p=kt+t_0}\\ =& f(\hat{z}, u_0) - k\eta(\hat{z}),\end{aligned} \tag{7}$$

with $\eta(\hat{z}) := \frac{\partial}{\partial p}\rho_p(\hat{z})\Big|_{p=0}$ the symbol of the infinitesimal transformation [5]. By noting that $h(z) = h(\rho_{kt+t_0}(\hat{z})) = h(\hat{z})$, the complete transformed model can be written as

$$\frac{d}{dt}\hat{z}(t) = f(\hat{z}, u_0) - k\eta(\hat{z}),\ \hat{z}(0) = \rho_{-t_0}(\bar{z}) \tag{8a}$$

$$y = h(\hat{z}). \tag{8b}$$

We refer to (8) as the *canonical model* of the system (3) excited by the inputs $u(t) = \pi_{kt+t_0}(u_0)$, with $k, t_0 \in \mathbb{R}$ and $u_0 \in U$. The canonical model corresponds to a time-invariant system of ODEs excited by the constant input u_0. Importantly, its dynamics only depend on the speed k of the input, whereas the factor t_0 only has an influence on the initial conditions. Based on the canonical model, we can readily derive the following theorem.

Theorem 1: Consider a $\mathcal{P}$-equivariant system (3) with the set of input and state transformations forming a Lie group. If there exists a set $KT \subseteq \mathbb{R}^2$ with non-empty interior such that the canonical model (8) of the system has at least one steady-state $\hat{z}^*_u \in \rho_{-t_0}(Z)$ for all $(k, t_0) \in KT$, the system realizes the (nonlinear) differential operator $D_{\pi_t(u_0)}$ with respect to the characteristic inputs $\mathcal{U}_{\pi_t(u_0)}$ defined by the prototype function $\pi_t(u_0)$, with $u_0 \in U$ and $\{\pi_p\}_{p\in\mathbb{R}}$ an additive parametrization of the input transformations $\mathcal{P}$.

The characteristic inputs $\pi_{kt+t_0}(u_0)$, with $(k, t_0) \in KT$ are proper. If for a given $(k, t_0) \in KT$ the steady-state of the canonical model is (globally) asymptotic stable, the system is (globally) convergent with respect to the input $\pi_{kt+t_0}(u_0)$.

Proof: The output of the canonical model initialized at any $\hat{z} \in \rho_{-t_0}(Z)$ equals the output of the original model (3) excited by $\pi_{kt+t_0}(u_0)$ and initialized at $\rho_{t_0}(\hat{z})$. If $(k, t_0) \in KT$ and the canonical model is initialized at its steady-state $\hat{z}^*_u$, its output $y = h(\hat{z})$ is constant; in consequence also the output of the original model initialized at $\bar{z}^*_u = \rho_{t_0}(\hat{z}^*_u)$ is constant. Since this holds for all $(k, t_0) \in KT$ and KT has a non-empty interior, the system realizes the differential operator $D_{\pi_t(u_0)}$, and–by definition–the inputs $\pi_{kt+t_0}(u_0)$ with $(k, t_0) \in KT$ are proper. Asymptotic stability of $\hat{z}^*_u$ for a given $(k, t_0) \in KT$ implies that there exists an open neighborhood $\hat{Z}$ around $\hat{z}^*_u$, such that for all initial conditions in $\hat{Z}$, the output of the canonical model–and, thus, of the $\mathcal{P}$-equivariant system (3) excited by $\pi_{kt+t_0}(u_0)$–converges to a constant value. Let $\hat{Z} = \rho_{-t_0}(\bar{Z})$, then the $\mathcal{P}$-equivariant system (3) converges to the constant output when excited by $\pi_{kt+t_0}(u_0)$ for all initial conditions $\bar{z} \in \bar{Z}$. Since ρ_{-t_0} is continuous and $\hat{Z}$ is open, $\bar{Z}$ is open, from which convergence of the $\mathcal{P}$-equivariant system with respect to the input $\pi_{kt+t_0}(u_0)$ follows. Global asymptotic stability implies that $\hat{Z} = \rho_{-t_0}(Z)$, and, since $\bar{Z} = \rho_{t_0}(\rho_{-t_0}(Z)) = Z$, global convergence. ■

