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Lattice Gas Simulations of Replicating Domains ¹

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Abstract

We use the lattice gas cellular automaton (LGCA) developed in Ref. [1] to simulate a process of pattern-formation recently observed in reaction-diffusion systems [2]. We study the reaction mechanism introduced in Ref. [3], which is an extension of the Selkov model for glycolytic oscillations [4]. We are able to reproduce the self-replicating domains observed in Ref. [2]. We use the LGCA simulation to estimate the smallest length-scale on which this process can occur under conditions encountered in the cell. These estimates are similar to those obtained for Turing patterns in the same setting [5].

Research into the mechanisms of pattern formation has entered a phase of explosive growth despite our inability to state precisely what constitutes a pattern. Reaction-diffusion systems are arguably the richest spatially extended systems that form what are normally thought of as patterns. Such systems can potentially provide insight into the backbone of mechanisms used in living organisms [6]. They also generalize to more complex systems than

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simple chemical reactions, forming a special case of dynamics arising from an underlying “smart” statistical mechanics with active interactions. We call the general scheme operator gases. In this article we study systems with reacting and diffusing chemistry and focus on chemical pattern morphology.

Reaction-diffusion systems are usually studied in the continuum approximation, which breaks down at small scales due to system fluctuations. Recently, Hasslacher *et al.* [5] investigated the length scales at which Turing patterns are destroyed by implicit fluctuations. With lattice-gas techniques, they showed that such patterns are stable against internal fluctuations down to distance-scales of about a tenth micron. Lattice gas methods are invaluable for probing small scales, since they provide a bridge between the continuum approximation regime and full molecular dynamics simulations.

Using numerical simulations, one of us (JP) recently discovered a novel pattern-formation process in a reaction-diffusion system whereby coherent structures (or domains) create copies of themselves. These self-replicating domains correspond to extrema in the concentration fields and have since been observed in laboratory experiments in other chemical systems. [7] The model equations used in Ref. [2] are a variation on the Sel’kov model of the glycolytic oscillator, which is a rather drastic approximation to the dynamics of the glycolytic pathway. The immediate question is to what extent these processes apply to the biochemical pathways within actual cell cytoplasm. The first question concerns domain dimensions: can these structures fit inside the smallest eukaryotic cells? This leads us to explore the small distance robustness of self-replicating domains of varying geometries.

The simplest model system having replicating domains is described by two coupled reaction-diffusion equations

$$\frac{\partial u}{\partial t} - D_u \nabla^2 u = g(u, v), \quad (1)$$

$$\frac{\partial v}{\partial t} - D_v \nabla^2 v = f(u, v), \quad (2)$$

that have a unique homogeneous stationary solution $\{u^*, v^*\}$, $g(u^*, v^*) = 0 = f(u^*, v^*)$, where the diffusion coefficient of the inhibitor, u is somewhat larger than that of the activator, v . In Eqs. (1)-(2) u and v are the densities of the inhibitor and activator respectively and D_u and D_v are the corresponding diffusion coefficients, ∇^2 is the Laplacian operator over the spatial coordinate, $\mathbf{x}$, and g and f are nonlinear functions of u and v that encode the chemical reactions. The nullclines $g(u, v) = 0$ and $f(u, v) = 0$ of the system must divide the (u, v) -plane in a special way and the homogeneous solution has to be initially perturbed with a localized finite amplitude perturbation in order to trigger domain replication [8].

We show an example of this process in Figs. 1 and 2 for the Gray-Scott system ($g(u, v) \equiv A(1 - u) - uv^2$; $f(u, v) \equiv uv^2 - Bv$). In Fig. 1 we have plotted the nullclines of the system for $A = 0.02$ and $B = 0.079$, showing the different regions in which the plane (u, v) is divided. It is clear that the system possesses a unique linearly stable fixed point at $u^* = 1$, $v^* = 0$.

Figure 1: Nullclines $g(u, v) = 0$ and $f(u, v) = 0$ for the Gray-Scott model with $A = 0.02$ and $B = 0.079$. The nullclines divide the quadrant $u > 0$, $v > 0$ in three regions: I, where $f < 0$ and $g > 0$, II, where $f < 0$ and $g < 0$ and III, where $f > 0$ and $g < 0$.

