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Input symmetry invariance, and applications to biological systems

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***Abstract*— This paper studies invariance with respect to symmetries in sensory fields, a particular case of which, scale-invariance, has recently been found in certain eukaryotic as well as bacterial cell signaling systems. We describe a necessary and sufficient characterization of symmetry invariance in terms of equivariant transformations, show how this characterization helps find all possible symmetries in standard models of biological adaptation, and discuss symmetry-invariant searches.**

I. Introduction

There has been recent interest, particularly in the systems biology literature, in the study of symmetry invariances of responses of dynamical systems. In great part, this interest was sparked by the discovery of an important transient property, related to Weber's law in psychophysics: *fold-change detection (FCD)* in adapting systems, 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 [1]–[3]. The mathematical analysis of FCD was started in [3], [4]. More generally, one may ask about invariance under the action of a more general set of symmetries in inputs. A particular instance is FCD, which amounts to scale invariance, i.e., invariance under the action of the multiplicative group of positive real numbers. The paper [3] obtained sufficient characterizations of symmetry invariance using a notion of equivariance, and this characterization was shown to be necessary as well as sufficient in [5]. Here, we discuss further the main result from [5], which is framed in terms of a notion which considerably extends equivariant actions of compact Lie groups. Both [3] and [5] sketched how to extend the results to motile systems that explore space, so long as the "motor dynamics" depends only on an invariant response. Specifically, these results predicted that *E. coli* bacteria would produce scale-invariant searches, meaning that distributions of bacteria, even under non-uniform and time-varying chemoeffector fields, should be invariant under any rescaling of the input field. This prediction was subsequently experimentally verified in [6]. In this note, we also remark that, for a velocity-jump Markov model, the PDE for the evolution of densities (or normalized concentrations) in time inherits the symmetry-invariance property from individual behaviors. Although not at all surprising, this provides further theoretical justification for passing from individual-based models to population predictions.

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II. Symmetries and equivariances

We review the general setup in [3], [5]. Consider dynamical systems with inputs and outputs [7],

$$\dot{x} = f(x,u)\,, \qquad y = h(x,u)\,. \tag{1}$$

The functions f, h describe respectively the dynamics and the read-out map.* Equation (1) is shorthand for

$$\frac{dx}{dt}(t) = f(x(t),u(t))\,, \qquad y(t) = h(x(t),u(t))\,.$$

Here, $u = u(t)$ is a generally time-dependent input (stimulus, excitation) function, $x(t)$ is an n-dimensional vector of state variables, and $y(t)$ is the output (response, reporter) variable. States, inputs, and outputs are constrained to lie in particular subsets $\mathbb{X}$, $\mathbb{U}$, and $\mathbb{Y}$ respectively, of Euclidean spaces $\mathbb{R}^n, \mathbb{R}^m, \mathbb{R}^q$.

We assume that for each piecewise-continuous input $u : [0,\infty) \to \mathbb{U}$, and each initial state $\xi \in \mathbb{X}$, there is a unique solution $x : [0,\infty) \to \mathbb{X}$ of (1) with initial condition $x(0) = \xi$, which we write as $\varphi(t,\xi,u)$, and we denote the corresponding output $y : [0,\infty) \to \mathbb{Y}$, given by $h(\varphi(t,\xi,u),u(t))$, as $\psi(t,\xi,u)$. We also assume that for each constant input $u(t) \equiv \bar{u}$, there is a unique solution $\bar{x} = \sigma(\bar{u})$ of the algebraic equation $f(\bar{x},\bar{u}) = 0$. Often one also assumes that this steady state is globally asymptotically stable (GAS): it 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 $\xi \in \mathbb{X}$. The GAS property is not required for the results to follow, however.

If $\mathbb{X}$ is an open set, or the closure of an open set, in $\mathbb{R}^n$, the system (1) is said to be *analytic* if f and h are real-analytic (can be expanded into locally convergent power series around each point) with respect to x, and *irreducible* if 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 [7]. An observable

*The results in [5] were stated for h not directly dependent on u, but the theory is the same in the more general case of u-dependence, as was also remarked there.

system 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; see [7], Remark 6.4.2 for a proof and discussion. In the context of applications to biomolecular systems, analyticity and irreducibility are weak techinal assumptions, often satisfied.

