Weakly coupled map lattice models for multicellular patterning and collective normalization of abnormal single-cell states

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Abstract

We present a weakly coupled map lattice model for patterning that explores the effects exerted by weakening the local dynamic rules on model biological and artificial networks composed of two-state building blocks (cells). To this end, we use two cellular automata models based on: (i) a smooth majority rule (model I) and (ii) a set of rules similar to those of Conway’s Game of Life (model II). The normal and abnormal cell states evolve according with local rules that are modulated by a parameter $\kappa$. This parameter quantifies the effective weakening of the prescribed rules due to the limited coupling of each cell to its neighborhood and can be experimentally controlled by appropriate external agents. The emergent spatio-temporal maps of single-cell states should be of significance for positional information processes as well as for intercellular communication in tumorigenesis where the collective normalization of abnormal single-cell states by a predominantly normal neighborhood may be crucial.

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I. INTRODUCTION

Biological and artificial networks composed of micro and nanoscale two-state building blocks (cells) are bound to operate under significant physical limitations because of individual diversity and thermal noise effects. These effects may weaken the local dynamic rules of the network and result in a distribution of individual cell states instead of the two generic Boolean states 0 and 1. We present two-dimensional, weakly coupled map lattice models based on cellular automata dynamics [1] to explore the consequences of this question, with emphasis on biophysical multicellular ensembles. In model I, the central cell state is determined by applying a smooth majority rule to the individual states of the multicellular neighborhood. In model II, the dynamical rules are similar to those of Conway’s Game of Life [2–6]. The above rules may favor the normal state (0) but permit also the existence of cells in the abnormal state (1). The predominance of state 0 over state 1 that occurs in the ensemble under certain conditions is named normalization.

For the two biologically-relevant models, the individual cell states evolve according with local dynamical rules modulated by a parameter $\kappa$ that quantifies the weakening of these rules due to the limited coupling of each individual cell to its local neighborhood. In general, low values of $\kappa$ tend to enforce the local rules over the ensemble while high values of $\kappa$ may be associated with limited intercellular communication. We note that $\kappa$ should have a wide physical significance. In the case of artificial networks, $\kappa$ could be related to the degree of heterogeneity characteristic of most nanostructures. For instance, nanowire field-effect transistors and nanoparticle-based single electron transistors do not show identical responses at the individual level because of significant physical variability and this experimental fact may result in weak collective performances [7]. Also, $\kappa$ can indirectly account for the decreased cooperativity observed in molecular monolayers because of thermal noise effects [8]. In these cases, static (individual variability) and dynamic (finite temperature) noise limitations eventually result in weak local rules for the system dynamics. Limited coupling may also be significant in clusters of protein ion channels with individually different threshold responses [9] and interacting cells forming spatio-temporal patterns [10], as considered here. These multicellular patterns are crucial to positional information processes such as embryogenesis and tumorigenesis [11, 12].

Abnormal tumour cells form pre-cancerous lesions that can rest dormant for a long time
because they are located in unsuitable sites or controlled by intercellular interactions with a
majority of normal cells [13, 14]. In this context, exploring the consequences of the interac-
tion between the abnormal tumor cells (state 1) and their neighboring normal cells (state 0)
should be of interest to new theoretical approaches [15–18]. In the tissue organization field
theory (TOFT) for instance, the disruption of local intercellular communication is associated
with the appearance of abnormal cells and carcinogenesis [16–18]. These facts suggest the
possibility of acting on the intercellular coupling by means of appropriate external agents.
However, strategies designed to modify multicellular ensembles are difficult to implement
because small changes at the local level may result in unexpected global outcomes. Indeed,
the emergent large-scale patterns cannot be easily anticipated from single-cell considera-
tions [10, 12]. This problem is crucial in carcinogenesis where small clusters of cells may establish
local interactions that escape from the morphogenetic control based on intercellular coupling
[15, 16, 18].

