Morphogenesis as Bayesian Inference: A Variational Approach to Pattern Formation and Control in Complex Biological Systems

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1 Abstract

Recent advances in molecular biology such as gene editing [Mahas et al., 2018], bioelectric recording and manipulation [Levin, 2012a] and live cell microscopy using fluorescent reporters [Mutoh et al., 2012], [V. Sekar et al., 2011] – especially with the advent of light-controlled protein activation through optogenetics [Bugaj et al., 2017] – have provided the tools to measure and manipulate molecular signaling pathways with unprecedented spatiotemporal precision. This has produced ever increasing detail about the molecular mechanisms underlying development and regeneration in biological organisms. However, an overarching concept – that can predict the emergence of form and the robust maintenance of complex anatomy – is largely missing in the field. Classic (i.e., dynamic systems and analytical mechanics) approaches such as least action principles are difficult to use when characterizing open, far-from equilibrium systems that predominate in Biology. Similar issues arise in neuroscience when trying to understand neuronal dynamics from first principles. In this (neurobiology) setting, a variational free energy principle has emerged based upon a formulation of self-organization in terms of (active) Bayesian inference. The free energy principle has recently been applied to biological self-organization beyond the neurosciences [Friston et al., 2015], [Friston, 2013]. For biological processes that underwrite development or regeneration, the Bayesian inference framework treats cells as information processing agents, where the driving force behind morphogenesis is the maximization of a cell's model evidence. This is realized by the appropriate expression of receptors and other signals that correspond to the cell's internal (i.e., generative) model of what type of receptors and other signals it should express. The emerging field of the free energy principle in pattern formation provides an essential quantitative formalism for understanding cellular decision-making in the context of embryogenesis, regeneration, and cancer suppression. In this paper, we derive the mathematics behind Bayesian inference – as understood in this framework – and use simulations to show that the formalism can reproduce experimental, top-down manipulations of complex morphogenesis. First, we illustrate this 'first principle' approach to morphogenesis through simulated alterations of anterior-posterior axial polarity (i.e., the induction of two heads or two tails) as in planarian regeneration. Then, we consider aberrant signaling and functional behavior of a single cell within a cellular ensemble – as a first step in carcinogenesis as false 'beliefs' about what a cell should 'sense' and 'do'. We further show that simple modifications of the inference process can cause – and rescue – mis-patterning of developmental and regenerative events without changing the implicit generative model of a cell as specified, for example, by its DNA. This formalism offers a new road map for understanding developmental change in evolution and for designing new interventions in regenerative medicine settings.

2 An Introduction to Bayesian Inference

Evolutionary change results from mutations in DNA and selection acting on functional bodies. Thus, it is essential to understand how the hardware encoded by the genome enables the behavioral plasticity of cells that can cooperate to build and repair complex anatomies. Indeed, most problems of biomedicine – repair of birth defects, regeneration of traumatic injury, tumor reprogramming, *etc.* – could be addressed if prediction and control could be gained over the processes by which cells implement dynamic pattern homeostasis. The fundamental knowledge gap and opportunity of the next decades in the biosciences is to complement bottom-up molecular understanding of mechanisms with a top-down computational theory of cellular decision-making and infotaxis. Relevant concepts have been developed in neuroscience and physics, but are generally not familiar to developmental or regenerative biologists [Friston et al., 2015], [Friston, 2013]. Here, we lay out the mathematical foundation of the type of Bayesian modeling employed by new approaches to understand metazoan cell cooperation to characterize – and simulate – pattern formation. We start by identifying a Lyapunov function that can be used to analyze and solve any dynamic system, using the fundamental theorem of vector calculus (i.e., the Helmholtz Decomposition). We use it to characterize the generalized flow of systemic states, in terms of convergence to a non-equilibrium steady-state. We then introduce the notion of a Markov blanket that separates the external and internal states of the system, where the Markov blanket is comprised of active and sensory states. Using this partition, we can then replace the Lyapunov function with a variational free energy to solve for the evolution of internal and active states and thereby characterize self-organization in far from equilibrium systems that can be partitioned into a cell (i.e., internal states and their Markov blanket) and the external milieu. Subsequent sections apply this formalism to illustrate morphogenesis and neoplasia using simulations. Bayesian inference is a statistical process, wherein Bayes theorem is used to update the probability of a hypothesis with respect to evidence obtained by measurement of the sensorium – or environment. In essence, any kind of information processing system infers unobservable (i.e., hidden) states of its environment by comparing sensory samples with predictions of sensory input and updating its expectations about the causes of that input. Bayes theorem rests on the three basic axioms of probability theory and is used to relate the conditional probability of an unobservable event A, given an observable quantity B, to the likelihood of B, given that A is true. This is written as:

$$P(A \mid B) = \frac{P(B \mid A)P(A)}{P(B)}\,, \tag{1}$$

where conditional probability $P(A \mid B)$ is also called the *posterior*; namely, the inferred probability of an event A, given an event B. Conversely, $P(B \mid A)$ is the probability of B, given A, called the *likelihood*. The probability P(A) is called a *prior* belief and the probability of P(B), is called marginal likelihood or *evidence*. In Bayesian inference, the above relationship is used to accumulate information about an unobservable or hidden state by sampling measurable events. This is known as Bayesian belief updating, because it converts prior beliefs into posterior beliefs – based on a generative model. This is known as Bayesian belief updating that is used to update the agent's prior beliefs based on its *generative model*, $P(A \mid B) = P(B \mid A)P(A)$. In short, the likelihood assigned to the observation and prior beliefs are combined to form posterior beliefs.

To describe the dynamics of an ensemble of information processing agents (as in cells, for example) as a process of Bayesian belief updating, we need to relate the stochastic differential equations governing Newtonian motion and biochemical activity

to the probabilistic quantities above. This is fairly straightforward to do, if we associate biophysical states with the parameters of a probability density – and ensure their dynamics perform a gradient flow on a quantity called variational free energy. Variational free energy is a quantity in Bayesian statistics that, when minimized, ensures the parameterized density converges to the posterior belief, as we will see below.

In neuroscience, the minimization of variational free energy is referred to as active inference. This approach to neuronal dynamics has been successfully used to reproduce a variety of neuronal phenomena [Friston et al., 2017], [Ungerleider and Leslie, 2000], [Adams et al., 2013], [Desimone and Duncan, 1995], [Barrett and Simmons, 2015], [Corbetta and Shulman, 2002]. Crucially, exactly the same scheme has been shown recently – through computational proof-of-principle simulations – to produce and maintain the somatic patterning of self-organization [Friston, 2013], [Friston et al., 2015]. We will see that when the basic condition for an inference type description of a system – namely, the existence of a Markov blanket separating external and internal states – is satisfied, agents such as biological cells form into organized conglomerations based on their generative models of how of their blanket states influence – and are influenced by – external states in the external milieu (i.e., the states of other cells) [Friston, 2013].

In classical thermodynamic descriptions, this would be accompanied by an increase of thermodynamic entropy over the entire system, through localized increases in organization (i.e., decrease in entropy) of the states associated with each cell (i.e., internal states and their Markov blanket). However, as biological systems, especially cells, are invariably open, far-from-equilibrium or non-equilibrium steady state systems, the dynamics of this process are almost impossible to compute. Instead, by focusing on a probabilistic account of self-organization, in terms of Bayesian belief updating, we can place an upper bound on the entropy of the system's blanket states that is computationally tractable. In brief, we will see that the dynamics of system with a Markov blanket that self-organizes to non-equilibrium steady-state can be described as a gradient flow on this computable (variational) free energy bound. This approach has been shown to have a high predictive validity in neurobiology; both in terms of behavior and the neuronal correlates of action and perception. However, its application in the broader biosciences has not been explored, even though the basic assumptions behind it apply broadly.

3 Mathematical Foundations

In what follows, we introduce the mathematics that underwrites the Bayesian interpretation of non-equilibrium steady-state dynamics. We will start with a brief overview of the Helmholtz decomposition and Lyapunov functions in dynamical systems. We will see that one can formulate any dynamics in terms of a potential function that plays the role of a Lyapunov function. This is illustrated from the point of view of classical mechanics with dissipative aspects. We then derive the same result in terms of density dynamics using the Fokker Planck equation, in generalized coordinates of motion. This formulation shows that the potential or Lyapunov function is simply the negative log probability of a state being occupied at non-equilibrium steady-state. Crucially, this quantity is bounded from above by variational free energy. This means the flow of particular states at non-equilibrium steady-state can be cast as a gradient flow on the same quantity that is minimized by Bayesian belief updating.

3.1 Stability and Convergence in Coupled Dynamical Systems

3.1.1 The Helmholtz decomposition

The Helmholtz decomposition states that any sufficiently smooth (i.e., possessing continuous derivatives) vector field $\mathbf{F}$ can be decomposed into an irrotational (curl-free) and a solenoidal (divergence-free) vector field. Because an irrotational vector field has only a scalar potential and a solenoidal vector field has only a vector potential, we can express the vector field as

$$\mathbf{F} = -\nabla\Phi + \nabla \times \mathbf{A}, \tag{2}$$

where $\nabla\Phi$ and $\nabla \times \mathbf{A}$ are the irrotational and solenoidal vector fields respectively.