Adaptation, invariance, and equivariances:

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

That is, the steady-state output value is independent of the actual value of the input, provided that the input is a constant (a step function).

Invariance will be defined relative to a set $\mathcal{P}$ of continuous and onto input transformations $\pi : \mathbb{U} \to \mathbb{U}$. For each input $u(t)$ and $\pi \in \mathcal{P}$, we abuse notation and denote by "πu" (even if π is nonlinear) the function of time that equals $\pi(u(t))$ at time t. (The continuity assumption is only made in order to ensure that πu is a piecewise continuous function of time if u is. The ontoness assumption, that is, $\pi\mathbb{U} = \mathbb{U}$, and can be weakened considerably: it is only used in in the main theorem in order to prove that a system $\dot{x} = f(x, \pi u)$, $y = h(x, \pi u)$ is irreducible if the original system is irreducible, but far less than ontoness is usually required for that.)

An example is *scale invariance*, in which $\mathbb{U} = \mathbb{R}_{>0}$ and $\mathcal{P} = \{u \mapsto pu, p \geq 0\}$. (Scale invariance is sometimes called "fold-change detection" (FCD), since the only changes that can be detected in a response are those due to different fold-changes in inputs.)

Definition 2: The system (1) has *response invariance to symmetries in* $\mathcal{P}$ or, for short, is $\mathcal{P}$*-invariant* if

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

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.

Definition 3: Given a system (1) and a set of input transformations $\mathcal{P}$, a parametrized set of differentiable mappings $\{\rho_\pi : \mathbb{X} \to \mathbb{X}\}_{\pi \in \mathcal{P}}$ is a $\mathcal{P}$*-equivariance family* provided that, for each π:

$$f(\rho_\pi(x), \pi u) = (\rho_\pi)_*(x) f(x, u),\ h(\rho_\pi(x), \pi u) = h(x, u)$$

for all $x \in \mathbb{X}$ and $u \in \mathbb{U}$, where $(\rho_\pi)_*$ denotes the Jacobian matrix of ρ_π. If this property holds, the system is said to be ρ_π-equivariant under the input transformation π. □

The main result in [5] is as follows.

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

Remark 1: An interesting consequence of this theorem is that, if $\mathcal{P}$-invariance holds, then a stronger property holds as well, namely that

$$\psi(t, x, u) \;=\; \psi(t, \rho(x), \pi u)$$

is valid for all $t \geq 0$, all inputs u, all transformations $\pi \in \mathcal{P}$, and *every initial state* x (not necessarily a steady state). Another interesting fact, which follows from the proof of the theorem, is as follows. Suppose that 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 these facts. □

III. Working examples

We will illustrate our results with the examples in Figs. 1 and 2. The constants $\alpha, \beta, \ldots$ are positive numbers.

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

(a) linear

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

(b) loglinear

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

(c) nonlinear I

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

(d) nonlinear II

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

$$\begin{aligned} \dot{x} &= \alpha u - \delta x \\ \dot{y} &= \beta \frac{u}{x} - \gamma y \end{aligned}$$

(a) activation inhibition

$$\begin{aligned} \dot{x} &= \alpha u - \delta x \\ \dot{y} &= \beta u - \gamma x y \end{aligned}$$

(b) degradation

Fig. 2. Incoherent feedforward loops (IFFL) (assuming $u, x > 0$ in (a))

Adaptation can be achieved by the architectures represented in Figs. 1 and 2, integral feedback and incoherent feedforward loops respectively.

Fig. 1(a) shows the linear integral feedback configuration (PI, or proportional-integral, control) that is classically treated in control theory. Two other integral feedback configurations, also perfectly adapting, are shown in Fig. 1. In (b), a "loglinear system," the only difference with (a) is that the input is logarithmically pre-processed; this does not change 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 that recasts (c) as a Hamiltonian system with added damping. (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 $K_m \ll 1$.)