Modeling the interplay between the local rules which govern intercellular coupling and
the emergent multicellular patterning is of current interest. We consider here two weakly
coupled map lattice models for the spatio-temporal patterning and normalization of model
cell ensembles. In particular, we describe the range of single-cell states between 0 and 1
that may originate from the weakening of the intercellular local rules and show the different
dynamical consequences of weak coupling on multicellular patterning.

II. BIOPHYSICAL MODELS

The states of biological cells can be defined in terms of dynamical variables such as the
concentration \(c\) of a signaling molecule in the cell [11, 19] and the membrane potential \(V\)
[10, 20]. In general, a variable \(x\) that characterizes the cell state can be mapped into a dimen-
sionless variable \(u\) varying in the range \([0, 1]\) by the transformation \(u = (x - x_0)/(x_1 - x_0)\),
where \(x_0\) and \(x_1\) are, respectively, the values of \(x\) in some reference normal (0) and abnormal
(1) states. The membrane potential \(V\), defined as the electric potential difference between
the cell cytoplasm and the extracellular microenvironment under zero current conditions,
constitutes a typical example of dynamical variable because depolarized potentials are char-
acteristic of abnormal cells [20, 23]. The corresponding dimensionless variable would be
\(u = (V - V_0)/(V_1 - V_0)\) where \(V < 0\) is the cell membrane potential, with \(V_0\) and \(V_1\) the
normal (polarized) and abnormal (depolarized) potentials ($V_0 \leq V \leq V_1$). The variable $u$ thus defined varies continuously, as $V$ does, between 0 and 1 and characterizes the cell state. Bioelectrical signals can promote tissue normalization [10, 20]. The biochemical signals that couple individual cells to their local multicellular environment may contribute to tissue normalization, which corresponds to a majority of cells in the normal state 0. In this section we describe two models to describe the dynamics of cells undergoing transitions between the normal (0) and abnormal (1) states based on local majority rules. The particular definition of the cell states and the local rules should be closely related in practical applications of the two models.

**Lattice and states**

We consider a two-dimensional square lattice with Moore neighborhoods of $3 \times 3$ cells. The positions of the cells within a neighborhood of the lattice site $(i, j)$ are specified by the generic pair $(i + k, j + m)$ where $k$ and $m$ can take the values $-1, 0, 1$. At time $t$, the state of the cell $(i, j)$ is given by the continuous dimensionless dynamical variable $u_{i,j}^t \in [0, 1]$. All cell states in the lattice are synchronously updated when the spatial map of cell states in the multicellular network evolves with time.

**Model I**

This model constitutes a *smooth majority* coupled map lattice. The coupling between cells is modulated by a continuous parameter $\kappa \in (0, \infty)$:

- **In the limit $\kappa \to 0$ (complete normalization) the central cell remains abnormal on to the next time step if and only if there are no less than 8 other abnormal cells in the neighborhood. Otherwise, it becomes normal.** This limiting case states that the only possibility for a cell to remain abnormal is that all cells in the multicellular ensemble are abnormal, for, otherwise, normalization of the whole ensemble occurs after a certain transient.

- **In the limit $\kappa \to \infty$ (loss of normalization) any normal cell with at least one abnormal cell in its neighborhood becomes abnormal.**
cell in the neighborhood becomes also abnormal at the next time step. Otherwise it remains normal on to the next time step. This limiting case corresponds to the total loss of normalization, the situation opposite to the above case $\kappa \to 0$.

At intermediate values of $\kappa$, normal and abnormal cells should coexist in the ensemble. The above cases are then the cellular automaton limits of the coupled map lattice.

According with these rules, the following map governs the spatio-temporal evolution of the state $u_{i,j}^{t}$ of cell $(i, j)$:

$$u_{i,j}^{t+1} = \frac{B_{\kappa} \left( 9 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}, \frac{1}{2} \right) B_{1/\kappa} \left( 5 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}, \frac{9}{2} \right)}{B_{\kappa} \left( 0, \frac{1}{2} \right) B_{1/\kappa} \left( 0, \frac{9}{2} \right)}$$  \hspace{1cm} (1)

where the $B_{\kappa}$-function of real variables $x$ and $y$ is [1]:

$$B_{\kappa}(x, y) \equiv \frac{1}{2} \left( \tanh \left( \frac{x + y}{\kappa} \right) - \tanh \left( \frac{x - y}{\kappa} \right) \right)$$  \hspace{1cm} (2)