Figure 2: Density distribution $v(x, t)$ at different times, t , for the Gray-Scott model with $A = 0.02$, $B = 0.079$ and initial condition $u(x, 0) = 0.5$, $v(x, 0) = 0.25$ for $-5 \leq x \leq 5$ and $u = 1$, $v = 0$ everywhere else. The simulation was done with periodic boundary conditions.

Fig. 2 shows the time evolution of the activator, $v(x, t)$, for a simulation with the same parameters as Fig. 1 and no-flux boundary conditions. The system has only one spatial dimension. The initial condition is such that $v = 0$ and $u = 1$ everywhere with the exception of the interval $[-5, 5]$, where $u = 0.5$ and $v = 0.25$. In the (u, v) -plane, this finite and local perturbation corresponds to the point that we indicate with an asterisk in Fig. 1. This point lies above both nullclines, where $g < 0$ and $f < 0$. For this particular case, the perturbation initially spreads both right and left while two “peaks” in v develop at the fronts. After a certain transient, it splits into two separate

peaks (domains in two dimensions) of high v traveling in opposite directions towards regions with $u = 1$ and $v = 0$ (e.g., essentially to the stable homogeneous solution). The density u evolves similarly, except that regions of high v correspond to regions of low u ($u < 1$) and vice versa. When the peak separation reaches a critical value, each peak begins to spread and shortly splits into two new peaks traveling in opposite directions. The domain-replication process repeats several times till the entire interval is filled with a periodic distribution of peaks or domains. This distribution corresponds to a stationary non-homogeneous solution of the system of equations [8]. In two spatial dimensions the evolution has the same morphology, with the sole difference that, depending on the system size and the initial condition, the system can either settle into a stationary and spatially periodic solution or domain division continues in a chaotic fashion.

The Selkov model, as extended in Ref. [3]:

is very similar to the Gray-Scott model. If the concentrations of the species A and B are assumed fixed by external flows, the system evolution is described by Eqs. (1)-(2) with u the density of the substrate (S), v the density of the product (P) and g and f determined by:

$$g(u, v) = k_1 \rho_a - k_{-1}u - k_2 uv^2 + k_{-2}v^3, \quad (4)$$

$$f(u, v) = k_{-3} \rho_b - k_3 v + k_2 uv^2 - k_{-2}v^3. \quad (5)$$

In this model the substrate, S , is the inhibitor and the product, P , is the activator. By an appropriate parameter choice, the corresponding nullclines, $g(u, v) = 0$ and $f(u, v) = 0$ separate the (u, v) -plane into regions which are qualitatively the same as those of the Gray-Scott model. Even if this nullcline structure is merely an indication that domain-replication *might* occur, we did find a parameter set for which this process occurs in the Selkov model (see Fig. 3).

The reaction mechanism described by (3) is based on a model derived by Selkov [4] to explain qualitative features of single-frequency oscillations in glycolysis. In this model the substrate, S , is ATP and the product, P , is ADP, which are known to inhibit and activate, respectively, different phosphofructokinases [4]. Selkov found that this simple model has dynamics similar to that of the fructokinase reaction. As argued in Ref. [5], this simple mechanism provides a “skeletal” model of what actually occurs in the cell cytoplasm. So, we expect it to reproduce, at least qualitatively, the main features of the physical system. The crucial question now is one of scale: whether the Selkov model generates self-replicating domains on distance scales compatible with measured cell structure.

Accordingly, we implemented the LGCA method used in [1, 9] to simulate the evolution of species S and P in two spatial dimensions. The chemical kinetics are given by the Selkov model (3) for fixed concentrations of A and B . We used an hexagonal lattice with unit lattice spacing, 256×256 nodes and six velocity vectors of norm one at each node. We followed the evolution of S and P on this lattice imposing the exclusion principle for each species separately (i.e., at most one particle of a given species was allowed to reside at each node with each velocity direction).