3.1.2 Lyapunov functions

Lyapunov functions have been used extensively in dynamical systems theory and engineering to characterize the stability of fixed points of a dynamical system [Lyapunov, 1992], [Mawhin, 2015]. Lyapunov functions are generally defined for smooth systems through the following conditions:

$$\begin{aligned} &(a) \quad L(x^*) = 0,\, and\, L(x) > 0\, if\, x \neq x^* \\ &(b) \quad \dot{L}(x) = \left.\frac{dL}{dt}\right|_x \leq 0,\, for\, all\, x \in O\,, \end{aligned} \tag{3}$$

where $O \subseteq \mathbb{R}$ is an open set containing all states x.

(a) requires the Lyapunov function L to be minimal for fixed points x^* representing local minima, and (b) denotes convergence to these fixed points over time.

Following [Yuan et al., 2014], we can generalize this local Lyapunov function of stability to a global Lyapunov function that plays the role of a potential function of any dynamical system. This follows by generalizing condition (a) to allow for saddle points:

$$\nabla L(x^*) = 0\,, \tag{4}$$

Following [Yuan et al., 2014] we show how a Lyapunov function is equivalent to a potential function, when characterizing the stability of a dynamical system. In physics, a potential function ψ can be constructed to describe the flow of – or forces acting on – a particle through a potential energy gradient:

$$\mathbf{F_{pot}} = \nabla\psi\,. \tag{5}$$

These forces are conservative, where the total work done on the particle is independent of its trajectory (e.g., Gravitational force). However, there are also dissipative, or non-conservative forces, for which the total work done depends on the particle's trajectory and is hence irreversible (e.g., frictional force). At steady-state, these components balance each other, so that the total Force $\mathbf{F}_{tot}$ is zero:

$$\mathbf{F}_{tot} = \mathbf{F}_{con} + \mathbf{F}_{dis} = 0\,, \tag{6}$$

where $\mathbf{F}_{con}$ and $\mathbf{F}_{dis}$ are the conservative and dissipative forces respectively. For example, in electromagnetics, the Lorentz force describes the forces acting on a moving charged particle:

$$\mathbf{F}_{Lorentz} = q\mathbf{E} + e\mathbf{v} \times \mathbf{B}\,, \tag{7}$$

where q is its charge, $\mathbf{v}$ the velocity of the particle, and $\mathbf{E}$ and $\mathbf{B}$ are the electric and magnetic forces, respectively. We can therefore write $\mathbf{F}_{con}$ as a combination of Lorentz force and potential energy induced force:

$$\mathbf{F}_{con} = -\nabla\psi(x) + e\mathbf{v} \times \mathbf{B}\,, \tag{8}$$

while the dissipative force can be expressed as a frictional force (due to dissipative random fluctuations):

$$\mathbf{F}_{dis} = -S\mathbf{v}\,. \tag{9}$$

Here, S is a symmetric and semi-positive definite friction tensor.

Combining these definitions, we can express the total force as a balance of the forces as defined above, resulting in:

$$S\mathbf{v} + e\mathbf{v} \times \mathbf{B} = -\nabla\psi(x)\,, \tag{10}$$

One can generalize this equation for arbitrary n-dimensional systems by replacing the vector-valued cross product $\mathbf{v} \times \mathbf{B} = T\mathbf{v}$, where T is an antisymmetric matrix to give the canonical form of (11):

$$(S + T)\mathbf{v} = -\nabla\psi(x)\,, \tag{11}$$

Finally, following [Yuan et al., 2014] we can transform this expression into a standard form using a diffusion tensor Γ (defined as half the covariance of the dissipative random fluctuations) and a tensor Q (describing friction) satisfying $\nabla \cdot Q\nabla\psi(x) = 0$, by setting $\psi(x)$ as the Lyapunov function $L(x)$ as defined above so that we get:

$$f(x) = \mathbf{v} = (Q - \Gamma)\nabla\psi(x)\,, \tag{12}$$

where $f(x)$ describes the flow of states. This equation describes the evolution or flow of states resulting from (conservative and dissipative) forces at non-equilibrium steady-state.

In summary, for any dynamical system at non-equilibrium steady-state, we can express the flow in terms of a scalar potential or Lyapunov function $\psi(x) = L(x)$, where the flow can always be decomposed into a gradient flow, which minimizes the potential, and a solenoidal component, that flows on the iso-contours of the potential. The final move is to associate the Lyapunov function or potential with variational free energy as follows.

3.2 Variational Free Energy

Variational free energy is a function of internal states that allows one to associate the Lyapunov function from (17) with Bayesian model evidence and hence characterize systemic dynamics in terms of Bayesian inference and the implicit generative models. This device works by unpacking the non-equilibrium steady-state flow of external, internal and blanket states. Under this partition, instead of minimizing the Lyapunov function or (thermodynamic) potential, the internal and active states come to minimize variational free energy. Crucially, the variational free energy is defined in terms of a generative model and implicit posterior beliefs encoded by internal states. This minimization licenses an interpretation of self-organization in terms of belief updating according to Bayes rules above. In turn, this allows us to specify the resulting non-equilibrium steady-state in terms of a generative model – and ensuing inference – as we will see below. First, we will revisit the standard form for dynamics above, in the setting of generalized coordinates of motion and density dynamics as described by the Fokker Planck equation.

3.2.1 Generalized Flow

We can describe dynamics in generalized coordinates of motion, denoted with a tilde, where $\tilde{x}$ is defined as:

$$\tilde{x} = (x, \dot{x}, \ddot{x}, ...)\,, \tag{13}$$

This augments a state with its velocity, acceleration and so on. Later, we will use generalized coordinates of motion to parameterize a posterior density over (the generalized motion of) external states (that are hidden behind the Markov blanket). Among other advantages, generalized coordinates of motion allow one to accommodate temporal correlations in random fluctuations. Assuming a smooth dynamical system, subject to random fluctuations, we can describe the motion of states with the Langevin equation:

$$\dot{\tilde{x}} = f(\tilde{x}) + \tilde{\omega}, \tag{14}$$

where $f(\tilde{x})$ is the generalized flow (or time evolution) of states due to forces acting on the states and $\tilde{\omega}$ are random fluctuations, under the usual Wiener assumptions (the flow of states is made up of a process of independent, Gaussian increments that follow a continuous path).

In statistical physics the ensuing dynamics is commonly described in terms of density or ensemble dynamics; namely, the evolution of the probability density $p(\tilde{x})$, through the Fokker-Planck equation. The Fokker Planck equation can be obtained for any Langevin equation, using the conservation of probability mass:

$$\dot{p}(\tilde{x}) = \nabla \cdot [\dot{\tilde{x}} p(\tilde{x})] = 0\,, \tag{15}$$

where $\dot{\tilde{x}} p(\tilde{x})$ describes the probability current. This turns the Fokker-Planck equation into a continuity equation, which reads:

$$\dot{p}(\tilde{x}) = \nabla \cdot \Gamma \nabla p - \nabla \cdot (f(x)p)\,. \tag{16}$$

This is a partial differential equation that describes the time evolution of the probability density $p(\tilde{x})$ under dissipative (first term) and conservative (second term) forces. At non-equilibrium steady-state, the density dynamics is just the solution to the Fokker Planck equation:

$$L(\tilde{x}) = -ln\, p(\tilde{x})\,, \tag{17}$$

such that $\nabla p = -p \nabla L$ and $\dot{p} = 0$.

Using the Helmholtz decomposition from (2), we can now express steady-state flow in terms of a divergence-free component and a curl-free descent on a scalar Lyapunov function $L(\tilde{x})$ to obtain

$$f(\tilde{x}) = (Q - \Gamma)\nabla L(\tilde{x}). \tag{18}$$

This is the solution at non-equilibrium steady-state and is exactly the same solution for the flow of particles in the classical treatment above. Crucially, we can now see that the Lyapunov function is the negative log probability of finding the system in any (generalized) state $L(\tilde{x}) = -lnp(\tilde{x})$. This is also known as the self-information of a state in information theory (also known as surprisal, or more simply surprise). In Bayesian statistics it is known as the negative log evidence.

In summary, any weakly mixing dynamical system that at non-equilibrium steady-state will evince a flow that can be decomposed into a gradient flow on surprise and an accompanying solenoidal flow. Because we can associate the Lyapunov function

in (18) with a free energy [Seifert, 2012], the system is effectively minimizing a free energy in its convergence to a set of attracting states (known as a random dynamical attractor), which have a high probability of being occupied [Crauel and Flandoli, 1994]; namely a high marginal likelihood or evidence. This construction is used extensively in biophysical research fields, such as protein folding to solve for steady-state solutions [Dinner et al., 2000], [Lammert et al., 2012].

3.2.2 Least Action Principles

Physics offers a useful formalism to understand, at a quantitative level, the ability of biological systems (as evidenced by regulative development and regeneration) to work towards an invariant outcome, despite various perturbations. Understanding this 'goal-directed' activity is an important open problem in biological control.

The least action principle can predict the emergence of form, in terms of the flow or paths of least action in biological systems. For example, in colonies, ants find the paths of least action to harvest food and bring it to the colony. This example considers their paths as flow channels, or trajectories, finding the least average action for each instance of foraging, given available resources. More generally, minimization of action in an open system leads to structure formation. The 'flows' in such (dissipative) systems are of energy, matter and constituent elements along the paths of least action. An open dynamical system tends towards its state of least action, or the 'most action efficient state'. A canonical example of the emergence of such dissipative structures is when a moving fluid (e.g., a river) erodes obstructions to its flow to form a network of flow channels.

