

Chaotic waves serve as universal pattern generators

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Excitable media are prevalent models for describing physical, chemical, and biological systems which support wave propagation. In this letter, we show that the time evolution of the medium state at the wave fronts can be determined by complicated chaotic attractors. Wave front dynamics can be controlled by initial data choice. Building on this groundwork, we show that there is a mechano-chemical analog of the Universal Turing machine for morphogenesis problems. Namely, a fixed mechano-chemical system can produce any prescribed cell pattern depending on its input (initial data). This universal mechanism uses fundamental physical effects: spontaneous symmetry breaking with formation of many interfaces (kinks), which interact non-locally via a fast diffusing reagent. This interaction creates chaos. We present algorithms allowing us to obtain a prescribed target cell pattern.

Introduction. — We propose a model of an excitable medium that can generate waves of a new kind. These waves consist of interacting narrow fronts. The evolution of the coordinates that define the localization of those fronts, is governed by a dynamical system. The key point is that we can control the attractors of these dynamical systems by positional information stored in spatially distributed initial data and by the choice of a few of parameters. These attractors may be chaotic and of high dimension. We show that this effect has important biological consequences. As an example, we consider applications to morphogenesis, in particular, to cell differentiation problems. We resolve the cell pattern generation problem: imagine an arbitrary string of cells of different types located along the x -axis (this might model 1D-organisms, like a worm, or a segmented embryo, see Fig. 1). The cell pattern can be generated by our excitable medium, and we present an algorithm for how to do so.

To better understand our approach to the cell differentiation problem in more detail, recall two fundamental biological concepts. An organism can be represented as a pattern consisting of different cells (see Fig. 1). The cells are “specialized”, i.e., each type of cell performs a unique and special function and each of the order of 100 – 200 different types of cells in multicellular organisms has different structures, sizes, shapes, and functions. The famous Turing instability approach [1] allows us to obtain periodical layered patterns, such as zebra stripes, however, we would like to explain more complicated observed structures. To this end, the concept of positional information was proposed by Wolpert [2]. Both approaches, Turing’s and Wolpert’s, assume that morphogens, special reagents, can change cell states.

Our new idea is that the waves with complex evolving

fronts can perform cell differentiation in a dynamical way. This allows us to create any pattern not just periodic ones. The waves transfer a family of morphogenes, which change the cell states and produce cell differentiation. In contrast with Wolpert’s gradient model, the wave act at long distances and can transfer dynamical information contained in an attractor.

The main idea of the pattern generation mechanism is as follows. We restrict ourselves to one-dimensional layered patterns (a generalization to multidimensional cases will be presented in future papers). Consider the pattern shown on Figure 1. That pattern can be considered as a string of cell types (blue, green, red). Our aim is to create any such string. Note that a universal Turing machine (UTM) may print any string. A UTM includes a head and a tape, the states of the head form a finite set. The head moves along the tape and prints symbols. Our medium generates waves, which move along the x -axis, and prints cells of different types. The type choice depends on the state of the wave front, defined by a chaotic hyperbolic dynamics. Here we use the beautiful idea from C. Moore [3, 4] on simulation of TM’s by chaotic dynamical systems. It is based on so-called Bernoulli shifts, chaotic dynamics can be encoded as a shift on a discrete set of symbols. So, the states of the waves can be encoded by a finite partition of all possible morphogen states. We present two variants of patterning algorithms, the first gives us a rigorous method to resolve any 1D problems of pattern generation, and the second is a simplified variant that works well in numerical simulations.

These results show that there are media that function as analogs of UTM’s. A UTM can make all computations, which can be done by other TM’s, and so, UTM’s generate all possible string outputs when we vary their input.

In our case, we have a fixed (up to a few parameters to adjust) spatially extended system, which, depending on initial data, generates all possible layered cell patterns. Note that UTM's admit a short description [5].

So, our results show that simple mechanochemical systems can serve as Universal Generators of spatio-temporal patterns (UPG). Thus they can be considered as analogs of UTMs. A UTM obtains a program as an input and performs computations prescribed by that program. In our case, the input of our UPG is determined by spatially distributed initial data localized in a narrow domain.

Cell differentiation waves are proposed in [6], see also [7]. Cell killer waves are found in [8]. Apoptosis (programmed cell death) propagates through the cytoplasm as self-regenerating trigger waves, which spread without slowing down or petering out. Cell differentiation waves in *Drosophila* morphogenesis are found experimentally and investigated in [9], where, moreover, a conceptual mathematical model is proposed, which involves reaction and diffusion, and exploits mechano-chemical effects, where chemical reaction terms are linear and quadratic. The model [9] describes the time evolution of concentrations of free Fog ligand, bound-receptor Fog, and MyoII protein.