We can consider the term $k\eta(\hat{z})$ in (8) as an additive, in general non-vanishing perturbation of the original system (3) excited by the constant input $u(t) = u_0$. Then, for $|k| \ll 1$, we can apply methods from perturbation theory (see e.g. [6]) to the canonical model (8) to compare the output dynamics of the $\mathcal{P}$-equivariant system (3) excited by $\pi_{kt}(u_0)$ with the dynamics when excited by the constant input $u(t) = u_0$. Specifically, if for constant inputs the $\mathcal{P}$-equivariant system (3) has an exponentially stable steady-state in the interior of Z and f and η are continuously differentiable, we can apply the implicit function theorem to show that the system realizes a nonlinear differential operator. However, for a given equivariant system it is typically simpler to directly analyze the existence and stability of steady-states of its

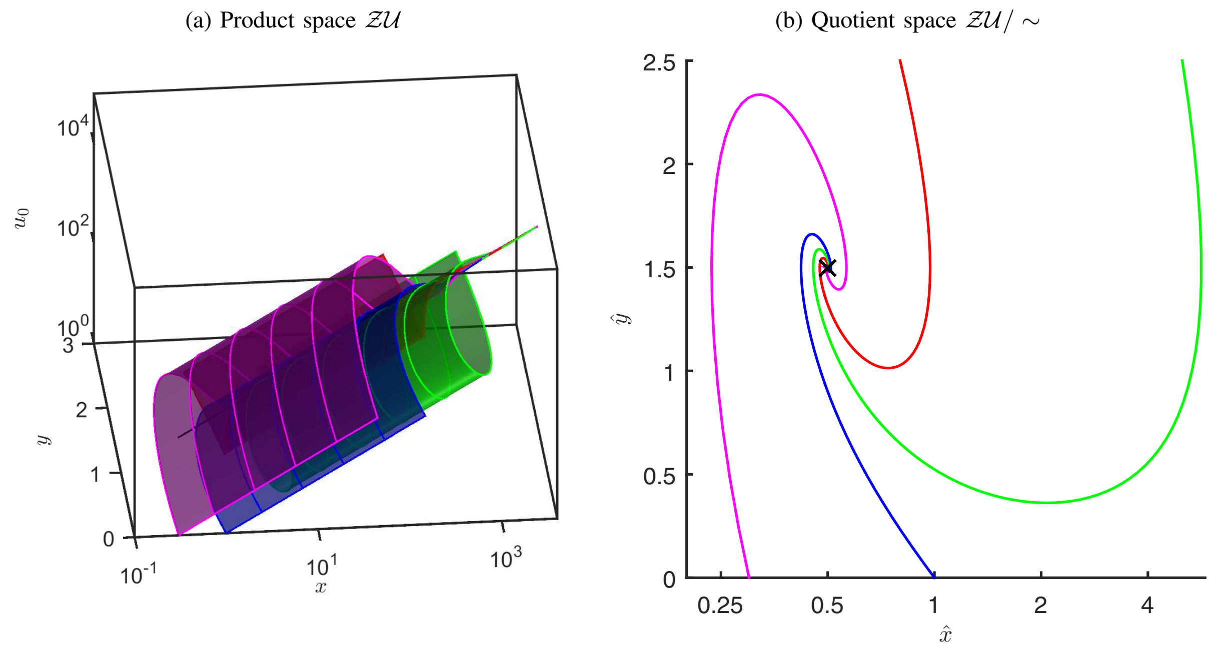

Fig. 2: Trajectories of the scale-invariant integral feedback system (4) in the product space $\mathcal{ZU} = Z \times \mathcal{U}$ (a), and in the quotient space $\mathcal{ZU}/\sim$ (b). Trajectories with the same color correspond to initial conditions $\bar{z}$ and inputs $u(t) = u_0 e^t$ in the same equivalence class. In $\mathcal{ZU}/\sim$, such trajectories are equivalent. Inputs were chosen in order that all trajectories evolve in the subspace $Z \times \{u \in \mathcal{U} | u(t) = u_0 e^t\}_{u_0 \in \mathbb{R}_{>0}} \subset \mathcal{ZU}$, i.e. that the trajectories are uniquely determined by the coordinates $x > 0$, $y \geq 0$ and $u_0 > 0$ shown in (a). In (b), the quotient space $\mathcal{ZU}/\sim$ can be naturally identified with $\mathbb{R}_{>0} \times \mathbb{R}_{\geq 0}$ (corresponding to a slice through $\mathcal{ZU}$ at $u_e \in \mathcal{U}$, $u_e(t) = e^t$). In $\mathcal{ZU}/\sim$, all trajectories spiral into $[(\bar{z}_u^*, e^t)]$ (black cross). Thus, the system (4) is globally convergent with respect to the proper characteristic inputs $u(t) = u_0 e^t$, $u_0 \in \mathbb{R}_{>0}$. Parameters were set to $a = 2$, $b = 3$, $d = 4$, and $y_0 = 1$.

canonical model (8) for different $(k, t_0) \in \mathbb{R}^2$.

