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LETTER

Self-organized pattern formation and noise-induced control based on particle computations

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Abstract. We propose a new non-equilibrium model for spatial pattern formation based on local information transfer. Unlike most standard models of pattern formation it is not based on the Turing instability or initially laid down morphogen gradients. Information is transmitted through the system via particle-like excitations whose collective dynamics results in pattern formation and control. Here, a simple problem of domain formation is addressed by means of this model in an implementation as stochastic cellular automata, and then generalized to a system of coupled dynamical networks. One observes stable pattern formation, even in the presence of noise and cell flow. Noise contributes through the production of quasi-particles to *de novo* pattern formation as well as to robust control of the domain boundary position. Pattern proportions are scale independent as regards system size. The dynamics of pattern formation is stable over large parameter ranges, with a discontinuity at vanishing noise and a second-order phase transition at increased cell flow.

Keywords: cellular automata, molecular networks (theory), pattern formation (theory), network dynamics

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A remarkable characteristic of the development of multicellular organisms is its extreme error tolerance and robustness [1]. A key mechanism for robust structure formation during development is the self-organization of spatiotemporal patterns of gene activity [2]. While detailed dynamical models of all gene regulation processes involved are not within close reach (due to a lack of experimental details), phenomenological models of developmental processes have been studied for quite a while. For example, in several organisms position-dependent gene activation is regulated by initially laid down morphogen gradients [3]; however, the extreme precision of gene expression domains points to additional, complex 'post-processing' in gene regulatory networks, establishing the observed high signal-to-noise ratio [4]. In other organisms, externally imposed gradients are excluded by the developmental dynamics itself. In such cases, one widely applied standard model is diffusion-driven pattern formation exploiting the Turing instability [5]. This principle has been applied to modelling biological organisms [6]–[8] and is able to account for a number of observed features of developmental processes, e.g., in the fresh water polyp *Hydra* [9]. However, several unresolved problems persist. For example, morphogen chemicals postulated by the model, as well as the necessary long range lateral inhibition, still have not been unambiguously identified. Further, parameter fine-tuning is needed, including a non-trivial hierarchy (separation by orders of magnitude) of diffusion constants [10]. Most importantly, several experiments are not explained by diffusion models: the reorganization of the body pattern from a fully random cell assembly [11] and the extreme sharpness of expression boundaries [12, 4], including position regulation of scale-invariant proportions. Indeed, recent experiments show that a large number of regulatory genes are involved in pattern formation and cell differentiation [13], hinting at more complex underlying information processing [14]. Also recent theoretical studies [15, 16] suggest that pattern self-organization in multi-cellular organisms is based on robust regulatory logic rather than on fine-tuning of specific biophysical parameters. The aim of this paper is to formulate and analyse a very general model for pattern formation based on local information transfer and regulatory interactions, and to study its dynamics with respect to some basic phenomenological observations made in developmental biology. In particular, it is demonstrated that this system performs *de novo* pattern formation, independently of initial conditions, and is stable in the presence of noise and cell flow.

Position-dependent gene activation is a frequently observed mechanism in animal development. One example is provided by the fresh water polyp *Hydra*, which has three distinct body regions—a head with mouth and tentacles, a body column and a foot region. The positions of these regions are accurately regulated along the body axis. In addition, new cells continuously move from the central body region along the body axis towards the top and bottom and, along the way, differentiate into the respective cell types according to their position on the head–foot axis. This cell flow requires considerable robustness of the regulatory processes. The two remarkable features of this regulation that we focus on are the scale-independent position regulation and the 'reboot'-like *de novo* pattern formation from random initial conditions. We do not intend to develop a detailed regulatory model of these processes, but rather investigate whether local information transfer could lead to stable, global activity patterns that are robust even against large scale perturbations, for example, cell movements. Indeed, a growing experimental record [17] and theoretical models indicate the significance of local signal processing in developing embryos, e.g. processing of mechanical stimuli in the regulation of tissue growth [18].