Biological motivations for studying these types of systems are discussed in [5]. Integral feedback plays a role in blood calcium homeostasis, neuronal control of the prefrontal cortex, the regulation of tryptophan in *E. coli*, and in *E. coli* chemotaxis

A different type of architecture is based on *feedforward* as opposed to feedback interconnections. Feedforward circuits are ubiquitous in biology, as emphasized in [8], where they were shown to be over-represented in *E. coli* gene transcription networks, compared to other "motifs" involving three nodes. In particular, in *incoherent feedforward loops (IFFL)*, as in Fig. 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. IFFL's, notably including the IFFL shown in Fig. 2(b) (often called the "sniffer" [9], [10]), are thought to play a role among other processes in EGF to ERK activation, glucose to insulin release, ATP to intracellular calcium release, nitric oxide to NF-κB activation, microRNA regulation, *Dictyostelium* chemotaxis and neutrophils, microRNA-mediated loops, and *E. coli* carbohydrate uptake via the carbohydrate phosphotransferase system. The work [11] shows experimentally and analytically that IFFL's are especially well-suited to controlling protein expression under DNA copy variability.

For both systems in Fig. 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 [10].

IV. 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 Figs. 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:

$$\begin{aligned} \dot{x} &= f(x,y,u) \\ \dot{y} &= g(x,y,u) \\ h(x,y) &= y\,. \end{aligned}$$

As with the examples, we write $x = (x,y)$. We also write for simplicity $(f(x,y,u), g(x,y,u))$ instead of $(f_1(x,y,u), f_2(x,y,u))$. 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:

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

(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 specialize next to special two cases that cover many examples of interest. Particular instances of the first case are the systems in Figs. 1(c,d) and 2(a). A particular instance of the second case is the system in Fig. 1(a). We assume that the systems in both of the next Lemmas are irreducible. For all our examples, irreducibility is shown in [5].

Lemma 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

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

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 be homogeneous of degree 1 in x.

Proof: Since G is one to one on y,

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

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

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. ■

A similar proof (see [5]) shows:

Lemma 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

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

and each p in the set. □

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

The linear integral feedback system in Fig. 1(a) fits the form in Lemma 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. Thus this system is $\mathcal{P}$-invariant with respect to translations.

The systems in Fig. 1(c,d) and Fig. 2(a) all fit the form in Lemma 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 Fig. 1(c,d) respectively, and is $+1$ for the system in Fig. 2(a). In Fig. 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 Fig. 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 Fig. 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 Fig. 1(a) and Fig. 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 Fig. 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 $\mathcal{P}$*.

V. Symmetry-invariant steering

We consider next a motile vehicle or organism which explores a space while measuring the "intensity" of an input cue (such as a chemoeffector or light). The sensed input at time t and position r is $U(t,r)$, where $r = r(t)$ is the current position of the vehicle. The current position $r(t)$ is derived from the output $y(t)$ of a system (1), through a computation that takes into account the dynamics of the motor and steering mechanisms.

Deterministic models for such mechanisms are sometimes appropriate, and one was described in [3], [5]. An easy argument for that deterministic model shows that, if y is invariant under symmetries in inputs, then positions $r(t)$ will be invariant under symmetry transformations on U.

Deterministic models: We review the argument in [3], [5]. The simplest model assumes that the position $r(t)$ is computed by a dynamical system that uses $y(t)$ as input,

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

where $q(t)$ is the internal state of the steering and motor mechanism; the output of this system is the position $r(t)$. Finally, the loop is closed by the measurement $u(t) = U(t, r(t))$. In other words, one has the following feedback system:

$$\begin{aligned} \dot{x}(t) &= f(x(t), u(t)),\; u(t) = U(t,r) \\ \dot{q}(t) &= Q(q(t), y(t)),\; y = h(x(t), u(t)),\; r(t) = R(q(t))\,. \end{aligned}$$

Suppose that the original system (1) is $\mathcal{P}$-invariant. One may then ask what happens if in this feedback system one replaces $U(t,r(t))$ by $\pi U(t,r(t))$, where $\pi \in \mathcal{P}$ is a symmetry, under the assumption that the system had pre-adapted to a constant environment $U(t,r) \equiv U_0$ when $t < 0$ before being placed in the current environment. Fig. 3 illustrates the situation. More precisely, suppose that (x,q) is the solution