In (dissipative) random dynamical systems [Arnold, 1995], [Crauel and Flandoli, 1994], action is not minimized for each element of the system, but, on average over an ensemble of elements (or repeated trajectories of the same element) [Georgiev and Georgiev, 2002], [Georgiev et al., 2015], [Georgiev and Chatterjee, 2016], [Georgiev et al., 2017]. Obstructive-constraint minimization therefore reduces action for each event within the system and self-organizes it, forming a flow structure that could be construed as a dissipative structure [England, 2015], [Evans and Searles, 2002], [Prigogine, 1978]. Crucially, since self-organizing open systems are not conservative, their structured flow is quintessentially dissipative. While the Lyapunov function of a physical system is readily used to establish the stability of a fixed point in dynamical systems, physicists commonly use the Lagrangian to solve the trajectory of a systems states. Classically, for a conservative system, the Lagrangian is defined as:

$$L = T - V \,, \tag{19}$$

where V is the potential energy of the system, defined through the constraints of the system, and T is the kinetic energy of the particles that constitute the system at hand. For any Lagrangian, the trajectory of states in generalized coordinates $(t, \tilde{x}(t), \dot{\tilde{x}}(t))$ are given by the solutions to the the Euler-Lagrange equation, which are bound by the principle of variations to be functions for which the following functional has extrema (i.e., is stationary):

$$S(\tilde{x}) = \int_{t_1}^{t_2} L(t, \tilde{x}(t), \dot{\tilde{x}}(t))\, \mathrm{d}t \,. \tag{20}$$

S integrates the Lagrangian of generalized states for boundary conditions defined for initial and final time points t_1 and t_2. The most likely path between these points is obtained when the functional derivative is zero; i.e., $\delta S = 0$. This is the Hamilton's principle. In this case, the equations of motion are derived from the Euler-Lagrange equations which are the solutions of the principle of least action:

$$\frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial L}{\partial \dot{\tilde{x}}_i} - \frac{\partial L}{\partial \tilde{x}_i} = 0 \quad \text{for } i = 1, 2, \ldots, n. \tag{21}$$

Where $\tilde{x}_i$ are the generalized coordinates and $\dot{\tilde{x}}_i$ the generalized velocities.

For dissipative systems, this equation has additional dissipative terms. For example, if the dissipative function depends on the square of the velocity:

$$F = \frac{1}{2}k\dot{\tilde{x}}^2 \tag{22}$$

Then the Euler-Lagrange equations become:

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L}{\partial \dot{\tilde{x}}_i}\right) - \frac{\partial L}{\partial \tilde{x}_i} + \frac{\partial F}{\partial \dot{\tilde{x}}_i} = 0 \tag{23}$$

The constraints to motion of the agents in a system are given additionally by the Lagrange multipliers.

$$\delta \int_{t_1}^{t_2} [L(t, \tilde{x}(t), \dot{\tilde{x}}(t)) + \sum_k \lambda_k(t) g_k(t, \tilde{x}(t))] dt = 0 \tag{24}$$

Where λ_k are the Lagrange multipliers, and g_k are the constraints [Arfken and Weber, 1995]. The solutions are the constrained Lagrangian equations of motion, which with the added dissipative terms are as follows.

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L}{\partial \dot{\tilde{x}}_i}\right) - \frac{\partial L}{\partial \tilde{x}_i} + \frac{\partial F}{\partial \dot{\tilde{x}}_i} = \sum_k \lambda_k \frac{\partial g_k}{\partial \tilde{x}_i} \tag{25}$$

Terms with random noise can also be added to this equation, which are pertinent for biological systems [El Kaabouchi and Wang, 2015]. Because the Lagrangian describes the trajectories of particles under forces, the functional S is the action of the system. Hence, when the variational principle is applied to the action of a system in this manner, it is referred to as a *least action principle*. To apply least action principles to the kind of systems of interest in biology, it is necessary to consider the action of an ensemble of systems of particles. Minimizing the average action allows individual trajectories to deviate from their paths of least paths, so that they can reduce the action of other particles. The most likely solution for an ensemble minimizes the ensemble average of action, compared to other arrangements of particles and implicit constraints on their flow. As the system evolves, it searches forever lower minima of this average action [Georgiev and Georgiev, 2002], [Georgiev et al., 2015], [Georgiev and Chatterjee, 2016], [Georgiev et al., 2017]. This means that the principle of least action does not apply in isolation to each member of the ensemble but is contextualized by coupling between particles that depend upon many characteristics. These characteristics include: the number of particles, the number of interactions, the total action of the system within certain interval of time, *etc.* Furthermore, these interdependent functions (interfunctions) are bound by power law relations [Georgiev et al., 2015], [Georgiev and Chatterjee, 2016], [Georgiev et al., 2017]. From our perspective, the key observation here is that any (dissipative) random dynamical system can be formulated as a gradient flow on the log likelihood of its states. This is reflected in our solution $L(\tilde{x}) = -\ln p(\tilde{x})$ to the Fokker-Planck equation in (17), which means the action is the time or path integral of the marginal likelihood or self-information:

$$S = \int_{t_1}^{t_2} L(\tilde{x}(t)\,\mathrm{d}t = \int_{t_1}^{t_2} \ln p(\tilde{x}|m)\,\mathrm{d}t\,, \tag{26}$$

for any system or model m. This means, the least action integral over the Lagrangian turns into an integration over the self-information of states, which is known as entropy in information theory. In short, the principle of least action manifests as a principle of least entropy – for systems that possess a random dynamical attractor – and thereby obtain non-equilibrium steady-state. We now consider the specific structure of the system or model m that underwrites Bayesian inference; namely, the Markov blanket.

3.2.3 Markov Blanket

A robust literature is developing around the ability of cells and many other aneural systems measuring aspects of their environment via specific sensors [Baluška and Levin, 2016]. All biological systems can be analyzed in terms of sensory and internal states and the relationships between them [Rosen, 2012].

A Markov partition separates all states $x \in X$ into external $e \in E$, sensory $s \in S$, active $a \in A$, and internal states $i \in I$ (with their generalized versions $\tilde{x}, \tilde{e}, \tilde{s}, \tilde{a}$, and $\tilde{i}$), so that

$$\tilde{x} \in X = E \times S \times A \times I \,, \tag{27}$$

where $\times$ denotes the Cartesian product that returns a product set of sets. The ensuing partition is defined in table 1. The Markov blanket separating external and internal states is hence given by $S \times A$, as depicted in Figure 1. The partition into external, internal and blanket states rests upon conditional independencies implicit in the system's equations of motion or dynamics. In brief, external and internal states depend only upon blanket states, subject to the constraint that sensory states are not influenced by internal states and active states are not influenced by external states.

With the Markov partition (and associated influences) in hand, the flow $f(\tilde{x})$ can then be decomposed into 4 parts:

$$\begin{aligned} &f_e(\tilde{e}, \tilde{s}, \tilde{a}) \\ &f_s(\tilde{e}, \tilde{s}, \tilde{a}) \\ &f_a(\tilde{s}, \tilde{a}, \tilde{i}) \\ &f_i(\tilde{s}, \tilde{a}, \tilde{i}) \end{aligned} \tag{28}$$

The response of active and internal states, to sensory stimuli, therefore, becomes

$$\begin{aligned} &(a)\;\; f_a(\tilde{s}, \tilde{a}, \tilde{i}) = (Q_a - \Gamma_a)\nabla_{\tilde{a}} L(\tilde{s}, \tilde{a}, \tilde{i}) \\ &(b)\;\; f_i(\tilde{s}, \tilde{a}, \tilde{i}) = (Q_i - \Gamma_i)\nabla_{\tilde{i}} L(\tilde{s}, \tilde{a}, \tilde{i}) \\ &(c)\;\; L(\tilde{s}, \tilde{a}, \tilde{i}) = -\ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) \,, \end{aligned} \tag{29}$$

where m describes the Markov partition that defines the underlying random dynamical system (e.g., a cell).

Set	Dependent sets	Description of set contents
sample space Ω		random fluctuations or outcomes
external states E	$E \times A \times \Omega$	hidden states causing sensory inputs.
sensory states S	$E \times A \times \Omega$	signals mapping from external to internal states.
active states A	$S \times I \times \Omega$	action determined by sensory and internal states.
internal states I	$I \times S \times \Omega$	internal states causing action.

Table 1. Table denoting variables of Bayesian Inference.

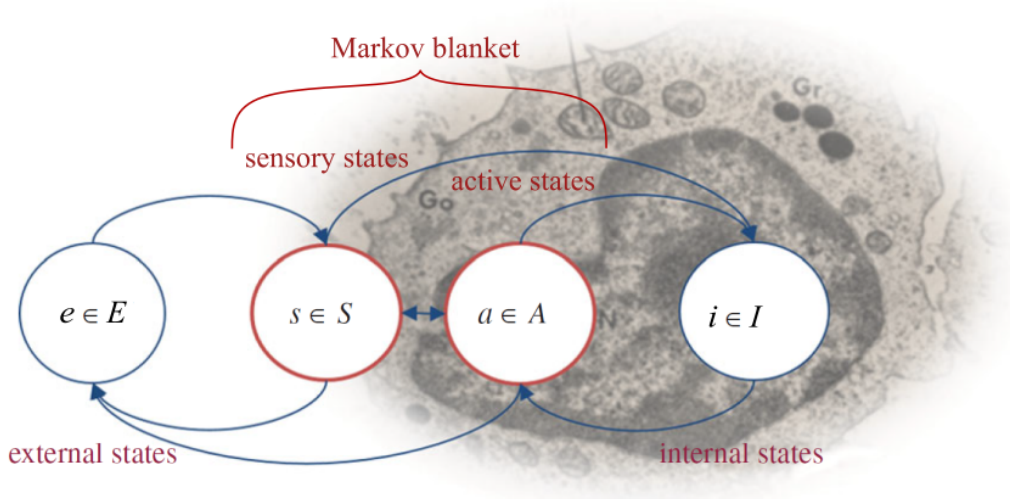

Fig 1. Markov blanket schematic. The internal and external states of each cell are separated by a Markov blanket, which comprises the cell's sensory and active states. The internal states can be interpreted as the intracellular states of a cell, such as its gene expression levels. While the sensory states correspond to the surface states of the cell membrane, such as receptors and ion channel states. The active states are given by the underlying active components of the cytoskeleton, such as actin filaments and microtubules. By associating the gradient flows of the Markov blanket partition with Bayesian belief updating, self-organization of internal states – in response to sensory fluctuations – can be thought of as perception, while active states couple internal states back to hidden external states vicariously, to provide a mathematical formulation of action and behavior. Adapted from [Friston et al., 2015].