The LGCA used has the usual steps [1, 9]: (i) free propagation and permutation of velocities for each species separately, (ii) chemical transformations that are invoked at each node independently in a probabilistic way. The step (i) models the elastic collisions between particles of species S and P with particles of a solvent whose evolution is not followed by the LGCA. The density of the solvent is much larger than that of S and P . This is the reason why we neglect elastic collisions of the S and P particles among themselves. The step (ii) encodes the chemical interactions among the particles that arrive at each node and with the particles of the background “bath” of species A and B . The occurrence or not of a particular reaction is controlled by a probability matrix which is a function both of the number of particles

at the node and on the reaction rates. This probability matrix is chosen so that, for very low probabilities, the densities u and v evolve according to Eqs. (1)-(2) with g and f given by Eqs. (4)-(5) [9]. The random walk that the step (i) induces is responsible for the diffusion term (see also [10]). To insure the desired ratio of diffusion coefficients ($D_u/D_v = 8$ in this case), we apply step (i) eight times to the S particles for each operation on the P particles.

Figure 3: Snapshots of the density distribution of species S for the Selkov model obtained with a lattice gas cellular automaton.

Fig. 3 displays a simulation we ran with this model for $D_u/D_v = 8$, $k_1\rho_a = 0.005$, $k_{-1} = 0.001$, $k_2 = k_{-2} = 0.04$, $k_{-3}\rho_b = 5 \cdot 10^{-6}$, and $k_3 = 0.00395$ and periodic boundary conditions. This figure plots the density distribution of species S at times $t = 2,000$, $t = 10,000$, $t = 14,000$ and $t = 20,000$. The color code is black corresponding to low values of density and gray to

high. In this figure one sees the process of domain replication. At time $t = 2,000$, a spot of low S density has emerged in the middle of a region of higher concentration, where u is approximately equal to the fixed point value $u^* = 5.00$. The spot stretches along some direction, and, after a while, splits into two new low density spots. The two spots are evident at $t = 20,000$. A similar process occurs for the P species, but the spots correspond to regions of high P concentration in a background of lower density where v is close to the fixed point value $v^* = 1.27 \cdot 10^{-3}$.

The presence of noise is clearly seen in Fig. 3. This means that fluctuations at the level of a lattice gas simulation do not destroy the process of domain-replication. We now address the main question of this paper: what actual spatial and time scales can this simulation describe assuming conditions encountered in the cell? For this purpose, we map the quantities involved in the simulation into the corresponding ones in the cell. Recall that in the original Selkov model the substrate is ATP and the product is ADP. Since we can always rescale densities in Eqs. (1) and (2) without altering their structure, we assume that u is proportional to the density of ATP and v is proportional to the density of ADP.

In the simulation, the natural space-time units are the lattice time step and the lattice spacing. Elastic collisions happen with probability one at each time step and the distance that the particles travel between successive collisions is equal to the lattice spacing. Accordingly, the smallest length that this spacing can correspond to is the mean free path between elastic collisions. We can assume that in the cell particles diffuse in a water background. Knowing the density of water is $3 \cdot 10^{22} \text{ cm}^{-3}$ and assuming a cross section of size $\pi \cdot 10^{-16} \text{ cm}^2$, one estimates a free path length of order $10 \text{ \AA}$. If we assume that the lattice gas simulation generates realistic evolution down to this length scale and that the lattice spacing corresponds to this mean free path, the characteristic size of the spots are fixed on the order of $0.1 \text{ }\mu\text{m}$.

In a typical cell, the density of ATP is of the order of $10^{18} - 10^{19} \text{ cm}^{-3}$.

This implies that the total number of ATP molecules in a spot is between 10^3 and 10^4 , a reasonable value from the viewpoint of mesoscopic descriptions. In the simulation both v and u are of order one inside the spot. So, when going back to physical units, one finds the constant of proportionality between these densities and that of ATP to lie between 10^2 and 10^3 . On the other hand, if we assume that u is the ATP density, the lattice spacing must be of order $100 \text{ \AA}$. In this case, the size of the spot would be of order $1 \mu\text{m}$ and there would be between 10^6 and 10^7 particles in the spot. For estimating time scales, if we assume that the diffusion coefficients are order $10^{-5} \text{ cm}^2/\text{s}$, one time step of the simulation is order 10^{-7} - 10^{-9} sec and, the characteristic time of the reactions, 10^{-6} sec - 10^{-3} sec . These estimates for characteristic space and time scales are similar to those obtained for Turing patterns in the cell [5]. Thus, the comments in Ref. [5] apply also in this case.