Waves of cell differentiation are studied experimentally in [10], where it is indicated that signaling patterns may be dynamic, and cells may use various strategies to interpret these dynamics. To investigate this dynamical mechanism, in [10] WNT and Nodal signaling pathways are studied. BMP signaling triggers waves of WNT and NODAL signaling activities, which move toward the colony center at a constant rate. It is shown that it is inconsistent with reaction-diffusion-based Turing models, suggesting that neither WNT nor NODAL forms a stable spatial gradient of signaling activity. So, the experiments and theoretical models show that, at least in certain situations, the morphogenesis proceeds with the help of waves, while the celebrated Turing instability does not work [10]. However, the pathways involved in the wave dynamics are extremely intricate.

Similarly to [9, 10], in our model we use reaction and diffusion, and also linear elastic waves but we also implement into our model the scalar Ginzburg-Landau (GL) equation with a small gradient term. That equation describes bistability, and spontaneous layered patterning. The GL equation simulates a trigger mechanism, which in real biological systems is generated by positive feedback loops in gene regulation networks (those loops are detected in killer waves [8]). This extends possibilities in a formidable way: spontaneous symmetry breaking creates complicated dynamical information and transfers that information through active media.

Let us outline our model. It consists of three equations. The first equation is a weakly perturbed Ginzburg-Landau (GL) equation for a scalar order parameter u .

We suppose that the coefficient ϵ^2 at the gradient term in the corresponding energy is small. It is well known that the non-perturbed GL equation has asymptotical solutions describing kink chains, where i -th kink is localized at $x = X_i(t)$. Kinks are narrow topological defects (of width $O(\epsilon)$) with the charge $(-1)^i$ describing a symmetry breaking: a separation of the entire domain on subdomains along x -axis, where $w \approx \pm 1$. Note that the direct interaction between kinks is exponentially small and therefore such a solution is correct within an exponentially long time $O(\exp(-c_1/\epsilon))$ while kinks are separated [11]. Furthermore, we use a simple perturbation, which makes the kink chain move as a whole at a low constant speed κ . The following equation describes the reaction-diffusion dynamics of v -reagent, where the order parameter u is involved. Reagent v diffuses fast. The kinks interact with the fast reagent and the reagent v acts on u , which that produces feedback and non-local non-direct kink interaction. We show that under an appropriate choice of system parameters the dynamics of the kink coordinates X_i can be described by the Hopfield system with continuous-time and non-symmetric interactions. It is well known that such Hopfield systems exhibit a remarkable universality property [12]: they can generate any structurally stable (hyperbolic) dynamics. Such dynamics may be chaotic (the best known examples are given by Anosov flows and Smale horseshoes [13, 14]). Following [3, 4] we can use this chaos to simulate Turing machines and we apply it to program pattern formation.

We would like to note that curved chaotic fronts can also be described by the Kuramoto-Sivashinsky (KS) equation [15, 16]. In our case, a physical mechanism of the chaos generation is absolutely different: instead of curvature effects, we use a non-local kink interaction via coupling with a fast diffusing reagent. While most of the known results for the KS model are numerical (see, for example, [17]), our model is analytically tractable and there is an algorithm to control the wave front dynamics.

The model and its properties. — The model consists of a reaction-diffusion part, a hyperbolic equation, and a scalar Ginzburg-Landau equation for an order parameter w :

$$u_t = \frac{\epsilon^2}{2} \Delta u + u - u^3 - \kappa u_x + \gamma v, \quad (1)$$

$$v_t = \Delta v + z u_x, \quad (2)$$

$$z_t + \kappa z_x = 0. \quad (3)$$

Here $\gamma, \kappa > 0$ and $\epsilon > 0$ are small parameters, $u = u(x, y, t)$ and $v(x, y, t)$ are unknown functions defined on $\Omega \times \{t \geq 0\}$, Ω is the strip $(-\infty, \infty) \times [0, 1] \subset \mathbf{R}^2$. Eq. (3) for z can describe elastic (mechanical) effects, and the deformation z affects v via a quadratic nonlinearity. To simplify the problem, and bearing in mind further

the propagation of waves, we set the periodic boundary conditions

$$v(x, y, t) = v(x + 2\pi, y, t), \quad u(x, y, t) = u(x + 2\pi, y, t). \quad (4)$$

At the boundaries $y = 0$ and $y = 1$ we set the zero Dirichlet conditions for v :

$$v(x, h, t) = v(x, 0, t) = 0 \quad (5)$$

and the zero Neumann condition for u

$$u_y(x, y, t) \Big|_{y=0,1} = 0. \quad (6)$$

The initial conditions are given by smooth functions u_0, v_0 and z_0 , for example,

$$z(x, y, 0) = z_0(x, y), \quad (7)$$

and similarly for u, v . The function z_0 plays a key role in long time behaviour control.