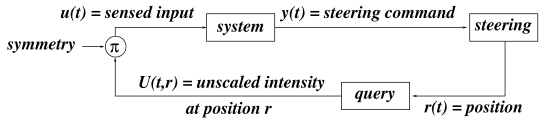

Fig. 3. Closed-loop diagram for search under symmetry uncertainty for inputs

with initial conditions $x(0) = \sigma(U_0)$ 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. We wish to compare this solution, for any given $\pi \in \mathcal{P}$, with the solution $(\widetilde{x}, \widetilde{q})$ of the system with initial conditions $x(0) = \sigma(\pi U_0)$ and $q(0) = q_0$, and intensity field $\pi U(t,r)$ instead of $U(t,r)$. It is easy to show [5] that $\widetilde{y}(t) = y(t)$, $\widetilde{u}(t) = \pi u(t)$, and $\widetilde{q}(t) = q(t)$ for all $t \geq 0$. In particular, for all $t \geq 0$ the position $r(t)$ is the same if the input intensity is U or πI.

Stochastic models: It is often the case that a more accurate description is one in which the output $y(t)$ drives a stochastic, not a deterministic, steering mechanism: the subsystem producing the location $r(t)$ is subject to randomness.

An important instance of this is bacterial *E. coli* chemotaxis, where $y(t)$ represents a signal, the level of phosphorylated protein CheY, which serves to bias the random switches between tumbling and swimming ("run") modes. Specifically, let us consider the Tu-Shimizu-Berg *E. coli* chemotaxis model [12], which may be formulated, for realistic parameters and input levels, as follows: $\dot{m} = F_0(y)$,

$y = h(m,u) = G(u/e^{\alpha m})$, where F_0 is a decreasing function which crosses zero at some value $y = y_0$ (and G is a suitable function whose precise form is immaterial for establishing symmetry). Letting $x := e^{\alpha m}$ and $F = \alpha F$, we may transform this system into a "nonlinear integral feedback" form,

$$\begin{aligned} \dot{x} &= x\,F(h(x,u)) \\ h(x,u) &= G\,(u/x)\ . \end{aligned}$$

For this system, homogeneity of $f(x,u) = xF(h(x,u))$ implies scale invariance, since the unique solution of the equivariance PDE is $\rho(x) = px$, for the scaling symmetry $u \mapsto pu$. Based on this verification of scale-invariant behavior, [3] predicted the invariance of distributions of bacteria locations under scalings of chemoattractant fields. This prediction was subsequently verified experimentally in [6] by means of molecular level analysis of intracellular signaling (FRET experiments) as well as measurements of swimming behavior at the level of individual cells and populations (in microfluidic environments).

A simple numerical simulation described in [13] serves to illustrate the point. This simulation uses (with no change in parameters) the SPECS agent-based model for *E. coli* chemotaxis that was developed in [14].† In this simulation, cells are allowed to swim in a rectangular channel that is $2000\mu m$ long and $400\mu m$ wide, and data is collected in bins of size 20 (so, there are 100 bins along the long axis). The ligand gradient is stationary and linear (see below for boundary values) along the length and constant along the width. We simulated 1000 cells, all initially placed at the middle (at length 1000, i.e. bin 50), and plotted the marginal distributions (along the long axis on which the chemoattractant varies). Since there behavior is random, the averages of several (five) trials under each of the conditions are shown. These average histograms are plotted for the cell distribution at time $t = 500$. The blue and green histograms in Fig. 4 represent, respectively, results for cells pre-adapted to a concentration 250 (units are μM), and linear gradient $200 \ldots 300$, and cells pre-adapted to a concentration 375, and linear gradient $300 \ldots 450$ (a scale change by $p = 1.5$). As expected, the distributions are very similar. As a control, we also plotted the results of using, once again, a linear gradient $300 \ldots 450$, but now pre-adapting cells to a concentration of 250. Since the initial state is not matched, there is no reason for invariance. Indeed, the resulting red histogram is very different from the previous ones.

One may mathematically formalize probabilistic behavior, and show symmetry-invariance of search under randomness, in several possible ways. For instance, in [5] a simple result was presented on symmetry-invariance search based on pathwise equality of stochastic processes. We describe next a different approach, discussed in [13], that employs the formalism of velocity-jump processes [15] with added internal dynamics [16].

†We thank Y. Tu for making this code available.