DISCUSSION

All self-reproducing eukaryotic cells must segregate their chromatids into two equal sets of chromosomes prior to cell division. This process is called mitosis. The mitotic process begins by forming a polar structure called the mitotic spindle, made of microtubule fibers radiating outwards from two organizing centers – the centrosomes, located in the nucleus at opposite poles. Centrosomes consist of two small microtubule structures – the centrioles, enveloped in pericentriolar material. As mitosis proceeds, the nuclear membrane dissolves and releases the replicated chromosomes. Microtubules are nucleated at the centrosomes and the kinetochores, which is the region where the replicated chromosomes are joined. Microtubules radiate out from these organizing centers. We comment that the role of the *centrioles* is not known. The microtubules nucleate from the pericentriolar material alone and *not* from the centrioles. The standard scenario is that tubules exert forces on the chromosomes causing them to migrate to the spindle equator. After aligning

on the equator, one observes that they separate with one copy of each of the replicated chromosomes migrating to each centrosome. The stage is then set for cell division with one set of each daughter chromosome going to each of the two new cells.

The forces required for the separation of the chromosomes and their subsequent migration are created by the ATPase proteins dynein and kinesin. The precise details of the action of these proteins remains controversial, but it is known that they use the energy provided by the breakdown of ATP into ADP in order to generate the necessary forces. The growth of microtubules primarily involves $\text{GTP} \rightarrow \text{GDP}$ hydrolysis although it is inhibited by high ATP concentrations [11]. Centrosome constituents are not yet known but glycolytic proteins have been isolated from the pericentriolar envelope. Thus, it seems plausible to us that self-sustaining chemical gradients in the nucleotide-phosphate concentrations could provide the positional information required to construct the spindle. Moreover, the centrosomes replicate just prior to cell division. It is considered unlikely that the centrosomes themselves carry any genetic information. There is no DNA in these organelles although several studies have confirmed that they do contain RNA [12]. Furthermore, there are known organisms in which centrosomes arise de novo. The process of centrosome replication is not understood.

One approach is to apply Occam's Razor and hypothesize that all these processes, including both centrosome replication and the de novo production of centrosomes, are driven by the spatio-temporal dynamics of the $\text{ATP} \rightarrow \text{ADP}$ conversion process. Of course all this requires much more work and refinement of models, especially models of growth of structures on underlying ATP emergent structures. A typical linear dimension for a eukaryotic cell is on the order of 5-50 microns. It is obvious that the self-sustaining chemical gradients discussed above could easily fit within the smallest eukaryotic cell. Of course the chemical length scale, given roughly by $\sqrt{D\tau_c}$ where D is a typical diffusion coefficient and τ_c is a chemical time scale, must be smaller

that the cell size. The actual cell is a complex and active gel with tremendous noise fluctuations due to complex chemistry. It is very reasonable to assume that sufficient finite or "hard" perturbations are a common event in cell cytoplasm, and so domain replication is also common. It is hard to understand why domain replication - this very special form of pattern formation in ATP space- would not be important to the ultimate morphology of ATP consuming structures.

The analogy is that of a photographic plate being exposed to light. One cannot see the image with the eye until the plate is developed, but the information is already encoded in the plate before development. Similarly with concentration space. Without the appropriate probes, one cannot see structures in ATP concentration within the cell. But all of the ATP engines, and especially the mitotic process, act as biological probes of ATP concentration space. The microtubule patterns that we see must reflect the underlying coherent structures evolved in concentration space, modulo some deformation coming from their own intrinsic dynamics. It would be very interesting if one could visualize ATP concentration within the cell using new bioimaging tools. Until then, large computers and lattice gas models can serve as digital laboratories for all of the ATP intensive processes at the cellular and sub-cellular scale.

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