Inserting (c) into (a) and (b), gives:

$$\begin{aligned} (a') \;\; & f_a(\tilde{s}, \tilde{a}, \tilde{i}) = (\Gamma_a - Q_a)\nabla_{\tilde{a}} \ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) \\ (b') \;\; & f_i(\tilde{s}, \tilde{a}, \tilde{i}) = (\Gamma_i - Q_i)\nabla_{\tilde{i}} \ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) \end{aligned} \tag{30}$$

The key aspect of this dynamics is that the autonomous (i.e., active and internal) states of an agent depend upon same quantity, which reduces to the log probability of finding the agent in a particular state; where the agent's states comprise the internal states and their Markov blanket. In this partition, autonomous states are those states that do not depend upon external states; namely, internal and active states. Solving equation (30) for the evolution f of active and internal states thus corresponds to evaluating the gradients of the log probabilities above that correspond to the Lagrangian of an open system. In general, this would be a very difficult problem to solve; however, we can now replace the Lagrangian with a variational free energy functional of a probabilistic model of how a system thinks it should behave, as follows.

3.2.4 Kullback-Leibler Divergence and Variational Free Energy

Using the above Markov blanket partition, we can now interpret internal states as parametrizing some arbitrary probability density $q(\tilde{e})$ over external states. This allows us to express the Lagrangian or Lyapunov function as a free energy functional of beliefs, and implicitly a function of the internal states. In probability theory, an ergodic random

dynamical system is a system which has the same behavior averaged over time as averaged over the system's states. In physics ergodicity implies that a system satisfies the ergodic hypothesis of thermodynamics, which says that over a sufficiently long time span, the time spent by a system in some region of state or phase space of individual states (with the same energy) is proportional the probability of the system be found in that region [Boltzmann, 2009].

Using the statistical definition for an expected value as averaged over all states $x \in \mathbf{R}$,

$$E[X] = \int_{\mathbf{R}} x p(x)\, dx\,, \tag{31}$$

we can then express the variational free energy through the introduction of the Kullback-Leibler Divergence:

$$D_{\mathrm{KL}}(p\|q) = \int_{-\infty}^{\infty} p(x)\, \ln \frac{p(x)}{q(x)}\, dx,\ , \tag{32}$$

which is the expectation of the logarithmic difference between the probabilities p and q, where the expectation is taken using the probabilities p.

Therefore, in place of the log density $\ln p(\tilde{s}, \tilde{a}, \tilde{i}|m)$ above, we can now write a variational free energy F that corresponds to the logarithmic difference between the (variational) density or Bayesian beliefs about external states $q(\tilde{e})$ and actual probability densities $p(\tilde{e}, \tilde{s}, \tilde{a}, \tilde{i}|m)$ of all states under the Markov blanket m defined in Table 1 and Figure 1:

$$\begin{aligned} F(\tilde{s}, \tilde{a}, \tilde{i}) &= \int_{\tilde{e}} q(\tilde{e})\, \ln \frac{q(\tilde{e})}{p(\tilde{e}, \tilde{s}, \tilde{a}, \tilde{i}|m)}\, d\tilde{e} \\ &= -\ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) + D_{\mathrm{KL}}(q(\tilde{e})\|p(\tilde{e}|\tilde{s}, \tilde{a}, \tilde{i}))\,. \end{aligned} \tag{33}$$

The first term is also called (Bayesian negative log) model evidence, or marginal likelihood, which essentially describes the likelihood that the sensory inputs were generated by a generative model implicit in the Markov blanket m. The second term is referred to as relative entropy and works as to minimize the divergence between the variational and posterior density $q(\tilde{e})$ and $p(\tilde{e}|\tilde{s}, \tilde{a}, \tilde{i})$ respectively. As a result, maximizing model evidence results into minimizing the free energy of the system, and because the divergence of the second term can never be less than zero, free energy is an upper bound on the negative log evidence. Using this expression, the flow of autonomous (i.e., active and internal) states becomes

$$\begin{aligned} (a'')\ \ f_a(\tilde{s}, \tilde{a}, \tilde{i}) &= (Q_a - \Gamma_a)\nabla_{\tilde{a}} F(\tilde{s}, \tilde{a}, \tilde{i}) \\ &= (\Gamma_a - Q_a)\nabla_{\tilde{a}} \ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) - (\Gamma_a - Q_a)\nabla_{\tilde{a}} D_{\mathrm{KL}} \\ (b'')\ \ f_i(\tilde{s}, \tilde{a}, \tilde{i}) &= (Q_i - \Gamma_i)\nabla_{\tilde{i}} F(\tilde{s}, \tilde{a}, \tilde{i}) \\ &= (\Gamma_i - Q_i)\nabla_{\tilde{i}} \ln p(\tilde{s}, \tilde{a}, \tilde{i}|m) - (\Gamma_i - Q_i)\nabla_{\tilde{i}} D_{\mathrm{KL}}\,. \end{aligned} \tag{34}$$

The key thing to note here is that the gradient descent on variational free energy will reduce the divergence in equation (32) to its lower bound of zero (because the divergence cannot be less than zero). At this point, the gradients of the divergence in equation (34) disappear and the dynamics reduce to the self-organization in equation (30), which is what we want to solve.

This is important because the variational free energy bound in equation (33) can be evaluated in a straightforward way given a generative model; namely, the joint

probability over (generalized) external, internal and blanket states. On this view, we can associate the joint probability in equation (33) with a likelihood; namely, the probability of an cell's states, given external states and a prior; namely, the prior probability of a cell's states (i.e., internal states and their Markov blanket). Finally, this means that $q(\tilde{e})$ plays the role of a posterior density over hidden or external states under a particular Markov blanket or model (m). Crucially, this variational posterior is parameterized by internal states. In other words, we can talk about the internal states encoding beliefs about external states.

In summary, to solve the problem of self-organization, we can specify a generative model for a cell and integrate (34). Before we turn to the construction of this generative model, we will briefly consider the ensuing (Bayesian filtering) scheme we used below to simulate self-organization in terms of dynamical belief updating in subsequent sections.

3.3 Bayesian Filtering and Self-Organization

We have seen above that one can replace the Lyapunov or Lagrangian function for any dynamics of a system that is equipped with a Markov blanket with a variational free energy that depends upon a generative model. This variational free energy is, effectively, a variational (upper) bound on model evidence; here, interpreted in terms of the probability of an agent's state (see equation (1)). This means that one can always interpret any self-organization to non-equilibrium steady-state (i.e., no time variation of the density over states) in terms of maximizing a quantity that plays the role of Bayesian model evidence. This is sometimes referred to as self-evidencing, a concept from brain sciences, where the agent (usually the brain) has to identify an evidentiary boundary between itself and its environment as a necessary condition for inference [Hohwy, 2016], [Moutoussis et al., 2014].

The variational free energy here is exactly the same mathematical construct used in statistics and variational Bayes. Simple examples of this include Kalman filtering and particle filtering, for inferring hidden states under dynamic Bayesian networks. Similar schemes have been used to infer genetic regulatory network structures from available genomic microarray time-series measurements [Lijun et al., 2008], [Noor et al., 2012]. The generalization of methods like Kalman filtering to a non-linear setting (in generalized coordinates of motion) leads to generalized (variational) filtering. These induce a variational free energy bound on model evidence by assuming under a fixed-form (usually a Gaussian) for the variational density $q(\tilde{e})$ above. This fixed form assumption underwrites the variational approximation that renders an intractable integration problem (30) into a tractable optimization problem that can be expressed as a gradient descent (34). The ensuing optimization rests upon a particular generative model – and implicit priors – which, in the research presented in this paper corresponds to the target morphology, or goal state [Friston et al., 2008], [Friston, 2008].

In summary, variational filtering is the quantification and minimization of a variational free energy, which places an upper bound on the dispersion of a particle's internal states and their Markov blanket [Buckley et al., 2017], [Friston et al., 2010]. Variational free energy hence converts any process of self-organization into a gradient descent on a free energy landscape, where basins correspond to attractor states, or goal states – akin to the target morphology – as described next.