Let us quickly revisit the integral feedback (4) and the feedforward loop (5) examples. For both systems, the additive parametrizations of the input and state transformations are given by $\pi_p(\bar{u}) = e^p \bar{u}$ and $\rho_p(x, y) = (e^p x, y)^T$, thus, $\eta(\hat{x}, \hat{y}) = \frac{\partial}{\partial p} \rho_p(\hat{x}, \hat{y})\Big|_{p=0} = (\hat{x}, 0)^T$. The canonical model of the integral feedback (4) is given by

$$\frac{d}{dt}\hat{x}_k(t) = a\hat{x}_k(t)(\hat{y}_k(t) - y_0 - \frac{k}{a})$$
$$\frac{d}{dt}\hat{y}_k(t) = b\frac{u_0}{\hat{x}_k(t)} - d\hat{y}_k(t),$$

with $\hat{x}_k > 0$ and $\hat{y}_k \geq 0$. For $k > K_L := -ay_0$, the canonical model has a steady-state at $(\hat{x}_k^*, \hat{y}_k^*)^T = (\frac{abu_0}{dk + ady_0}, y_0 + \frac{k}{a})$. The steady-state is globally asymptotic stable (see Corollary 5.2 in [3]). We can conclude that the original model (4) is globally convergent with respect to exponential inputs with $k > K_L$.

The canonical model of the incoherent feedforward loop (5) is

$$\frac{d}{dt}\hat{x}_k(t) = -(a + k)\hat{x}_k(t) + bu_0$$
$$\frac{d}{dt}\hat{y}_k(t) = c\frac{u_0}{\hat{x}_k(t) + u_0} - d\hat{y}_k(t).$$

For $k > K_L := -a$, the canonical model has a globally asymptotically stable steady-state at $(\hat{x}_k^*, \hat{y}_k^*)^T = \left(\frac{bu_0}{a+k}, \frac{c}{d}\frac{a+k}{a+b+k}\right)$, such that the feedforward loop (5) is globally convergent with respect to exponential inputs with $k > K_L$.

A. *TOPOLOGICAL INTERPRETATION*

The relationship between a $\mathcal{P}$-equivariant system (3) with input- and state-transformations being a Lie-group, and its canonical model (8) has an intuitive interpretation in the product space $\mathcal{ZU} = Z \times \mathcal{U}$ of the state and the input spaces. Consider the binary relation $\sim$, with $(z_1, u_1) \sim (z_2, u_2)$ if there exists a $\pi \in \mathcal{P}$ such that $u_2 = \pi(u_1)$ and $z_2 = \rho_\pi(z_2)$. Then, $\sim$ is an equivalence relationship on $\mathcal{ZU}$ with the equivalence classes in $\mathcal{ZU}/\sim$ representing each a set of initial conditions and inputs leading to the same output dynamics. Note, that we could alternatively apply the more general but less convenient equivalence relationship $\approx$, with $(z_1, u_1) \approx (z_2, u_2)$ if $h(\xi(t, z_1, u_1)) = h(\xi(t, z_2, u_2))$ for all $t \geq 0$.