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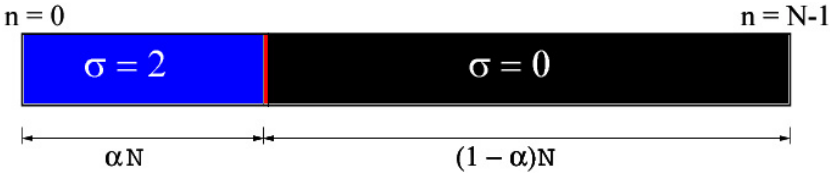

Figure 1. The morphogenetic problem of boundary formation and scale-independent proportion regulation of adjacent domains considered here. The target pattern consists of one domain with a fraction of αN cells ($0 < \alpha < 1$) in state $\sigma_i = 2$, a boundary state $\sigma_i = 1$ at the position αN and $\sigma_i = 0$ for the remaining domain.

Let us consider the simplified problem of regulating one domain, say the foot region versus the rest of the body. We consider this as a one-dimensional problem as suggested, for example, by the well-defined head–foot axis in *Hydra*. Figure 1 formulates the target pattern of this problem.

We base our approach on local information transfer between neighbouring cells, combined with information processing of a cell-internal gene network. This is motivated by the observed mechanism of direct contact induction in animals [20, 2, 16], as well as by increasing evidence of the role of gene regulation circuits in morphogenesis.

A simple setting for implementing pattern formation and local communication is provided by cellular automata (CA). Whereas their earlier use in developmental models, for example, Lindenmayer systems [19], remained obscure as regards specific biological interpretations, our model can easily be generalized to biologically more realistic settings, e.g., coupled regulatory networks.

Consider a one-dimensional stochastic cellular automaton [21] with parallel update. N cells are arranged on a one-dimensional grid, and each cell is labelled uniquely with an index $i \in \{0, 1, \ldots, N-1\}$. Each cell can take n possible states $\sigma_i \in \Sigma := \{0, 1, \ldots, n\}$. The state $\sigma_i(t+1)$ of cell i is a function $f : \Sigma^3 \mapsto \Sigma$ of its own state $\sigma_i(t)$ and of its nearest neighbour's states $\sigma_{i-1}(t)$ and $\sigma_{i+1}(t)$ at time t. Furthermore, we consider stochastic update errors with probability p; hence the dynamics is given by

$$\sigma_i(t+1) = \begin{cases} \sigma_i^f & \text{with probability } 1-p \\ \sigma_\varepsilon \in \Sigma \setminus \{\sigma_i^f\} & \text{with probability } p \end{cases} \tag{1}$$

where $\sigma_i^f := f(\sigma_{i-1}(t), \sigma_i(t), \sigma_{i+1}(t))$ and σ_ε are taken at random from $\Sigma \setminus \{\sigma_i^f\}$. At the system boundaries we set $\sigma_{-1} = \sigma_N = \text{constant} = 0$. Other choices, e.g., asymmetric boundaries with cell update depending only on the inner neighbour cell, lead to similar results.

In the following, let us study the morphogenetic problem formulated above for $\alpha = 0.3$. We searched for possible solutions in rule space with the aid of genetic algorithms (for details see [22]). The rule table of the best solution found is shown in table 1. Figure 2 demonstrates the resulting *de novo pattern formation* for different initial configurations.

Let us first analyse the dynamics of the system with respect to the rate $r_e = p\,N$ of stochastic update errors as the *control parameter* of the pattern formation. Depending on r_e, three different dynamical regimes are found.