Note that $\kappa$ is the only free parameter of the model and modulates the local rules that couple the multicellular ensemble. For all finite values of the real variables $x$ and $y$, the $B_{\kappa}$-function satisfies the limits [1]:

$$\lim_{\kappa \to \infty} B_{\kappa}(x, y) = 0 \quad \lim_{\kappa \to \infty} \frac{B_{\kappa}(x, y)}{B_{\kappa}(0, y)} = 1$$  \hspace{1cm} (3)

$$\lim_{\kappa \to 0} B_{\kappa}(x, y) = B(x, y) = \frac{1}{2} \left( \frac{x + y}{|x + y|} - \frac{x - y}{|x - y|} \right) = \begin{cases} \text{sgn } y & \text{if } |x| < |y| \\ \text{sgn } y & \text{if } |x| = |y| \\ 0 & \text{if } |x| > |y| \end{cases}$$  \hspace{1cm} (4)

where we have introduced the $B$-function, $B(x, y)$, which allows a universal map for cellular automata to be formulated [21].

In the limit $\kappa \to 0$, Eq. (1) becomes the Boolean cellular automaton

$$u_{i,j}^{t+1} = B \left( 9 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}, \frac{1}{2} \right) = \begin{cases} 1 & \text{if } \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t} = 9 \\ 0 & \text{otherwise} \end{cases}$$  \hspace{1cm} (5)

for initial conditions for which $u_{i,j}^{0} = 0$ or 1. Therefore, a cell that is abnormal at time $t$ is also abnormal at time $t + 1$ if and only if its surrounded by other 8 abnormal cells. Otherwise, the cell is normalized at $t + 1$. 
In the limit $\kappa \to \infty$, Eq. (1) becomes

$$u_{i,j}^{t+1} = B \left( 5 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^t, \frac{9}{2} \right) = \begin{cases} 0 & \text{if } \sum_{k,m=-1}^{1} u_{i+k,j+m}^t = 0 \\ 1 & \text{otherwise} \end{cases}$$

which corresponds to another Boolean cellular automaton for all initial conditions $u_{i,j}^0$ with values either 0 or 1. Symmetry considerations [25, 26] show that Eq. (6) is the global complement of Eq. (5) so that the respective evolutions of these equations are the ‘negative’ of each other if one exchanges normal and abnormal cells.

Fig. 1 shows $u_{i,j}^{t+1}$ in Eq. (1) as a function of the neighborhood sum value $n_{i,j}^t = \sum_{k,m=-1}^{1} u_{i+k,j+m}^t$ for different values of $\kappa$. Note that normalization is enforced in the limit of low values of $\kappa$ (Fig. 1 left) because an abnormal cell is viable only if all cells in the neighborhood are abnormal. On the contrary, normalization is discouraged in the limit of high values of $\kappa$ (Fig. 1 right) because an abnormal cell is now viable when there is just one abnormal cell in the neighborhood.

**Model II**

In the limit $\kappa \to 0$, the rules of this model are similar to Conway’s Game of Life [2–4] for all initial conditions $u_{i,j}^0 = 0$ or 1:

- **1.** Any abnormal cell with fewer than two abnormal neighbors becomes normal at the next time step. The rule establishes the normalizing effect of the local neighborhood when normal cells predominate.

- **2.** Any abnormal cell with two or three abnormal neighbors remains abnormal on to the next time step. The rule assumes that the normalization effect of the local neighborhood is lost when sufficient abnormal cells are present.

- **3.** Any normal cell with three abnormal neighbors becomes abnormal at the next time step. The rule considers the promotion of a normal cell to an abnormal state.