The evolution $\xi(t, z, u)$ of an equivariant system corresponds to an indexed family of mappings from $\mathcal{ZU}$ to $\mathcal{ZU}$:

$$\{\lambda_t : \mathcal{ZU} \to \mathcal{ZU} | \lambda_t((\bar{z}, u)) = (\xi(t, \bar{z}, u), T_t u) \geq 0\}_{t \geq 0},$$

with $T_t : \mathcal{U} \to \mathcal{U}$, $T_t u(\tau) = u(\tau + t)$ $\forall \tau \geq 0$, the shift operator.

Trivially, if two output trajectories are the same, also their ends have to be the same. Thus,

$$(\bar{z}_1, u_1) \sim (\bar{z}_2, u_2) \Rightarrow \lambda_t((\bar{z}_1, u_1)) \sim \lambda_t((\bar{z}_2, u_2)) \; \forall t \geq 0.$$

This implies that each λ_t maps equivalence classes to equivalence classes:

$$\lambda_t([(z, u)]) \subseteq [\lambda_t(z, u)] \; \forall t \geq 0.$$

Given these definitions, a characteristic input $u_{k,t_0} \in \mathcal{U}_g$ is proper (i.e. $u_{k,t_0} \in \bar{\mathcal{U}}_g$) if there exists an initial condition $\bar{z}_u^* \in Z$, such that

$$\lambda_t([(\bar{z}_u^*, u_{k,t_0})]) \subseteq [(\bar{z}_u^*, u_{k,t_0})] \; \forall t \geq 0.$$

The evolution of a $\mathcal{P}$-equivariant system excited by a proper characteristic input and initialized at a corresponding initial condition $\bar{z}_u^*$ corresponds to a single point, or steady-state, in $\mathcal{ZU}/\sim$ (see Fig. 2).

The canonical model is associated with a different indexed family of mappings $\{\hat{\lambda}_{u,t}\}_{t\geq 0}$. In the following, we show that for a given characteristic input u_{k,t_0}, the mapping of the original model is equivalent to the mapping of its canonical model, i.e.

$$\lambda_t((z, u_{k,t_0})) \sim \hat{\lambda}_{u,t}((z, u_{k,t_0}))$$

for all $t \geq 0$ and $z \in Z$. For $dt \ll 1$,

$$\begin{aligned}
&[\lambda_{dt}((z, u_{k,t_0}))] \\
&=[(\xi(dt, z, u_{k,t_0}), \pi_{kdt}(u_{k,t_0}))] \\
&=[(z + f(z, u_{k,t_0}(0))dt + O(dt^2), \pi_{kdt}(u_{k,t_0}))] \\
&=[(\rho_{-kdt}(z + f(z, u_{k,t_0}(0))dt + O(dt^2)), u_{k,t_0})] \\
&=[(z + f(z, u_{k,t_0}(0))dt - k\eta(z)dt + O(dt^2), u_{k,t_0})] \\
&=[\hat{\lambda}_{u,dt}((z, u_{k,t_0})) + (O(dt^2), 0)].
\end{aligned}$$

For $dt \to 0$, $[\lambda_{dt}((z, u_{k,t_0}))] \to [\hat{\lambda}_{u,dt}((z, u_{k,t_0}))]$, thus, $\lambda_t((z, u_{k,t_0})) \sim \hat{\lambda}_{u,t}((z, u_{k,t_0}))$. Specifically, since $\hat{\lambda}_{u,t}$ maps the characteristic input to itself ($u_{k,t_0} \mapsto u_{k,t_0}$) instead of applying a time-shift as the mapping λ_t of the original model ($u_{k,t_0} \mapsto \pi_{kt} \circ u_{k,t_0} = T_t \circ u_{k,t_0}$), the canonical model is excited by a constant input.

In summary: we can interpret the evolution of the canonical model in the product space $\mathcal{ZU}$ to be the *projection* of the evolution of the original model onto a plane defined by a specific characteristic input, with the projection having the property that it conserves the equivalence relation $\sim$ (see Fig. 3). This interpretation is closely related to the proof of the relationship between equivariances and invariances, which appeal to realization theory of nonlinear systems (see proof and comments in [3]).