4 Modeling Morphogenesis

In this section, we illustrate self organization to non-equilibrium steady-state using the variational principles described above, by trying to explain the behavior of a model of pattern regulation by considerations of information processing and error minimization

with respect to a specific target morphology. In this setting, the game changes subtly but profoundly. Above, we have seen that the dynamics of any random dynamical system, equipped with a Markov blanket, can be formulated in terms of a gradient flow on variational free energy. As a reminder, a Markov partition separates all states $x \in X$ into external $e \in E$, sensory $s \in S$, active $a \in A$, and internal states $i \in I$ (with their generalized versions $\tilde{x}, \tilde{e}, \tilde{s}, \tilde{a}$, and $\tilde{i}$). Variational free energy rests on an unknown generative model that produces the dynamics responsible for self-organization. Here, we turn this formulation on its head by specifying a generative model – and implicit variational free energy function – and simulate self-organization by solving the equations of motion in equation (34). In other words, we specify the form of the attracting set in terms of a probabilistic generative model of how external states perturb blanket states (i.e., a likelihood model) and how external states evolve (i.e., a prior). To do this, we have to simulate both the flow of autonomous (i.e., internal and active) states of each cell or agent and the external states that constitute its immediate milieu. In other words, we have to specify the external dynamics as a generative process and a generative model of that process entailed by the flow of internal states.

To illustrate the basic phenomenology, we will consider the self-assembly of an ensemble of cells to simulate morphogenesis, under different conditions. The generative model required is relatively simple but serves to illustrate the potential utility of this variational (free energy) formulation of self-assembling autopoietic behavior.

4.1 Constructing the Model

We need to specify the generative model given by the probability density $p(\tilde{s}, \tilde{a}, \tilde{i}|m)$ of sensory states s, active states a and internal states i, as well as the dynamics of the environment, determined through the flow $f_{\tilde{e}}$ and $f_{\tilde{s}}$ of external states e and sensory states s, respectively. This allows us to specify the requisite equations of motion for the system and its external states. Here, we will adopt a probabilistic nonlinear mapping with additive noise:

$$\begin{aligned} s =& g^{(1)}(e^{(1)}) + \omega^{(1)} \\ e^{(1)} =& g^{(2)}(e^{(2)}) + \omega^{(2)} \,, \end{aligned} \tag{35}$$

where the superscripts denote the first and second levels of our hierarchical model g. Gaussian assumptions about the random fluctuations or noise ω mean that we can write the requisite likelihood and priors as:

$$\begin{aligned} p(\tilde{s}, \tilde{a}, \tilde{i}|\tilde{e}^1) =& \mathcal{N}(g^{(1)}(e^{(1)}), \Pi^{(1)}) \\ p(\tilde{e}^1|\tilde{e}^2) =& \mathcal{N}(g^{(2)}(e^{(2)}), \Pi^{(2)}) \,. \end{aligned} \tag{36}$$

where $\mathcal{N}$ is the normal distribution, and $\Pi^{(t)})$ denotes the precision (or inverse variance) of the random fluctuations.

We then construct the approximate posterior density $q(\tilde{e})$ introduced in (32) using the associated Lagrangian or Lyapunov function

$$\begin{aligned} L(\tilde{x}) =& -\ln p(\tilde{s}, \tilde{a}, \tilde{i}, \tilde{e}|m) \\ =& -\ln p(\tilde{s}, \tilde{a}, \tilde{i}|\tilde{e}^1) - \ln p(\tilde{e}^1|\tilde{e}^2) \,, \end{aligned} \tag{37}$$

Under a Laplace assumption, the variational density becomes a normal distribution:

$$q(\tilde{e}) = \mathcal{N}(\tilde{i}, -\nabla_{\tilde{i}\tilde{i}} L(\tilde{s}, \tilde{a}, \tilde{i}, \tilde{i})) \,, \tag{38}$$

where $\nabla_{\tilde{i}\tilde{i}} L(\tilde{s}, \tilde{a}, \tilde{i}, \tilde{i}))$ denotes the curvature of the Lagrangian with respect to internal states. With this generative model and assumed form for the variational density, we can now evaluate the variational free energy for any given sensory state and perform a gradient descent according to equation (34).

An interesting technical detail here rests upon the use of generalized coordinates of motion. This means that one can associate the dissipative flow with a gradient descent on the expected energy function in equation (37) (noting that the entropy term of the variational free energy does not depend upon the means encoded by internal states). Furthermore, we can associate the divergence-free flow with an update term, so that

$$\begin{aligned} \Gamma \nabla F(\tilde{s}, \tilde{a}, \tilde{i}) =& \nabla E_q[L(\tilde{s}, \tilde{a}, \tilde{i})] \\ Q_i \nabla F(\tilde{s}, \tilde{a}, \tilde{i}) =& D\tilde{i} = (i^t, i, ...) \\ \nabla \cdot D\tilde{i} =& 0\,. \end{aligned} \tag{39}$$

Here, D is a block matrix operator that acts upon generalized coordinates of motion to return generalized motion (with zero divergence). Γ and Q are the diffusion and friction tensor introduced previuosly, and $E_q[L]$ is the expected value of L under the variational density; i.e., posterior belief $q(\tilde{e})$. This divergence free component effectively plays the role of an update term in Bayesian filtering – that can be interpreted as a gradient descent on variational free energy in a moving frame of reference. See [Friston et al., 2010] for details. In summary, this scheme can be regarded as a generalized (variational) filter, in which the internal states become the expected values of the external (hidden) states.

Finally, we assume that action is sufficiently fast to use the adiabatic approximation $\tilde{e} \approx \tilde{a}$, which greatly simplifies the specification of external dynamics.

4.2 Variational Free Energy Minimization

By effectively minimizing variational free energy, each Markov blanket or agent will appear to engage in belief updating, under the generative model, so that the evolution of the system will inevitably lead to a non-equilibrium steady state of minimal free energy. This provides a rigorous foundation for an intuitive concept familiar to all students of development and regeneration: cells act, remodeling tissues and organs, to minimize the global difference between the current configuration and a species-specific anatomical goal state [Pezzulo and Levin, 2015], [Pezzulo and Levin, 2016]. Cells and cell groups change their behavior based on signals they perceive from their environment (measurement) and act with respect to expectations (genetically encoded, and shaped by cellular learning) [Baluška and Levin, 2016].

Because free energy corresponds to (an upper bound on) Bayesian model evidence $-\ln p(\tilde{s}, \tilde{a}, \tilde{i}|m)$ as introduced in equation (33), this self-organizing behavior will also appear to be self-evidencing. This description of dynamics uses terms like Bayesian beliefs $q(\tilde{e})$ and self-evidencing in a purely technical (non-propositional) sense, which can be ascribed to simple systems like macromolecules and cells. The simulations below consider a small set of cells that are equipped with the same generative model such that they collectively self-organize to minimize variational free energy in an interdependent way, which has all the hallmarks of morphogenesis. This example is appropriate to models such as the highly-regenerative planaria [Levin et al., 2019], [Durant et al., 2016].

All the cells in the simulation start off with random initial signaling profiles near the center of their environment. In order for them to self-organize to the target configuration, each cell must infer its own location in the ensemble by forming and testing beliefs (or predictions) $q(e)$ about the hidden causes of the signaling concentrations it senses (i.e., , the secretion profiles and hence cell identities of the other