The key difference between this system and the model of [9] is the presence of the GL equation (1), which describes phase transitions and layered patterning. So, we can take into account basic mechanical, chemical, and physical effects, and we think that this model is the most efficient among all those providing the effects described in the manuscript. Note that our model is two-dimensional that is important for the control of large time dynamics. To obtain analogous results in one-dimensional case, we have to use a number of reagents replacing a single eq. (1) by a reaction-diffusion system.

Asymptotic solutions and mechanism of chaos onset.— In this model, chaos appears as a result of a non-local kink interaction. For each integer N and sufficiently small $\epsilon, \kappa > 0$ and γ there exist solutions describing interaction of N kinks. The u -component of these solutions are perturbed 2π -periodic in x kink chains $U_N(x, X(t))$ consisting of N kinks well localized at points $X_i(t) - \kappa t$, where $X_1 > X_2 < \dots < X_N > \delta_0 > \epsilon$ are slowly evolving in time relative kink coordinates. Analogous kink solutions for (1) are described first in [11]. Such solutions are metastable and exist while kinks are well separated, and the kink existence time interval I_ϵ is of the order $\exp(-c_0\epsilon^{-1})$ [11]. So, our solutions have the form

$$u(x, y, t) = U_N(x, t) + \tilde{u}(x, y, X(t)), \quad (8)$$

$$v(x, y, t) = V_N(x, y, t) + \tilde{v}(x, y, t), \quad (9)$$

where \tilde{u}, \tilde{v} are small corrections with respect to the main terms U_N and V_N . The following relation is important:

$$V_N(x, y, t) = \sum_{i=1}^N X_i(t) W_i(x - \kappa t, y), \quad (10)$$

where W_j are smooth functions. The function W_i defines a response of v -reagent to the excitement generated by

i -th kink. In turn, the v -reagent acts on kinks via the small perturbation γv in Eq. (1). So, we obtain a feedback and a non-local nonlinear interaction between the kinks, which is much stronger than exponentially small interactions between nearby kinks. For an appropriate choice of the small parameters ϵ, γ, κ , and the initial data $z_0(x, y)$ one can show that, up to small corrections, the time evolution of kink coordinates X_i is governed by the time continuous Hopfield system

$$\frac{dX_i}{dt} = \sum_{j=1}^N K_{ij} \sigma(X_j - h_j) - \lambda X_i, \quad (11)$$

where σ is a smooth sigmoidal function, the matrix \mathbf{K} with entries K_{ij} defines an interaction between X, h_j are thresholds and $\lambda > 0$. The form of this system depends on parameters $\mathbf{P}, \mathbf{P} = \{\mathbf{K}, N, h, \lambda\}$. The matrix \mathbf{K} and λ are linear functionals of initial data z_0 . The key point is that by variation of z_0 we can obtain any given \mathbf{K} (not necessarily symmetric, see SM).

The Hopfield systems with general non-symmetric interactions K_{ij} enjoy remarkable properties. We know that multilayered perceptions can approximate any output (Theorem on Universal Approximation). By that basic result, one can show that the Hopfield system has the property of Universal dynamical approximation. Namely, they can simulate, within any prescribed accuracy, any finite-dimensional dynamical systems (see [12, 18] and SM). This simulation works via hidden slow variables, which appear in the Hopfield dynamics under an appropriate choice of \mathbf{K} . Then, that matrix defines an interaction between slow and fast variables. As is typical, in such slow-fast systems, the slow variable dynamics captures the entire system's long-time behavior. By parameter \mathbf{P} we can completely control the slow dynamics (up to small smooth corrections).