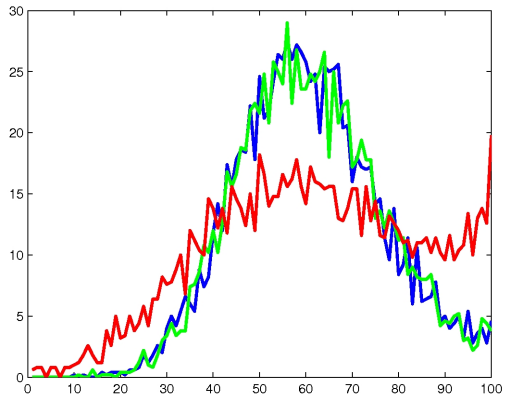

Fig. 4. Simulations using SPECS code

We wish to model motions in a space $\mathbb{R}^N$ (typically $N = 1, 2, 3$; and we assume for simplicity that motion can occur on the entire space) of individuals (bacteria, vehicles, etc) whose internal dynamics are described by the states x in (1) and which change velocities as a function of the output y. To avoid confusion with the variable x used for the internal state, we use the letter "s" to denote points in the space $\mathbb{R}^N$ in which movement occurs. The input $u = u(t,s)$ represents an external signal present at time t in location s. The subset $V \subseteq \mathbb{R}^N$ denotes the space of possible velocities.

We assume that the system can instantaneously change orientations. (For *E. coli* bacteria this would mean that we are ignoring tumble durations.)

The concentration at time t of individuals present at time t in location s and having internal state x and velocity v is denoted by $c(t,s,v,x)$. We interpret $c(t,s,v,x)\,ds\,dv\,dx$ as the number of individuals located between s and $s+ds$, having velocity between v and $v+dv$, and whose internal state is between x and $x+dx$. Normalized by the total number of individuals, one may also think of c as a probability density, at each time t.

We assume that velocities change at random. The *times* at which velocities jump are controlled by a Poisson process with intensity $\lambda(y)$. Given that a jump in velocity occurs, *which* particular new velocity is picked is itself the result of a random choice; the kernel $T_y(v,v',y)$ gives the probability of a change in velocity from v' to v. Since T is a probability density, $\int_V T_y(v,v')\,dv = 1$ for every y. Notice that, just as with the jump instants, the kernel also depends on the state only through the output y.

Then the evolution (transport, Fokker-Planck, or forward Kolmogorov) equation for $c = c(t,s,v,x)$ is:

$$\begin{aligned} \frac{\partial c}{\partial t} + \nabla_s \cdot cv + \nabla_x \cdot cf \ = \\ -\lambda(y)c + \int_V \lambda(y) T_y(v,v') c(t,s,v',x)\,dv'\,. \end{aligned} \tag{3}$$

The input at location s and time t is $U(t,s)$, and it appears in these equations through the vector field f in (1).

The reference [16] discusses mathematical aspects of the PDE (3), which will not be discussed here. We focus, purely formally, on symmetry invariance.

Let us assume given π and an associated equivariance $\rho = \rho_\pi$. We will also make the following assumption on the divergence of f:

$$(\nabla_x \cdot f)(\rho(x), \pi u) \;=\; (\nabla_x \cdot f)(x,u) \tag{4}$$

for all $x \in \mathbb{X}$ and $u \in \mathbb{U}$. This property is automatically satisfied for most of the examples treated in [5], since in these examples, which are for scale invariance $\pi u = pu$, ρ is a linear mapping. In general, if $\rho(x) = Rx$ for a matrix R, then the equivariance condition $f(Rx, \pi u) = Rf(x,u)$ implies, taking Jacobians, that $f_*(Rx, \pi u) = Rf_*(x,u)R^{-1}$. Since two similar matrices have the same trace, and $\nabla_x \cdot f$ is the trace of the Jacobian of f, it follows that (4) is valid.

Our main observation is that the same distribution of individuals will result if the input field U is replaced by πU, provided that the internal states are transformed by ρ. A precise statement is as follows.

Theorem 2: Suppose that c satisfies (3) with respect to an input field U. Define

$$\widetilde{c}(t,s,v,x) = c(t,s,v,\rho^{-1}(x))\,.$$

Then $\widetilde{c}$ satisfies (3) with respect to the input field πU.