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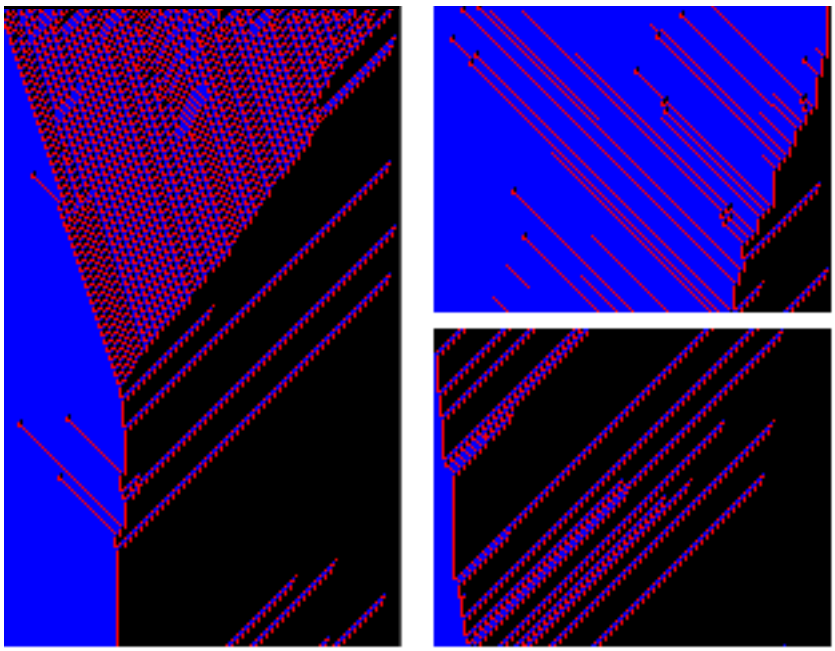

Figure 2. Left panel: cellular automata dynamics starting from a random initial configuration (error rate $r_e = 0.1$). Right panels: pattern formation starting from homogeneous initial configurations. Stochastic errors produce two different kinds of quasi-particle excitations, that lead to self-organization of the target pattern.

Table 1. Rule table of the three-state cellular automaton. First column: rule table index R. Second column: input states $\vec{\sigma} = (\sigma_{i-1}, \sigma_i, \sigma_{i+1})$ at time $t-1$. Third column: corresponding output states at time t.

R	$\vec{\sigma}(t-1)$	$\sigma_i(t)$	R	$\vec{\sigma}(t-1)$	$\sigma_i(t)$	R	$\vec{\sigma}(t-1)$	$\sigma_i(t)$
0	$(0,0,0)$	0	9	$(1,0,0)$	0	18	$(2,0,0)$	0
1	$(0,0,1)$	2	10	$(1,0,1)$	1	19	$(2,0,1)$	0
2	$(0,0,2)$	1	11	$(1,0,2)$	1	20	$(2,0,2)$	0
3	$(0,1,0)$	0	12	$(1,1,0)$	0	21	$(2,1,0)$	1
4	$(0,1,1)$	2	13	$(1,1,1)$	1	22	$(2,1,1)$	2
5	$(0,1,2)$	2	14	$(1,1,2)$	2	23	$(2,1,2)$	2
6	$(0,2,0)$	1	15	$(1,2,0)$	0	24	$(2,2,0)$	1
7	$(0,2,1)$	2	16	$(1,2,1)$	0	25	$(2,2,1)$	2
8	$(0,2,2)$	2	17	$(1,2,2)$	1	26	$(2,2,2)$	2

(1) $r_e \to 0$. Starting from a random initial configuration, the pattern self-organizes towards the target pattern within a finite number of updates (compare the left panel in figure 2). One observes proportion regulation with $\alpha_\infty = 0.281 \pm 0.001$ independently of N in the large system size limit [22]. Pattern formation is based on differential propagation of domain boundaries; hence it does not work for non-random (e.g. homogeneous) initial configurations in this limit.

(2) $0 < r_e < 1/2$. In this regime, pattern formation succeeds for arbitrary (even homogeneous) initial configurations (figure 2, right panels). Two different kinds of