For example, suppose we would like to simulate the Lorenz dynamics within accuracy δ . Then we can adjust parameter \mathbf{P} in such a way that (11) becomes a slow-fast system, and the slow part dynamics is defined by the δ -perturbed Lorenz system. This simulation holds, in general, on large time intervals, but if the attractor of the prescribed system is structurally stable (for example, hyperbolic), i.e., does not change its topology under sufficiently small and smooth perturbations, then for small δ -the simulating Hopfield dynamics is the same (up to topological equivalency of trajectories). Roughly speaking this means that system (11) can simulate all hyperbolic dynamics, for more precise formulation see [12] and SM). These facts lead to the results described in the coming section. Note that a connection between the neural network Hopfield model and reaction-diffusion systems was first discovered in [19], see [12] for a rigorous proof.

Formation of cell patterns. — To describe patterns consisting of differentiated cells and cell differentiation via the reagent u , we use the model, which follows the

biological ideas [1, 2] outlined in the introduction. Consider, for simplicity, two cell types, say, red and blue cells. We encode them by 1 and 2, respectively (the generalization for a larger number of cell types is quite straightforward). We assume that cells occupy strips of the same small length δ_c forming a layered pattern along the x -axis. We thus have $M = \lfloor L/\delta_c \rfloor$ equidistant layers. The output cell pattern can be considered as a binary string s_{out} : $s_{out} = \{a_1, a_2, \dots, a_M\}$, where a_i is either 1, or 2. We also introduce a state 0. The state zero corresponds to cells that are not yet differentiated.

Next, we describe how the cell pattern can be produced in our model. The cell pattern is a result of terminal differentiation which goes by morphogens. Suppose that the u is a morphogen. It is natural to assume that cells interpret morphogen signals by averaging in space and time. For simplicity, we assume that this interpretation goes through linear convolution operators, which act on the u -pattern (see SM). So, the cell obtains information about kink coordinates X at the moments when the kinks reach the cell. Let us consider how this information can be used. The range of all possible values X will be denoted by Π . We introduce the partition of Π consisting of disjoint subsets Π_k , $k = 0, 1, 2$ such that their union is Π and each subset has an open interior. This partition has a simple meaning: we encode the continual space of wave states by a discrete code. The set Π_0 corresponds to non-differentiated cells, the set Π_k with $k > 0$ corresponds to cells of k -th type. We encode kink states $X = (X_1, \dots, X_N)$ by functions $Z(X)$. The coding function $Z(X)$ takes the value k if $X \in \Pi_k$. Let $u(x, y, t)$ be the asymptotic kink solution. Then the output string $s_{out}[u]$ can be defined as follows: j -th element of the string is k , if $Z(X(t_j)) = k$, where t_j is the moment when kink chain wave reaches j -th cell. This construction replaces thresholds in the Wolpert positional information approach, but in our case, this information is transferred in the cells by waves instead of gradients. We refer to $s_{out}[u]$ as wave cell differentiation operator, for more details see SM.

Note that at the moment $t = t_j$ the corresponding cell accepts k -th state and does not change its type anymore. We assume here the biological fact that typical cells do not change their cell types after terminal differentiation when they acquire their specialized type. At $t = 0$ all cells are in an indefinite state 0.

Main results.—Concluding the ideas presented above we formulate the following statements.

On dynamical complexity: Kink dynamics of our model has the property of universal dynamical approximation.

This means that when we vary the model parameters, initial data and the kink number, kink coordinate dynamics can generate all possible kinds of structurally stable large time behavior (up to topological equivalency). Since hyperbolic dynamics is persistent [14], kink motions generate all hyperbolic dynamics. Hyperbolic dynamics

may be chaotic [13, 14], and further, we show how hyperbolic chaos generates all possible 1D layered patterns. It can be done by an algorithm, which allows us to obtain a prescribed cell pattern.

The next statement unwraps the main problem of cell pattern formation.

On the cell pattern generation problem: Let $s = \{a_1, \dots, a_M\}$ be a prescribed string of cell types, $a_i \in \{1, 2\}$. To find parameters ϵ, κ, γ and initial data u_0, v_0, z_0 such that the corresponding solution of Initial Boundary Value Problem (IBVP) defined by eqs. (1)-(3) and conditions (6)-(7) satisfies

$$s_{out}[u] = s, \quad (12)$$

where $s_{out}[u]$ is the wave cell differentiation operator.

The last statement can be formulated as follows.

The pattern generation problem has a solution.

We describe algorithms to resolve this problem in the coming section.