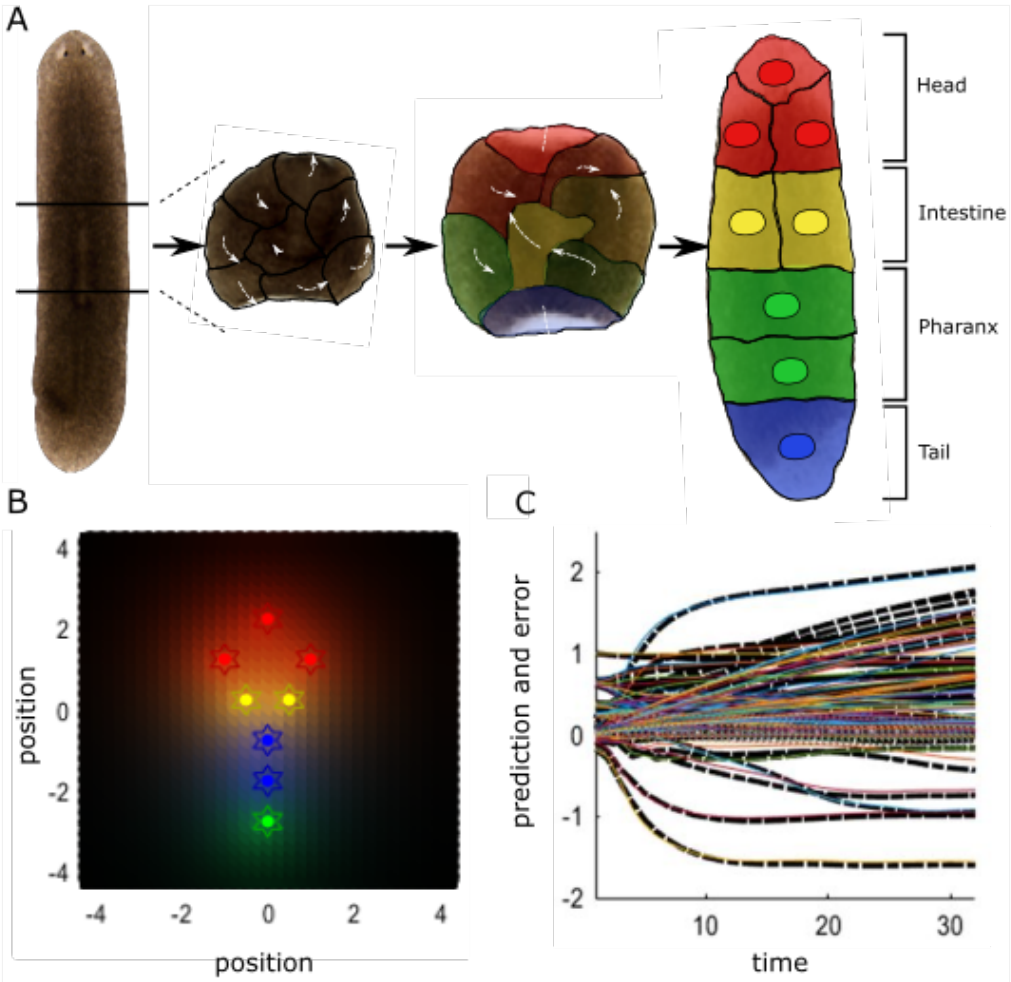

Fig 2. Schematic of variational Bayesian simulation of morphogenesis illustrated via a type of regenerative patterning observed in planarian flatworms and other organisms. **A:** When dissecting out the center piece of a planarian flatworm, the constituent cells will remodel into a new worm. Here, cells that form different tissue types were grouped together as one cell in the simulation for simplicity, with the cell signaling types defined in Figure 3. **B:** Expected Signal concentrations (background color) at each final position (colored stars) in the target morphology encodes the cellular model of inference, with the color coding from **A**. **C:** Cells are constantly comparing their sensed signal concentrations to their expectations by minimizing their free energy functional, which effectively aims to reduce the prediction error $\tilde{\epsilon}$ defined in equation (47) (dashed lines) on expected sensory states s defined in equation (40) (continuous lines).

cells (Figure 2). This can be formalized in terms of minimizing free energy, which effectively minimizes prediction errors $\tilde{\epsilon}$.

In more detail, in these simulations, each cell has control over what level of signals it can secrete of the four different generic types used here, and each cell can move in any direction. Furthermore, each cell has a generic place-encoded model of some (shared) target configuration based on signaling concentrations that would be sensed under that configuration. This means that for each of the four possible cell types associated with specific positions in the cell cluster cells expect to sense specific concentrations of

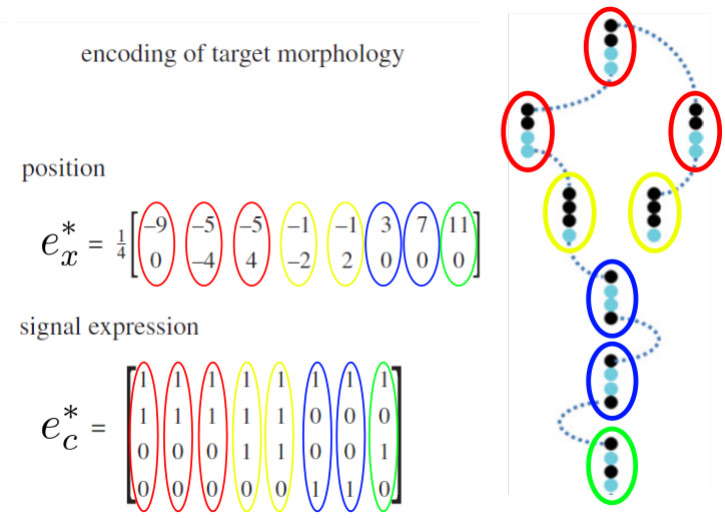

Fig 3. Encoding of Target morphology. This modeling scheme casts the arrangement of cells as an inference process, where the target morphology is encoded in each cell by expectations of external signals e_c^* for any given position e_x^* in the defined target morphology that constitutes the final configuration of cells. Each row in e_c^* corresponds to a different signaling type, while every column represents the signal expression states for a different cell. This figure uses the same color coding used to differentiate cell types as in Figure 2.

signaling molecules. See Figure 3.

Sensory states s corresponded to chemotactic concentrations of intracellular, exogenous and extracellular signals, such that:

$$s = \begin{bmatrix} s_c \\ s_x \\ s_\lambda \end{bmatrix} = \begin{bmatrix} e_c \\ e_x \\ \lambda(e_x, e_c) \end{bmatrix} + \omega \,, \tag{40}$$

where e are the external states of concentrations c and positions x of other cells. The signal concentration s_λ at each position of the i-th cell is given through the secretion and diffusion of signaling molecules of each other cell j and itself, given by the coefficient:

$$\lambda_i(e_x, e_c) = \tau \cdot \sum_j e_{cj} \cdot exp(-k\, d_{ij}) \,, \tag{41}$$

where e_{cj} is the combination of the four signals expressed at each position j, depicted in Figure 2B as colored coded around the target positions e^*, which are defined in Figure 3, and

$$d_{ij} = \mid e_{xi} - e_{xj} \mid \,, \tag{42}$$

is the distance between the i-th cell and the remaining cells, to which the secreted signal diffuses with diffusion coefficient k.

To preclude over-sensitivity to concentration gradients in early simulation steps – and model the emergence of cellular response to extracellular signals (e.g., through increased expression of cell surface receptors over time) – a time sensitivity factor $\tau \in [0, 1]$ was included, with

$$\tau = 1 - \exp\left(\frac{t}{T}\right), \tag{43}$$

where $T = \frac{1}{ln(2)}$, analogous to the half-life in exponential decay. This can be thought of as modeling changes in interfunctions that describe the characteristics of systems, which we introduced in section 3.2.2.

By analogy to stem cell-like behavior, we specify the same generative model g for each cell:

$$g(e) = \begin{bmatrix} e_c^* \\ e_x^* \\ \lambda^* \end{bmatrix} \sigma(e), \tag{44}$$

where $\lambda^* = \lambda(e_c^*, e_x^*)$ is the signal concentration at the target locations, and

$$\sigma(e_j) = \frac{\exp e_j}{\sum_j \exp e_j} \tag{45}$$

is the softmax function (or normalized exponential). This function is often used in neural networks to enforces a sum to one constraint, which allows an interpretation as a categorical distribution over mutually exclusive outcomes.

Using these expressions – and the equations of motion from the previous sections – we can express the flow of internal and active (*i.a.* autonomous) states from (34) as

$$\begin{aligned} &(a'') \;\; f_a(\tilde{s}, \tilde{a}, \tilde{i}) = (Q_a - \Gamma_a)\nabla_{\tilde{a}} F(\tilde{s}, \tilde{a}, \tilde{i}) = D\tilde{a} - \nabla_{\tilde{a}}\tilde{s} \cdot \Pi^{(1)}\tilde{\epsilon} \\ &(b'') \;\; f_i(\tilde{s}, \tilde{a}, \tilde{i}) = (Q_i - \Gamma_i)\nabla_{\tilde{i}} F(\tilde{s}, \tilde{a}, \tilde{i}) = D\tilde{i} - \nabla_{\tilde{a}}\tilde{\epsilon} \cdot \Pi^{(1)}\tilde{\epsilon} - \Pi^{(2)}\tilde{i}\,, \end{aligned} \tag{46}$$

while suppressing higher order terms (under the assumption of a smooth system, which is guaranteed by (43)). Here, $\epsilon = s - g(i)$ is the prediction error associated with sensory states – the state of chemotactic signal receptors – and can hence be expressed as:

$$\epsilon = \begin{bmatrix} \epsilon_c \\ \epsilon_x \\ \epsilon_\lambda \end{bmatrix} = \begin{bmatrix} s_c - e_c^*\sigma(i) \\ s_x - e_x^*\sigma(i) \\ s_\lambda - \lambda^*\sigma(i) \end{bmatrix}. \tag{47}$$

D corresponds to the matrix derivative operator on generalized states and the signal precision $\Pi^{(1)}$ is set to 1. We assumed Gaussian priors (with a mean of 0) over the hidden states with a small precision $\Pi^{(2)}$ (i.e., high variance) with a log precision of minus two.

In summary, under this sort of generative model (with continuous states and additive Gaussian noise), the internal states organize themselves to minimize (precision-weighted) prediction error based upon predictions of sensed signaling states from neighboring cells. In neurobiology, this scheme is also known as predictive coding and can be regarded as a generalized form of Bayesian filtering as described in section 3. Predictive coding refers to describing the dynamics of the system in terms of prediction errors ϵ through accumulation of model evidence $lnp(\tilde{s}, \tilde{a}, \tilde{i}|m)$, which maximizes likelihood $p(\tilde{s}, \tilde{a}, \tilde{i}|\tilde{e}^1)$ [Friston and Kiebel, 2009]. This is the process underlying the formulation of variational free energy above.

In the next section, we describe the results of some numerical analyses that underwrite the validity of this variational formulation by reproducing empirical behaviors *in silico*. In particular, we simulate responses of this multicellular ensemble to perturbations commonly used experimentally.

4.3 Perturbation Simulations

4.3.1 Animal Body Polarity Inversion

First, we introduced a gradient in the generative process for the signaling inputs that each cell receives from its environment, depending on each cell's chemotactic behavior (sensing and acting upon signals) and signaling outputs (secretion). This represents either a change in the way signaling concentrations are spread, maintained or counterbalanced in the extracellular environment of the cell (reflecting the experimental use of viscosity or osmolarity modifying compounds for example), or in sensitivity of the cell to changes in its environment (similar to the way we use the time sensitivity factor τ). This manipulation could be implemented experimentally by using receptor activity modifying drugs; for example, ethanol for neurotransmitters in the brain, [Banerjee, 2014], or retinoic acid through cross-modulation of cell-surface receptor signaling pathways. [Chambon, 1996].