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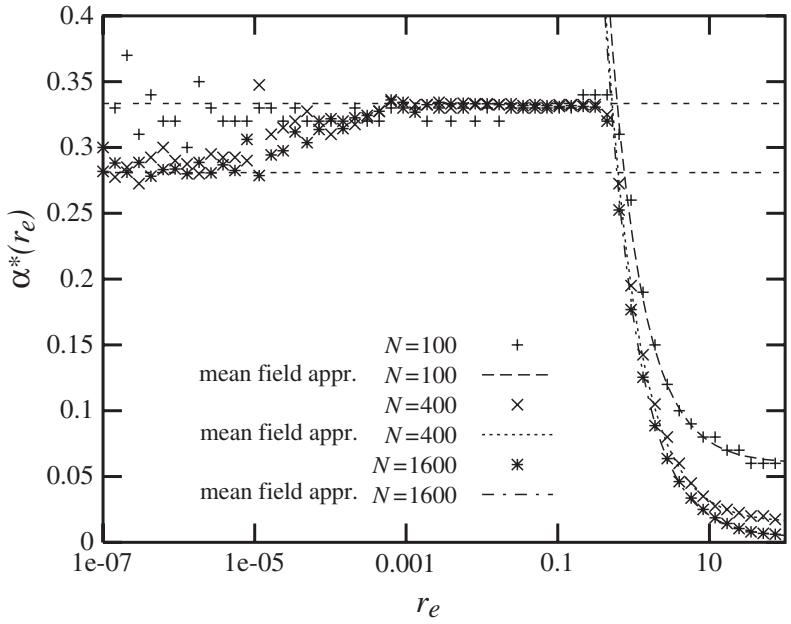

Figure 3. Average boundary position α^* as an order parameter in the presence of noise. Transitions are shown as a function of the error rate r_e. Numerics averaged over 200 initial conditions with 2×10^6 updates each. Dashed curves: mean field approximation given by equation (3). Horizontal dashed lines: unperturbed solution $\alpha^* = 0.281$ and solution under noise $\alpha^* = 1/3$.

quasi-particles [23] (i.e. soliton-like state perturbations moving through the homogeneous phases) are observed. In the following, these quasi-particles are called Γ and Δ. The Γ particle is started in the σ_2 phase by a stochastic error $\sigma_i = 2 \to \sigma_i \neq 2$ at some $i < \alpha N$ and moves to the right. On reaching the domain boundary, the particle is destroyed, and the boundary is reestablished two cells to the left of its original position. The Δ particle is started in the σ_0 phase by stochastic errors $\sigma_i = 0 \to \sigma_i \neq 0$ at some $i > \alpha N$ and moves to the left. Interaction with the interface boundary readjusts it to one cell to the right.

Thus we find that the average position α^* of the boundary is given by the rate equation

$$2\alpha^* r_e = (1 - \alpha^*) r_e, \tag{2}$$

i.e. $\alpha^* = 1/3$. Interestingly, for not too high error rates r_e, α^* is independent of r_e and thus of p. Obviously, proportion regulation independent of N is also preserved; this can also be concluded from the overlap of the numerically obtained curves for different system sizes in figure 3. Equation (2) implies that the system undergoes a discontinuity, similar to a first-order phase transition, with respect to α^* at $p = 0$. For finite system sizes and finite observation times, however, the transition from $\alpha = 0.281$ to $\alpha = 1/3$ is observed at finite values of r_e (figure 3). Fluctuations of α around α^* are Gaussian distributed with variance vanishing $\sim N^{-1}$ [22].

(3) $r_e > 1/2$. In this regime, the solution $\alpha^* = 1/3$ becomes unstable due to particle interference. The interaction of a Γ particle with the boundary needs only one update time step, whereas the boundary readjustment following a Δ particle interaction takes three update time steps. Therefore, the term on the right-hand side of equation (2), the flow