Pattern generation.— We propose algorithms to solve the pattern generation problems based on celebrated results of dynamical system theory on hyperbolic sets, in particular, the existence of Markov partitions that implies the correspondence between maps on invariant hyperbolic sets and Bernoulli shifts [3, 4, 14]. The idea of the algorithm can be outlined as follows. We first encode a cell pattern as a string in an alphabet \mathcal{K}_c of cell types. The algorithm input is then a string $s_{out} = \{a_1 a_2 \dots a_M\}$ of symbols from \mathcal{K}_c (see Fig. 1). We would like to produce such a string. We know that a UTM can print that string: the UTM head moves along the tape and prints. Similarly, our wave moves along the x -axis and prints different cells. Although states X of that wave lie in a bounded domain of \mathbb{R}^N , we can make a partition of that domain to encode the wave states. Then the wave becomes an analog of the UTM head. Here we use Bernoulli shifts and the same idea that allows realizing TM's by dynamical systems, see SM for more details.

Note that the algorithm is based on the well-known biological fact that cells (except for stem cells) are not capable of further differentiation. When a wave comes to an area occupied by a cell, it changes its type (depending on the amplitude of the wave), that is, it makes differentiation and after that, the cell no longer changes.

So, we conclude that there is a universal reaction-diffusion system, which can produce any cell phenotypes depending on initial data and a few parameters, i.e., we can obtain a needed final (terminal) phenotype.

The chaotic hyperbolic attractor can be taken, in principle, in an arbitrary way, however, it is natural to take a low dimensional one. The choice of the Markov partition depends on the coding scheme, which we use for cell types.

Our chaotic attractors generate strings within time intervals, but by waves described above, we can obtain a generation along the x -axis.

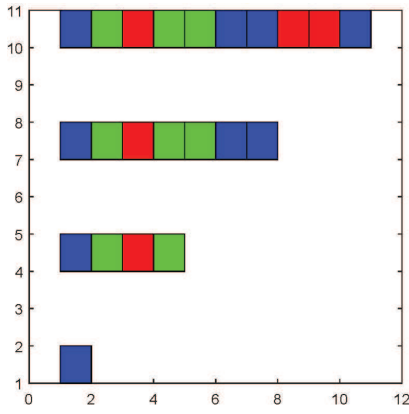


FIG. 1. The generalized French Flag model in terms of wave morphogenesis. A cell pattern can be considered as a string in the alphabet (red, blue, or green). Universal Turing machine can print any strings on a tape. Chaotic waves can do the same: they propagate along the x -axis and transform non-differentiated cells into differentiated ones. We can obtain any prescribed string by a choice of initial data z_0 and the kink number N .

Numerical example and simplified algorithm.— As an example of the algorithm application, let us consider how to create the pattern in Fig. 1. Numerical simulations show that the sophisticated algorithm stated above can be strongly simplified. We can, instead of the Markov partitions, use almost arbitrary partitions of phase space on disjoint subsets. We consider first how to generate layered pattern like the famous French flag by waves instead of gradients. Consider the pattern in Fig. 1 consisting of 4 layers: blue, green, red, and again green. Suppose for simplicity that all layers of the cell pattern have the same width then the string corresponding to that pattern is $s = (1, 2, 3, 2)$. We take the Lorenz system for variables $q = (q_1, q_2, q_3)$ with the standard choice of parameters to produce a chaotic attractor Γ . Further, we find the Hopfield system such that the kink coordinates X evolve according to weakly perturbed Lorenz system, $X(t) \approx X(q(t))$.

Let us introduce $q_{\min} = \min_{q \in \Gamma} q_1$, $q_{\max} = \max_{q \in \Gamma} q_1$, and $\Delta q = q_{\max} - q_{\min}$. Then we take the partition $E_1 = [q_{\min}, q_{\min} + \Delta q]$, $E_2 = [q_{\min} + \Delta q, q_{\min} + 2\Delta q]$ and $E_3 = [q_{\min} + 2\Delta q, q_{\max}]$. Then one can check numerically that there exist points $q(0)$ on the Lorenz attractor and ΔT such that $X(\Delta T) \in E_1$, $q(2\Delta T) \in E_2$, $q(3\Delta T) \in E_3$ and $q(4\Delta T) \in E_2$. Here E_1, E_2, E_3 correspond to blue, white and red cells, respectively. The partition of X -space, which define cell differentiation, is formed by ranges of E_k under the map $q \rightarrow X(q)$. So, we obtain the layered aperiodic 1D-pattern consisting of four layers (see Fig. 1, the second row from bottom). The same construction allows us to obtain more complicated patterns, for example, consisting of five and more layers. Note one can take other sets E_k so the choice