- **4.** Any abnormal cell with more than three abnormal neighbors becomes normal at the next time step. The rule establishes a limit to abnormal cell expansion, e.g. because of the finite available resources, representing a change from positive to negative cooperativity.
FIG. 1: The cell state $u_{i,j}^{t+1} \in [0,1]$ vs. the neighborhood sum value $n_{i,j}^{t} = \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}$ for the values of $\kappa$ indicated on the curves. The panels are separated to better show the changes obtained in Eq. (1) with increasing $\kappa$. Note that values of $n_{i,j}^{t} > 9$ are only considered to better show the mathematical trends of Eq. (1).

However, $\kappa$ is generally finite and non-vanishing, $u_{i,j}^{t} \in [0,1]$ is a continuous variable and we further have that

- 5. The coupling between cells due to the above local rules is modulated by the continuous parameter $\kappa \in (0, \infty)$. This parameter loosely incorporates the collective influence of biological phenomena such as the stochastic intercellular diffusion of signaling molecules, the intrinsically probabilistic gene expression, and the individual cell heterogeneity. These phenomena should weaken rules 1 to 4 above, which hold exactly in the limit $\kappa \to 0$.

Note that a predominantly normal neighborhood may constitute a normalizing microenvironment for the single central cell because of the abnormal cell under-population (rule 1). On the contrary, a significantly abnormal neighborhood may impair the normalization effect and promote the abnormal state (rules 2 and 3). In the case of abnormal cell overcrowding, however, limited proliferation could arise because of the competition for finite resources (rule 4).

All rules above are concisely implemented using the following map for the spatio-temporal evolution of the state $u_{i,j}^{t}$: 

$$u_{i,j}^{t+1} = B_{\kappa} \left( 3 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}, \frac{1}{2} \right) + u_{i,j}^{t} B_{\kappa} \left( 4 - \sum_{k,m=-1}^{1} u_{i+k,j+m}^{t}, \frac{1}{2} \right)$$  

(7)
where the $B_\kappa$-function is given by Eq. (2). In the limit $\kappa \to 0$, the map is equivalent to the popular *Game of Life* [24], an outer totalistic cellular automaton discovered by Conway [2],

$$
u_{i,j}^{t+1} = \begin{cases} 
1 & \text{if } \sum_{k,m=-1}^{1} u_{t}^{i+k,j+m} = 3 \\
u_{i,j}^{t} & \text{if } \sum_{k,m=-1}^{1} u_{t}^{i+k,j+m} = 4 \\
0 & \text{otherwise}
\end{cases} \quad (8)$$

for any initial conditions for which $\nu_{0}^{i,j}$ is either 0 (normal cell) or 1 (abnormal cell).

### III. RESULTS AND DISCUSSION

In the simulations carried out with *models I* and *II*, we assume that local perturbations may give small clusters of cells in state 1 initially and study then the multicellular ensemble evolution at a later stage. This assumption is realistic because of the inherently probabilistic gene regulation processes and the stochastic nature of the intercellular diffusion of signaling molecules.

#### A. Model I

Fig. 2 shows snapshots of the multicellular ensemble corresponding to the cell states $\nu_{t}^{i,j}$ obtained from Eq. (1) at different dimensionless times. After a sufficiently long time, the system reaches a homogeneous state that can be either normal (upper panels) or abnormal (bottom panels). The transient duration to homogeneity depends on the distance to the transition separating the two trends of Fig. 2 (see the bifurcation diagram in Fig. 3 later). The reversion of abnormal (blue color) to normal (red color) cell states is only possible for low enough values of $\kappa$ promoting a self-correction mechanism of the locally corrupted pattern at $t = 0$. Indeed, the weakening of the local rules favoring the normal state can occur at high enough values of $\kappa$. This fact causes the expansion of the abnormal state over the multicellular ensemble at the particular values of $\kappa$ shown in Figs. 2 and 3.