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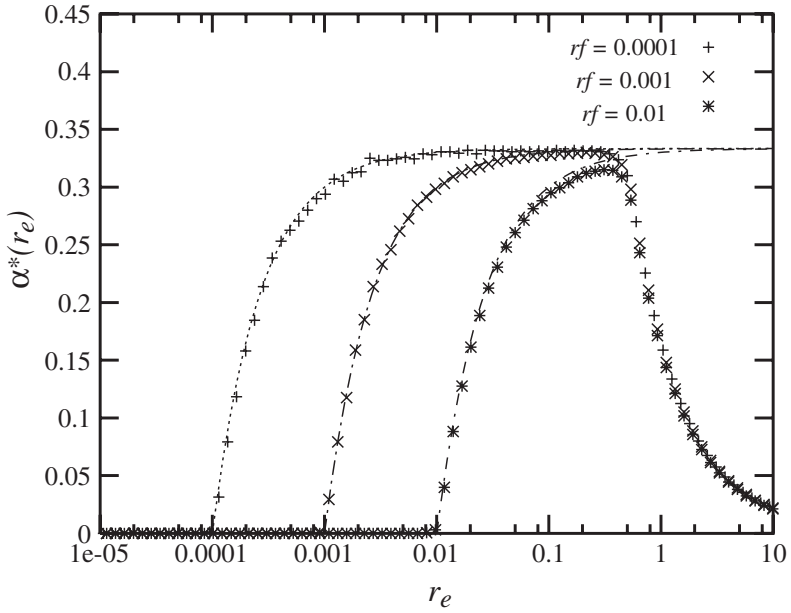

Figure 4. Average boundary position α^* as a function of error rate r_e for different cell flow rates r_f. Dashed curves: corresponding solutions of equation (4). Note that a minimum error rate is necessary to regulate the boundary in the presence of cell flow.

rate of Δ particles at the boundary, will saturate at 1/3 for large r_e, leading to $2\alpha^* r_e = 1/3$ with the solution $\alpha^* = (1/6)\, r_e^{-1} + \Theta(N)$. Hence, there is a crossover from the solution $\alpha^* = 1/3$ to another solution vanishing with r_e^{-1} around $r_e = 1/2$ (figure 3). The finite size scaling term $\Theta(N)$ can be estimated to vanish $\sim N^{-1}$ from statistical considerations [22].

In a biological organism, a pattern has to be robust not only with respect to dynamical noise, but also with respect to 'mechanical' perturbations. In *Hydra*, for example, there is a steady flow of cells directed towards the animal's head and foot, due to continued proliferation of stem cells. The stationary pattern of gene activity is maintained in spite of the cell flow. Let us now study the robustness of the model with respect to this type of perturbation. Consider a constant cell flow with rate r_f directed towards the left system boundary. In equation (2), we now get an additional drift term r_f on the left-hand side: $2\alpha^* r_e + r_f = (1 - \alpha^*) r_e$, with the solution

$$\alpha^* = \begin{cases} \dfrac{1}{3}\left(1 - \dfrac{r_f}{r_e}\right) & \text{if } r_e \geq r_f \quad \text{and} \quad r_e \leq 1/2 \\ 0 & \text{if } r_e < r_f \end{cases} \tag{3}$$

with α^* exhibiting a second-order phase transition at the critical value $r_e^{\text{crit}} = r_f$. Below r_e^{crit}, the domain size α^* vanishes, and above r_e^{crit} it grows until it reaches the value $\alpha^*_{\text{max}} = 1/3$ of the system without cell flow. The second-order phase transition at r_e^{crit} bears some similarity with error catastrophes in models of viral evolution [24]. Figure 4 compares the numerical results with the mean field approximation of equation (4). In numerical simulations, cell flow was realized by application of the translation operator $\Theta\, \sigma_i := \sigma_{i+1}$ to all cells with $0 \leq i < N - 1$ every r_f^{-1} time steps and leaving σ_{N-1}