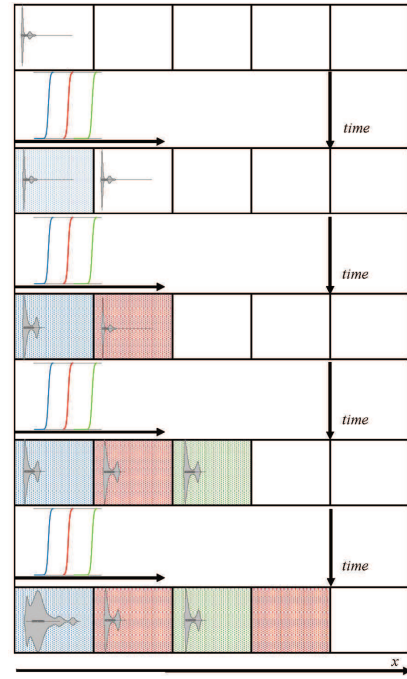


FIG. 2. The active medium described in the paper can generate waves, which can transfer a complicated time behaviour. A cell colony that has created such a medium (or is immersed in it) can have important selective advantage. For example, suppose that a cell, a member of that colony, finds a complex dynamical adaptive answer to a ecological challenge (the top row, the first cell). Then this answer can be transferred to other cells by the waves, and thus the whole colony obtains an ability to survive. Moreover, it is shown that the wave front dynamics is defined by the Hopfield networks, so, those waves also may transport associative memory.

of the partition is almost arbitrary. However, the longer the cell pattern becomes, the smaller the set of starting points $q(0)$ will be, and thus it is more difficult to find that set.

This simplified variant of the algorithm can be analytically explained under the assumption that the dynamics on the attractor is strongly mixing (see SM, subsect.). Moreover, this variant is robust with respect to the choice of partitions. However, the sophisticated algorithm with Poincaré map has an advantage: by the Bernoulli shifts and the Markov partitions, we can find the set of initial data $q(0)$ and the corresponding initial kink coordinates $X(q(0))$ in an explicit way. The pattern generation by the simplified algorithm can be observed in a video, see [20].

Conclusions. — A key component for achieving functionally stable multicellular structures is a physical embodiment. Any relevant model of the evolution of multicellular organisms should actually take into account basic physical mechanisms. It is shown that there exists a simple physical model defined by three equations with quadratic and cubic nonlinearities which create the

chaotic waves of a new type. These waves have fronts, which can be interpreted as "moving" attractors and they can transfer information since dynamical systems with a complicated behavior can simulate all Turing machines [3, 4]. Such waves can transfer information in space, for example, innovations. Following [21] one can say that excitable media can create programmed and self-organized flows of information. Propagation of complicated information, which may seem to be the exclusive prerogative of human society is possible in simple physical media. These results can be applied, in particular, to cell differentiation problems. New pattern formation mechanism described here can produce any target cell $1D$ patterns.

Physical processes mobilized by genes can establish morphological templates. Most animal body plans and morphological motifs arose between 500 and 700 million years ago, during relatively brief periods of innovation. The genes, whose products control morphogenesis and pattern formation, were present in the unicellular ancestors of the animals; billion years of evolution failed to generate substantial additional morphological novelty. The work [22] reconciles these facts by proposing that chemically and mechanically active media can create the main motifs of animal forms. Our results support this concept of physical determinism in development. We also think that the proposed pattern generation mechanism can appear in other applications, for example, in ecology and economics.

The active media that generate complex waves are simple and the generation mechanism involves fundamental physical and chemical effects of physics. A few genes is sufficient to correctly encode that mechanism. Therefore, it is natural to expect that such media could appear as a result of biological evolution. One can imagine, for example, such a model (see Fig. 2). Consider a cell colony that must adapt to a new environment and develops products necessary for survival. It is clear that a colony, where it is possible to transfer complex adaptive innovations from one cell to another, has a clear selective advantage. This transmission can be done by means of the waves, studied in this paper, and these waves can not only transmit simple information, but they can also transfer complex behavior (which can be described by an attractor or a Turing machine, or a neural network with associative memory), similarly to human society.

Acknowledgments.— S. V. and J. R. are supported by the grant of National Institutes of Health (NIH) 2R01 OD010936. IS gratefully acknowledges support from the Division Of Physics at the U.S. National Science Foundation (NSF) through Grant PHY-2102906.

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