The above results can be understood if we reduce the map Eq. (1) to the case of homogeneous neighborhoods, thus taking $\nu_{t}^{i+k,j+m} = \nu_{t}^{i,j}$ for all $k, m \in [-1,1]$ and $\sum_{k,m=-1}^{1} \nu_{t}^{i+k,j+m} = 9 \nu_{t}^{i,j}$. In this particular case, all neighborhoods in Eq. (1) are decoupled and the labels $i, j$ can be dropped because we are describing an average single-cell behavior.
FIG. 2: Spatio-temporal evolution of the cell states $u_{i,j}^t$ taking values between 0 and 1 (right bar) for model $I$ obtained by iterating Eq. (1) in a multicellular ensemble of $159 \times 159 = 25281$ cells at different times $t$ for three $\kappa$ values. The initial ($t = 0$) state with cells randomly distributed in the 0 and 1 states is the same for the three cases.

(Note that, because of dynamical fluctuations, the local value of the general dynamics may depart from this single-cell mean-field value.) This coarse-grained approximation is useful for capturing the dynamics because no inhomogeneous neighborhoods can persist in the cellular automata limits of the model. While this is not the case of the intermediate values of $\kappa$ where curvy and circular interfaces are observed (see Fig. 2), the contribution of the interfacial cells can be neglected compared with the dominant bulk domains. Under this assumption, Eq. (1) simplifies to

$$u_{t+1} = \frac{B_0 (9 - 9u_t, \frac{9}{2})}{B_0 (0, \frac{9}{2})}$$

This is a one-dimensional map whose bifurcation diagram can be readily calculated (see Fig. 3). The diagram provides the stable fixed points that can be dynamically reached depending on the initial condition. For constructing the diagram, the whole interval of initial conditions $u_0 \in [0, 1]$ was sampled and the dynamics then iterated to calculate $u_\infty$. A bistable regime is obtained for $2.75 \lesssim \kappa \lesssim 5.2$. Depending on the initial conditions, the system can converge either to the homogeneous normal state or to the abnormal state. For
the particular initial condition of Fig. 2, the critical value $\kappa \approx 4.855$ marks the boundary separating both attractors. Outside this intermediate range of $\kappa$ values, there is only one stable stationary state for the normal or abnormal regimes. Note that the above mean-field analysis is independent of the total number of cells in the multicellular ensemble.

Experimentally, the initial cancer stages have been associated with limited or defective intercellular communication in multicellular ensembles [13, 16, 18, 27, 28]. As expected, Fig. 2 suggests that restoring the intercellular coupling (i.e. lowering the value of $\kappa$) by means of external agents could contribute to ensemble normalization. However, the effects of this restoring procedure depend on the local rules and the particular initial conditions, as we will show in the next model.

B. Model II

Imagine a multicellular ensemble with a small number of abnormal cells at $\kappa$ finite. Because the Game of Life rules are exact in the limit $\kappa \to 0$, full normalization can no longer be warranted in this model. Indeed, the Game of Life displays an unpredictable behavior for generic initial conditions and then abnormal cells could persist in this limit.
FIG. 4: Spatio-temporal evolution of the cell states $u_{i,j}^t$ taking values between 0 and 1 (right bar) for model II obtained by iterating Eq. (7) in a multicellular ensemble of $159 \times 159 = 25281$ cells for six different $\kappa$ values. The initial ($t = 0$) state with cells randomly distributed in the 0 and 1 states is the same for all cases.

Furthermore, lowering $\kappa$ from a sufficiently high value may even enhance the contribution of the abnormal cells to the total ensemble for certain particular cases.

Fig. 4 shows the snapshots of the multicellular ensemble for model II obtained from Eq. (7) at different times. After a transient, the system reaches a homogeneous state for $\kappa$ sufficiently large that appears to be only slightly abnormal. However, as $\kappa$ is lowered,
FIG. 5: Spatio-temporal evolution of the cell states $u_{i,j}^t$ taking values between 0 and 1 (right bar) for model II obtained by iterating Eq. (7) in a multicellular ensemble of $159 \times 159 = 25281$ cells for six different $\kappa$ values. The initial ($t = 0$) state is the same for all cases. The abnormal cells are concentrated in a central cluster of the ensemble.