Proof: We start by writing all the arguments in (3) explicitly:

$$\begin{aligned}
&\frac{\partial c}{\partial t}(t,s,v,x) + (\nabla_s \cdot \Gamma_1)(t,s,v,x) + (\nabla_x \cdot \Gamma_2)(t,s,v,x) \\
&\quad = \quad -\lambda(h(x,U(t,s)))c(t,s,v,x) \\
&\quad + \quad \int_V \lambda(h(x,U(t,s)))T_{h(x,U(t,s))}(v,v')c(t,s,v',x)\,dv'
\end{aligned}$$

where

$$\begin{aligned}
\Gamma_1(t,s,v,x) &= c(t,s,v,x)v \\
\Gamma_2(t,s,v,x) &= c(t,s,v,x)f(x,U(t,s))\,.
\end{aligned}$$

Since this equation must hold for all x, it holds also when $\rho^{-1}(x)$ is replaced for x. From the definition of $\widetilde{c}$ and the property $h(\rho(x),\pi u) = h(x,u)$, which implies that $h(x,\pi u) = h(\rho^{-1}(x),u)$ for all u, we conclude that:

$$\begin{aligned}
&\frac{\partial \widetilde{c}}{\partial t}(t,s,v,x) + (\nabla_s \cdot \Gamma_1)(t,s,v,\rho^{-1}(x)) \\
&\quad + (\nabla_x \cdot \Gamma_2)(t,s,v,\rho^{-1}(x)) \\
&\quad = -\lambda(h(x,\pi U(t,s)))\widetilde{c}(t,s,v,x) \\
&\quad + \int_V \lambda(h(x,\pi U(t,s)))T_{h(x,\pi U(t,s))}(v,v')\widetilde{c}(t,s,v',x)\,dv'\,.
\end{aligned}$$

It will follow that $\widetilde{c}$ is a solution of (3) with respect to the input field πU provided that we show:

$$\begin{aligned}
(\nabla_s \cdot \Gamma_1)(t,s,v,\rho^{-1}(x)) &= (\nabla_s \cdot \widetilde{\Gamma}_1)(t,s,v,x) \\
(\nabla_x \cdot \Gamma_2)(t,s,v,\rho^{-1}(x)) &= (\nabla_x \cdot \widetilde{\Gamma}_2)(t,s,v,x),
\end{aligned}$$

where

$$\begin{aligned}
\widetilde{\Gamma}_1(t,s,v,x) &= \widetilde{c}(t,s,v,x)v \\
\widetilde{\Gamma}_2(t,s,v,x) &= \widetilde{c}(t,s,v,x)f(x,\pi U(t,s))\,.
\end{aligned}$$

These easily follow by elementary calculus (see [13]). ∎

In applications, one is often interested in the distribution of positions irrespective of internal states x and velocities v:

$$Q(t,s) = \int_{\mathbb{X}} \int_V c(t,s,v,x)\,d\mu_{\mathbb{X}}(x)\,d\mu_V(v)$$

where $\mu_{\mathbb{X}}$ and μ_V denote appropriate measures on $\mathbb{X}$ and V (and we assume that c is integrable). Take the density corresponding to πU, $\widetilde{c}(t,s,v,x) = c(t,s,v,\rho^{-1}(x))$, and its marginal $\widetilde{Q}(t,s) = \int_{\mathbb{X}} \int_V \widetilde{c}(t,s,v,x)\,d\mu_{\mathbb{X}}(x)\,d\mu_V(v)$. This is the same as $\int_{\mathbb{X}} \int_V c(t,s,v,x) r(x)\,d\mu_{\mathbb{X}}(x)\,d\mu_V(v)$, where $r(x) = 1/\det \rho_*(x)$. In the special (but usual in examples) case that ρ is linear, r is a constant, so $\widetilde{Q}(t,s) = rQ(t,s)$. It follows that the normalized densities are equal:

$$\frac{\widetilde{Q}(t,s)}{\int \widetilde{Q}(t,\sigma)\,d\sigma} \;=\; \frac{Q(t,s)}{\int Q(t,\sigma)\,d\sigma}\,.$$

Alternatively, one could introduce a new measure $d\widetilde{\mu}_{\mathbb{X}}(x) = r(x)\mu_{\mathbb{X}}$, and define $\widetilde{Q}$ using this new measure, for all times t and space positions s, so that $Q(t,s) = \widetilde{Q}(t,s)$.

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