To simulate formal changes – such as body polarity inversion – one can change the process that generates sensory inputs, as given by (40); namely, the mapping between sensory states s and external states e that constitute chemotactic concentrations of intracellular, exogenous and extracellular signals. Specifically, we changed the mapping $s_x = \tilde{e}_x$ to:

$$\begin{aligned} &(a)\ \ s_x = (\tilde{e}_x)^2 \\ &(b)\ \ s_x = -(\tilde{e}_x)^2 \end{aligned} \tag{48}$$

for the vertical axis, thereby changing the perceived distance of each cell to another in the vertical direction. In this instance, (a) results in a double head formation, and (b) in a double tail formation (*cf.* Figure 4).

Essentially, by introducing the terms corresponding to the square of the gradients with a different sign in (48), we changed the way sensory states (signaling inputs) were updated from changes in extracellular concentrations (external states) depending on the position of other cells. The squared gradient produces two things:

(1) it causes the signal concentrations to be updated only based on positive (or negative with the minus sign in (48)(b)) values, essentially causing each cell to explain all sensory inputs as an increased signal from one direction.

(2) It increases the sensitivity of sensory inputs to extracellular concentrations (external states), thereby increasing the effective precision.

4.3.2 Anomalous Cell Behavior

Some of the deepest insights into biological regulation come from observing instances where the normally tight processes go awry such as the cellular defection known as cancer [Moore et al., 2017], or disorders of development seen in birth defects. These processes can readily be modeled in our paradigm via changes of cellular decision-making. If we introduce the same type of gradient as in the previous simulations, but for only one cell, then we are effectively altering the sensitivity of that cell to changes in its environment (*cf.* Figure 5).

This can be specified formally as

$$s_{x,j} = (\tilde{e}_{x,j})^2 \ for\ j = j_f \ and\ s_{x,j} = \tilde{e}_{x,j} \ for\ j \neq j_f\,, \tag{49}$$

where j_f denotes the affected cell.

By introducing a local increase in a cellular signaling, this phenotype can be rescued enabling other cells to respond more definitively to their joint signaling. For example, the induced mutant phenotype above can be rescued by applying a square root to the

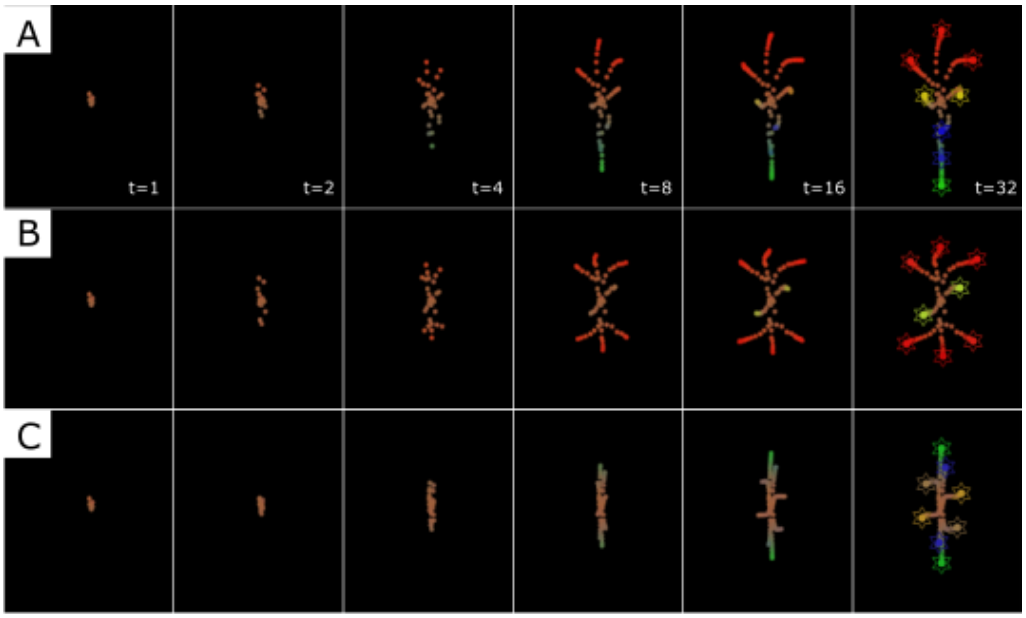

Fig 4. Time-lapse movie montage of simulations of morphogenesis with mirrored anterior/posterior polarity (head and tail positioning). **A:** 8 cells with initially unspecified cell types start to infer a correct target morphology by performing chemotaxis and updating their posterior beliefs, or predictions, q – and hence secretion profile. **B:** Using (48)(a), we introduced a positive squared gradient in the generative process for the signaling inputs that each cell receives from its environment, resulting in double head formation. **C:** Using (48)(b), we introduced a negative squared gradient in the generative process for the sensory inputs that each cell receives from its environment, resulting in double tail formation.

distance exponent in the signal concentration of the misbehaving cell. This attenuates the diffusion of signals given by λ in (41) for the affected cell j_f into:

$$\lambda_{j_f} = \tau \cdot \sum_l e_{cl} \cdot exp(-k\sqrt{d_{j_f l}})\,. \tag{50}$$

In short, with a simple manipulation of extracellular diffusion one can reinstate normal pattern formation. These examples illustrate how simple changes to extracellular signaling can have a profound effect on self-organization – an effect that depends sensitively on the ensemble behavior of cells – that depends upon a shared generative model. A key point – made by these kinds of simulations – is that one can reproduce aberrant morphogenesis (and an elemental form of cancer) without changing any intracellular mechanisms (i.e., the encoding of an implicit generative model). The message here is that casting morphogenesis, in terms of an inference process means that the ability of a cell to model its external milieu depends upon the coherence between the external generative processes and the model of those processes. Perturbations to either can result in profound changes in ensemble dynamics. Here, we restricted the manipulations to the external biophysics; i.e., the generative process. In future work, we will explore a larger repertoire of manipulations that speak to key empirical phenomena. Matlab software running these simulations, under different conditions is available from the author and can be downloaded as part of the academic SPM software from https://www.fil.ion.ucl.ac.uk/spm/software/ (accessed via a graphical user interface invoked with the command >> DEM).

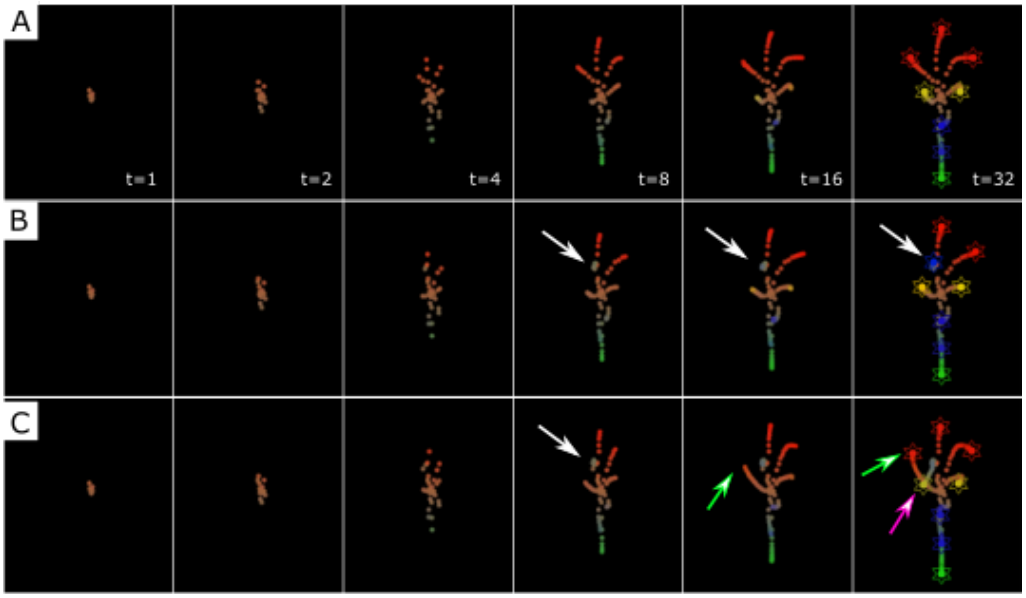

Fig 5. Time-lapse movie montage of simulations of morphogenesis with single cell aberrant signaling. **A:** 8 cells with initially unspecified cell fates start to infer a correct target morphology by performing chemotaxis and updating their beliefs and hence secretion profile. **B:** One of the cells (white arrow) has a perturbed signaling response mechanism and hence fails to correctly infer its place in the ensemble. **C:** The same aberrant cell from B initially is rescued by an increased signaling sensitivity of the other cells, leading another cell (green arrow) to switch position with the aberrant cell (pink arrow).

5 Discussion and Conclusion

Here, we provide a rigorous mathematical foundation for a poorly-understood but very important phenomenon: cellular decision-making, such as occurs during pattern regulation. The Bayesian inference framework enables quantitative models linking sensory mechanisms with functional behaviors in cells and tissues. In section 3 we have shown that the variational free energy that is being minimized in Bayesian inference follows out of classical analytical and statistical physics considerations as a unique form of a least action principle. Specifically, we showed that a Lyapunov function plays the role of a potential function in any dynamical system, and is being minimized to solve the flow of states in that system through a gradient descent. We then introduced the notion of a Markov blanket partition of states that allowed us to replace the Lyapunov function – or the related Lagrangian that is being used to compute the gradient descent in classical least action principles – with a variational free energy functional. This functional turns the classical gradient flow of any dynamical system into a gradient descent on the expectation of the (logarithmic) difference between (Bayesian) beliefs about external states and an actual probability density of all the states – as given by the Kullback-Leibler divergence. For non-equilibrium systems, this transforms an intractable integration problem of a thermodynamic potential into a tractable integration over a probabilistic model of how a system thinks it should behave.