A bifurcation to oscillatory behavior is observed for domains of abnormal cells. Lowering $\kappa$ further, the number of oscillatory components is increased and the system exhibits a transition to apparently chaotic behavior, that is most prominent at $\kappa = 1$. For $\kappa < 1$ the patterns are noisy and the variable $u_{i,j}^t$ describing the cell state varies continuously with time within the unit interval. However, the intermediate states collapse as $\kappa \to 0$ and the system shows only discrete cell states 0 and 1. In this limit, the dynamics reduces to the Game of Life. For generic initial conditions, therefore, the ensemble may fail to normalize when $\kappa$ is decreased from a particular value.

To emphasize further the complexity of the ensemble normalization, Fig. 5 shows the snapshots obtained from Eq. (7) for the case of an inhomogeneous region occupying initially a central cluster. The central inhomogeneity can only grow if $\kappa \lesssim 1.9$. Otherwise, a homogeneous normal state is obtained at long times. As $\kappa$ is lowered, domain formation and oscillations are observed within the growing inhomogeneity (see also Fig. 4). The homogeneous quiescent region remains unaffected.

To better understand the results of Fig. 5 let $w_t \approx 0$ denote the value $u_{i,j}^t$ of a cell in the homogeneous region of the ensemble far away from the inhomogeneity. Let $\Omega = n^2$ denote the total number of cells, with $n$ the number of cells on a side of the square lattice. Then,
the time-dependent variable

$$M_t = \frac{1}{\Omega} \sum_{i=1}^{n} \sum_{j=1}^{n} u_{i,j}^{t,j} - w_t$$

provides an estimate for the relative weight of abnormal cells in the lattice with respect to $w_t$.

Fig. 6 shows the values of $M_t$ obtained from Eqs. (7) and (10) for the same initial condition as in Fig. 5 for the values of $\kappa$ indicated on the curves. $M$ constitutes a measure of the ensemble abnormality.

For $\kappa = 1$, the optimal growth of the abnormal region is obtained. The impact of the domain oscillations within the abnormal region is clearly visible for $\kappa = 1.2$. Also, the effects of noise are more prominent as $\kappa < 1$ is decreased. Statistically, fluctuations are more noticeable when addition is performed over the values $u_{i,j}^{t,j} = 0$ or 1 only (the case $\kappa \rightarrow 0$), as opposed to addition over a continuous range of values for $u_{i,j}^{t,j}$ (the case $\kappa \approx 1$).

Note also that while inhomogeneities are removed after a transient for $\kappa > 1.9$, the resulting homogeneous state is not completely normalized in Fig. 5. Taken together, the results in Figs. 5 and 6 show that decreasing the parameter $\kappa$ in model II yields behaviors that depend dramatically on the value of $\kappa$ characterizing the ensemble.

The results of Figs. 4-6 for model II can be analyzed further in the mean field approximation where $u_{i+k,j+m}^{t,k,m} \approx u_{i,j}^{t,j}$ for all $k, m \in [-1, 1]$. Then, $\sum_{k,m=-1}^{1} u_{i+k,j+m}^{t,k,m} \approx 9u_{i,j}^{t,j}$. In this particular case, all neighborhoods are decoupled in Eq. (7). The labels $i, j$ can be dropped since we are describing an average, coarse-grained single-cell behavior. Eq. (7) takes then
the simplified form:

\[ u_{t+1} = B_\kappa \left( 3 - 9u_t, \frac{1}{2} \right) + u_t B_\kappa \left( 4 - 9u_t, \frac{1}{2} \right) \tag{11} \]

The bifurcation diagram of Eq. (11) can be readily obtained (see Fig. 7). We describe it as \( \kappa \) is lowered from \( \kappa \geq 2 \) to 0:

- A bifurcation is encountered at \( \kappa \approx 1.95 \), which is close to the value \( \kappa \approx 1.9 \) found in the simulations with the exact dynamics (Eq. (7)). The system abruptly splits into two branches leading to a bistable regime \( A \) shown in the diagram. Remarkably, the system would normalize when \( \kappa \to 0 \) only if the lower branch in Fig. 7 were followed. These facts establish practical limits for restoring and normalization procedures.