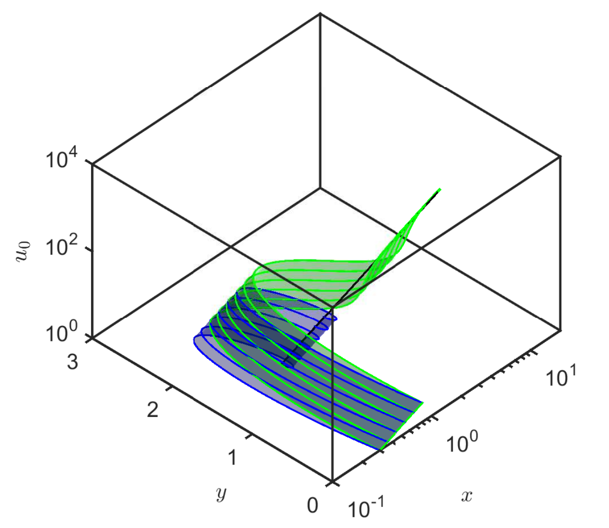

Fig. 3: Trajectories of the (green) scale-invariant integral feedback system (4), and (blue) of its canonical model for different u_0 in the product space $\mathcal{ZU} = Z \times \mathcal{U}$ (see legend of Fig. 2). All initial conditions $\bar{z}$ and inputs $u(t) = u_0 e^t$, $u_0 \in \mathbb{R}_{>0}$ were in the same equivalence class. Parameters were set to $a = 2$, $b = 3$, $d = 4$, and $y_0 = 1$.

V. Conclusion

In this article, we showed that–under weak assumptions–systems invariant to input transformations forming a Lie group realize nonlinear differential operators, and provided a first attempt for a mathematical formalization and typification. Given our analysis, scale-invariant systems can best be described to realize the nonlinear differential operator $\frac{d}{dt} \circ \log$, while the "usual" differential operator $\frac{d}{dt}$ can be realized by translational-invariant systems. As demonstrated in the introduction, it is trivial to define systems realizing other nonlinear differential operators. For which of these operators we can find naturally evolved biomolecular networks (approximately) realizing them, or easily construct synthetic ones, remains a question for future research.

In the introduction, we provided the simple example of a sinusoidal input with increasing frequency to show that an equivariant system does in general not realize a nonlinear differential operator with respect to any input signal, motivating our notion of characteristic inputs. However, it seems that systems realizing a differential operator can also perform the "correct" operation on certain non-characteristic inputs. Consider e.g. the scale-invariant system (4) excited by a ramp. Since $\frac{d}{dt}\log(u_0 + kt) \to 0$ for $t \to \infty$ and $k, u_0 > 0$, we would expect the output to converge to a value corresponding to constant inputs, and this is indeed the behavior we observe in simulations. In this context, it is interesting that three second-order scale-invariant systems were recently shown to have similar dynamics as the "log-differentiator" $h(u(t)) = \frac{d}{dt}\log(u(t))$ for slowly varying inputs [7]. These results are based on the assumption of a time-scale separation between the input dynamics (slow) and the system's dynamics (fast) justifying to only consider the first terms in the asymptotic expansion of the system. We can explain the results in [7] by recalling that differentiable inputs (slow and fast ones) can be locally approximated by exponential functions, i.e. the characteristic inputs associated to scale-invariant systems. If such an approximation stays valid sufficiently long, the output (approximately) converges to a function of the slowly varying exponential coefficient, i.e. the log-derivative of the input. Thus, for a future extension of our theory to also describe the output dynamics of invariant systems excited by non-characteristic inputs, it seems rather important how long such inputs can sufficiently well be approximated by the proper characteristic functions of the system, than if the timescales of the system and the input dynamics are well separated.

Finally, we remark that there exists another class of interesting inputs for $\mathcal{P}$-equivariant systems to which we refer to as π-quasiperiodic. These are inputs $u_{\pi,T}$ satisfying

$$u_{\pi,T}(t+T) = (\pi \circ u_{\pi,T})(t),$$

for some quasiperiod T and $\pi \in \mathcal{P}$. Our preliminary results indicate that–under weak assumptions–the output of a $\mathcal{P}$-equivariant system excited by a corresponding quasiperiodic input is periodic, i.e. $y(t+T) = y(t)$. These preliminary results are in agreement with experimental data on bacterial chemotaxis gathered more than 30 years ago, which were explained by a log-linear, scale-invariant model [8].

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