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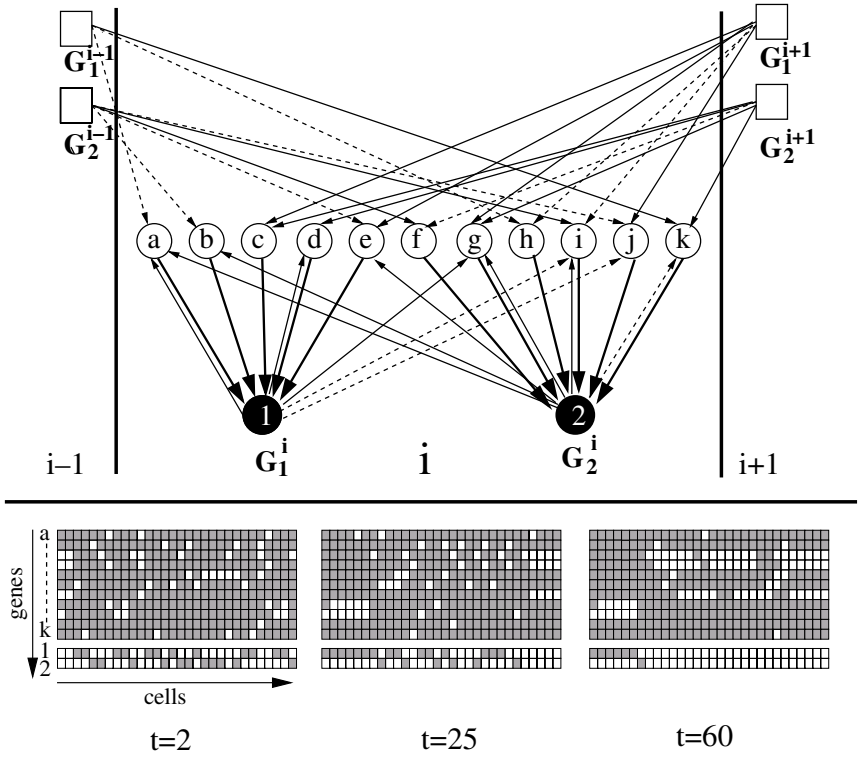

Figure 5. Upper panel: threshold network realization of the pattern formation system. Solid arrows denote links with $w_{ij} = +1$, dashed arrows with $w_{ij} = -1$. Inputs from the genes in the neighbour cells (squares) are processed by a layer of genes (circles with letter indices) with different thresholds h. Lower panel: snapshots of pattern formation at three different times t in a system of 30 cells; $r_e = 0.05$ per gene. The first rows refer to the states of genes $a - k$ in each cell (grey if active, white otherwise). Compare the final pattern of the genes G_1^i and G_2^i (two bottom rows) with the CA pattern in figure 2.

unchanged. Note that stochastic errors in dynamical updates for $r_e > r_f$ do indeed *stabilize* the global pattern against the mechanical stress of directed cell flow.

Finally, let us demonstrate that the proposed non-equilibrium model of pattern formation is not limited to the particular implementation as a CA, but can also be realized as a system of coupled, identical dynamical networks [25, 26], similar to communicating regulatory networks in multi-cellular organisms. Let us approximate the regulatory dynamics of a gene i as a sigmoidal function of the weighted sum of regulatory inputs $w_{ij} \in \{-1, 1\}$ that it receives from other genes, plus some threshold h_i [27, 28]. In the simplest case, its state $\sigma_i(t) \in \{-1, 1\}$ is given by

$$\sigma_i(t) = \mathrm{sgn}\left(\sum_j w_{ij}\sigma_j(t-1) + h_i\right), \tag{4}$$

where j runs over all regulatory inputs that i receives from other genes, either in the same cell or in the two neighbour cells. Figure 5 shows the structure of a threshold network constructed from the CA rule table, containing three levels of hierarchy and a number

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of feedback loops (for details, see [22]). A row of 30 cells each containing this network self-organizes to the target pattern of figure 1.

To summarize, we considered a problem of pattern formation motivated by animal morphogenesis in a non-traditional setting. Accurate regulation of position information, exhibiting proportional scaling with system size, and robust *de novo* pattern formation from random conditions have been obtained with a mechanism based on local information transfer rather than the Turing instability. Non-local information is transmitted through soliton-like quasi-particles instead of long range gradients, and fine-tuning of parameters is not needed. Noise contributes to the stability by generating quasi-particles that control the pattern. We observe considerable stability also under cell flow. A second-order phase transition is observed at increasing cell flow. The pattern formation mechanism studied here is very general and not limited to cellular automata. In particular, implementations as regulatory networks work as well, and are of comparable complexity to regulatory circuits observed in the cell [13].

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