- A bifurcation of the upper branch is found at \( \kappa \approx 1.35 \) leading to period-2 oscillations. Further period doubling bifurcations are then observed at \( \kappa \approx 1.2 \) as in Fig. 4, leading through a cascade into chaos which is most prominent at \( \kappa = 1 \) (regime B in the diagram of Fig. 7).

- In regimes C and D of Fig. 7, the mean-field approximation fails because it can no longer be assumed that all neighborhoods are uncoupled and well-described by an average cell value. The full model of Eq. (7) needs to be considered in this case. Noise is high in regime C (see Figs. 4 and 5 for \( \kappa = 0.5 \)) but this noise may have a thermal-like origin (see Ref. 4). More degrees of freedom may be involved here and it is not possible to use the one-dimensional model of Eq. (11) to account for this dynamics. Note that the results of Fig. 7 clearly show the complex role of the modulating parameter \( \kappa \) in the system normalization.

The bifurcation diagram (Fig. 7) explains the pattern formation in Figs. 4 and 5 for \( 1 \leq \kappa \leq 1.9 \): the upper branch with bifurcations corresponds to the inhomogeneous region and the lower branch to the homogeneous one in Fig. 5. The bifurcation diagram also explains why oscillations occur only in the inhomogeneous region.

An analysis of the noise in the time series of \( u_{i,j}^{t,j} \) for each cell of the multicellular ensemble has also been carried out in regimes C and D of Fig. 7. The spectrum shifts from uniform noise at \( \kappa = 1 \) to low-frequency \( (1/f) \) noise at \( \kappa \to 0 \). The strong correlations found in the limit \( \kappa \to 0 \), together with the need to take into account local details within a neighborhood,
FIG. 7: Bifurcation diagram calculated from the asymptotic behavior of Eq. (11). The stationary cell state $u_\infty$ obtained at large times is shown as a function of the parameter $\kappa$. The black curves correspond to stationary states. The red points indicate the period doubling bifurcation cascades into chaos. Note the correspondence of this figure with the results of Figs. 4 and 5.

make necessary to use the full model (Eq. (7)) instead of the reduced, coarse-grained model (Eq. (11)) in that regime.

The different results obtained with models I and II emphasize the inherent complexity of collective normalization processes based on the restoring of weakened local rules in model multicellular ensembles. When attempting to induce externally normalization procedures, a detailed knowledge of the local intercellular rules is necessary to achieve the desired outcomes.

IV. CONCLUSIONS

Theoretical approaches to multicellular processes tend to focus on biochemical signals and pathways at the single-cell level [15–18]. Extensions to tissues are usually based on reaction-diffusion [29–31] and bioelectrical schemes [10, 32] but network models with different local rules have also been proposed [33–35]. We have shown here that a weakly coupled map lattice [1] can provide significant insights on intercellular coupling by using two biologically-relevant
sets of local rules for the multicellular ensemble dynamics.

Intercellular coupling can be mediated by the protein gap junctions between adjacent cells but the particular mechanisms linking these junctions to tumorigenesis are not completely known [36]. For instance, the bystander effects associated with the coupling may enhance the antitumor effect by transferring signaling molecules between adjacent cells [37]. However, the intercellular junctions should not be seen only as tumor suppression agents because they have specific roles that are context-dependent. Indeed, these junctions may show pro- and anti-proliferative effects which depend on the particular cell state and the information to be transferred [36]. In this context, simple physical models relating the local rules and the intensity of intercellular coupling to the context-dependent functionality of gap junctions are needed.

The spatio-temporal maps of single-cell states change dramatically with the parameter $\kappa$ modulating the local rules for intercellular interaction. The observed evolutions can be very different according to the set of local rules considered (models I and II here). Therefore, acting externally on the coupling should produce effects which depend on the local rules dominant in the ensemble at each particular stage. These results should be of qualitative value to predict the time evolution of ensembles amenable to experimental visualization. For instance, the electrical potential domains formed by cell clusters can be imaged locally by membrane voltage-reporting dyes [12, 22, 23] and the intercellular coupling may be externally controlled by appropriate agents such as blockers of the specific ion channels regulating the cell membrane potential [10, 12, 20, 27].

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