In section 4, we showed how the attractor (or goal) states of the variational free energy landscape – on which the gradient descent described occurs – can be associated with a target morphology in a developmental, regenerative, or aberrant biology setting, thereby casting morphogenesis as an inference process. Through Bayesian inference

simulations of such processes, we showed how we can control the morphogenesis outcome through manipulations to the external biophysics (i.e., the generative process of our simulations) through knowledge of the underlying generative model of the inference process.

Before discussing these simulation results in more detail and drawing conclusions for the applications of this Bayesian formulation of self-organization to the experimental control of morphogenesis in real biological systems, we will first analyze the the mathematical assumptions that went into this model.

5.1 Summary of Mathematical Assumptions Underlying the Model

The variational formulation that underlies the simulations above demand a sufficiently smooth system. This means that abrupt changes in signaling can disrupt the simulations. In our applications, this effect was finessed by using a time sensitive coefficient from (43).

This type of time dependent sensitivity emerges from theoretical considerations and can, in principle, be tested for empirically in real biological systems. This sort of time sensitivity may manifest either through an increase of receptors, or proteins modifying the efficiency of signal transduction inside the cell; for example, in the levels of G-proteins, which act as molecular switches for multiple signaling pathways [Gilman, 1987]. When analyzing a cellular system that starts from a pre-specified configuration, such as in later stages of development or regeneration, this time-sensitivity may not be a prominent feature of the (implicit) generative model.

We have also made Gaussian assumptions about the fluctuations ω in the flow of states and a Laplace assumption for the approximate posterior density (*cf.* (38)). The Laplace assumption is often applied to modelling dynamics in neuronal populations, by a Gaussian neuronal population density. This allows population dynamics to be described by equations concerning the evolution of the population's mean and covariance, using the Fokker-Planck equation [Marreiros et al., 2009], [Friston et al., 2007]. This assumption has also been applied to gene regulatory networks [Imoto et al., 2001], which motivate the notion of internal states used in this work.

Most fundamentally, we have assumed the existence of a Markov blanket, which separates external and internal states through a set of active and sensory states. This statistical boundary does not necessitate a stationary or unique boundary between agents, but can be mutable [Clark, 2017], and conform to the type of simulations in [Friston, 2013]. Nevertheless, it needs to be verified empirically that signal transmission and adaptive responses on a cellular level are not instantaneous (as in our adiabatic approximations), and that active states indeed cause changes in sensory states.

Finally, we have appealed to nonequilibrium steady-state (under ergodic assumptions) for the type of dynamics studied here. While this is a common assumption made in the description of dynamical systems, some argue that any biological system is non-ergodic at a molecular level [Longo and Montévil, 2013]. Yet it remains unclear whether this holds true for states of cellular signaling and genetic expression investigated here. Furthermore, the ergodic (e.g., weakly mixing) assumptions that underlie the free energy principle are only those inherent in the existence of a pullback attractor. The pullback attractor is defined as a state, or set of states, to which a random dynamic system would converge to (yet not necessarily reach due to random fluctuations) if given enough time and with continuous mixing under these ergodic assumptions. In other words, the key assumption that underlies the variational formulation on offer here is the existence of an attracting set that underwrites non-equilibrium steady-state.

5.2 Extending Variational Principles to Open Systems

Because we have shown that the variational free energy minimization in active inference is related to the variational principle of least action, it is worth pointing out where these two approaches diverge. Due to the nature of the variational calculus and least action principles, in which action is integrated over a time interval between fixed time points, it is normally only applicable to closed systems – as opposed to biological systems that operate far from thermodynamic equilibrium.

In order to measure action efficiency in complex open systems, the principle of least action needs to be modified from the minimal action along a single, fixed trajectory, to the minimum of the average action over an ensemble of trajectories within a certain interval of time.

In open systems, there is a constant flow and change of the number of states and constraints, as well as of the energy of the system itself. This will cause the system to converge onto an attractor state, without ever truly reaching it, but instead to be in a constant process of reorganization . [Georgiev, 2012].

The same is true for the simulations in this paper, where the system starts in a far from equilibrium state, which necessitated the introduction of the time sensitivity *tau*. Furthermore, while the variational free energy is minimized over time and the system appears to approach an attractor state, partial information flow remains in the updating of prior beliefs, largely due to the intrinsic random fluctuations ω of the external states.

5.3 Applicability of Bayesian Inference to Biological Systems

One central aspect of the modeling based on the Bayesian inference proccess employed above is the updating of prior beliefs (that is the parameters of an agent's internal model encoding its expectation of its environmment) via evidence accumulation through the Bayes theorem of (1), as dictated by ever changing active states which, effectively, fulfil predictions. Because this process rest on the minimization of the variational free energy and with it the divergence of prior belief and posterior density introduced in (33), this necessarily implies an observable non-random exploratory mechanism that can accumulate the evidence needed to update priors. For example, in visual perception, saccadic eye movements have been identified and modeled as just such an exploratory mechanism that accumulates model evidence efficiently [Friston et al., 2012].

In this setting, actions are selected that minimize expected free energy, where expected free energy features uncertainty reducing, information seeking aspects. In non-neural biology, adaptation to environmental stresses have been shown to elicit an exploratory response in gene expression, such as previously unexpressed exogenous genes in rats following stress stimulation [Elgart et al., 2015]. Theoretical simulations from the same group have shown that this compensation can – in theory – be explained using random exploratory expression of genes until the correct gene is expressed [Soen et al., 2015], [Schreier et al., 2017], but the question must be asked how efficient this would be in the context of short term adaptation, and how negative effects resulting from random expression of detrimental genes would be counterbalanced. Instead, we hypothesize along the lines of Bayesian inference, that this gene expression is not random, but follows distinct trajectories that are encoded by changes in active states of the cell (e.g., protein translation, cytoskeletal rearrangement and membrane permeability and receptor activity modifications).

In other words, we postulate that expression of exogenous or otherwise unexpected genes is driven by a directed, explorative process where active states become expression profiles that aim to minimize variational free energy through prior beliefs encoded by the internal epigentic states in the Bayesian sense as outlined above. If none of these

distinct trajectories are present, we would have to conclude that no Bayesian inference process can take place on the level of gene expression in such an adaptation experiment but would instead have to move towards an adaptation mechanism on a different time-scale, such as its transient bioelectric states. As seen in the previous sections, the same is true for prior beliefs (such as encoded by the epigenetic state of a cell), which need to be able to be updated within a time window smaller than that of physiological adaptation.

5.4 Predictive Capability of the Simulations

In our simulations, we were able to systematically perturb the overall morphology of our model system without changing the internal, generative model of the constituent cells; i.e., the gene regulatory networks that motivate the internal states. First, we produced alterations of anterior-posterior polarity (i.e., two head or two tail regions), which emulate phenotypes as inducible in planarian regeneration [Durant et al., 2017]. While the mechanism of the phenotype induced by transient bioelectric pattern perturbations explored by Durant *et al.* was not explicitly used in this model, it is worth pointing out that both leave the underlying, hardwired internal states – i.e., the genetic level – unmodified, but instead work on the computational cellular processes that encode map of the final target morphology [Levin, 2012b].

Second, we reproduced abnormal signaling and functional behavior of a single cell within a cellular ensemble as a first step in cancer formation. We show that with simple modifications of the inference process we can induce – and rescue – mispatterning of these developmental and regenerative events – without changing the hard-wired generative model of the cell as determined by its DNA. We conclude that macro- onto micro-scale feedback during development and regeneration – especially considering the capability of developing tissue to dynamically adapt to changes in its environment – implies the need for active inference on a cellular level, and that the variational formalism explored in this work provides us with the means to predict and control its outcomes.

5.5 Concluding Remarks

A major challenge in current attempts to control the morphogenetic outcomes in developmental or regenerative biological systems is the quantitative modeling of how the signaling and sensing activities of individual cells are coordinated and regulated to result in large-scale anatomical patterns that enable robust structure and function [Levin, 2012b], [Gilbert and Sarkar, 2000].

An important gap in the field is that the complexity and non-equilibrium nature of the biological systems investigated have made the computation of the flow of states over time – and thereby the control of that flow to a different stable attractor state corresponding to a desired morphogenetic outcome – near impossible.

Here, we show how a variational free energy formulation – which casts morphogenesis as a (Bayesian) inference process – allows us to control specific morphogenesis outcomes through manipulations to the external biophysics; by providing the fundamental insight and modeling capability of how these biophysical, morphogenetic fields [Levin, 2012b], [Goodwin, 2000] are interpreted by individual cells and used to coordinate on a macroscopic level. Notably, this capability is achieved without changing the implicit generative model of a cell as specified, for example, by its DNA. Therefore, this formalism offers a new road map for understanding developmental change in evolution and for designing new interventions in regenerative medicine settings, where system-level results of interventions on the genomic level hard to predict.

Equipped with these proof-of-principle results, we can now explore a larger repertoire of manipulations that speak to key empirical phenomena in developmental and regenerative biology. Crucially, the challenge will be to write – and test at the bench – a generative model for a real developmental, regenerative, or aberrant biological system, where realistic biophysical parameters can be fed into an experimentally tractable *in vivo* model for unprecedented rational control of growth and form [Pezzulo and Levin, 2015], [Pezzulo and Levin, 2016].

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