Continuum percolation theory of epimorphic regeneration

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Abstract

A biophysical model of epimorphic regeneration based on a continuum percolation process of fully penetrable disks in two dimensions is proposed. All cells within a randomly chosen disk of the regenerating organism are assumed to receive a signal in the form of a circular wave as a result of the action/reconfiguration of neoblasts and neoblast-derived mesenchymal cells in the blastema. These signals trigger the growth of the organism, whose cells read, on a faster time scale, the electric polarization state responsible for their differentiation and the resulting morphology. In the long time limit, the process leads to a morphological attractor that depends on experimentally accessible control parameters governing the blockage of cellular gap junctions and, therefore, the connectivity of the multicellular ensemble. When this connectivity is weakened, positional information is degraded leading to more symmetrical structures. This general theory is applied to the specifics of planaria regeneration. Computations and asymptotic analyses made with the model show that it correctly describes a significant subset of the most prominent experimental observations, notably anterior-posterior polarization (and its loss) or the formation of four-headed planaria.

PACS numbers: 87.17.Pq, 05.65.+b, 87.10.Mn

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I. INTRODUCTION

The understanding of the biophysical mechanisms behind reparative regeneration, i.e. the remarkable ability of some organisms to replace a lost or damaged part of the body following amputation [1], is a major unsolved problem of basic biology and biomedicine [2]. A most dramatic example is the regeneration of the amputated limb or tail of a salamander or newt through a regeneration blastema that produces an almost exact replica of the amputated part [1, 3–7]. Another striking example is provided by the reconstitution, within 1-2 weeks, of the entire body of a planarian [8–15] starting from a fragment that can be as small as 1/279th of the worm [16], or having as few as 10000 cells [17]. Most characteristic of epimorphic regeneration is that a morphogenetic pattern is set up within the blastema, and it is expressed as the blastema grows [1].

A few models of regeneration exist (see [18] for a review). Former proposals include a serial theory of regeneration based on comparison and regeneration of sequentially coded territories [19] and dynamical reaction-diffusion chemical models based on local self-activation and long-range lateral inhibition [20]. More recently, a few further models are found in the literature and include a simplified dynamical model based on three diffusible molecules [21]; a reverse-engineered dynamic regulatory network [22]; a model of pattern regeneration based on cell memory and signal comparisons [23] and a symbolic model based on membrane computing [24]. A recent review [8] nicely summarizes, for a broad readership, a subset of most prominent experimental observations that successful models of planarian regeneration should attempt to describe. Many models above are only able to address one or two aspects of planarian regeneration [8].

In this article we formulate a physical theory for epimorphic regeneration based on continuum percolation in two-dimensions and apply it to the specifics involved in the regeneration of planaria. The theory provides a link between systems biology and a robust, universal and lattice-free mechanism that may govern regenerating processes of some organisms. The model is described by a discrete map that can be easily computed, leading to quantitative predictions that can, in turn, be validated/falsified by experiment. With this model we are able to describe a significant subset of the most prominent experimental features discussed in [8], notably, the regeneration of four-headed planaria.

We assume that there are at least two time-scales in the problem. The slow time scale
which is explicitly addressed by means of the discrete time variable $t$) describes the dynamics of neoblasts and neoblast-derived mesenchymal cells in the blastema that are crucial for regeneration \cite{25}. This dynamics concerns the spatiotemporal evolution of a compactly-supported function $P_t(x,y)$ defined on each point $(x,y)$ of the plane $\mathbb{R}^2$ which governs the growth of the regenerating organism by means of a continuum percolation process (well above the percolation threshold \cite{26, 27} and, thus, far away from criticality). The fast time scale governs the spatiotemporal evolution of the $V_{\text{mem}}(x,y)$ landscape, where the cell membrane potential $V_{\text{mem}}(x,y)$ is defined as the potential difference between the cell cytoplasm and the extracellular microenvironment at the stationary state (zero current conditions) \cite{29, 30} and is produced by the movement of ions across the cell membrane \cite{28}. This quantity is here regarded as an ensemble-averaged value defined at each location $(x,y)$, governing the hyperpolarized or depolarized state of the cells at that location. The fast time scale also governs the relaxation process of any (average) nonequilibrium potential drop across a cell $V(x,y,t)$ to the stable rest value $V_{\text{mem}}(x,y)$. These fast degrees of freedom can be adiabatically eliminated, leading to the emergence of an underlying morphogenetic field, where the electric polarization state of the cells at the global attractor (obtained in the infinite time limit) is stored. This field is given by a compactly-supported function $\mathcal{P}(x,y)$ which is also generally dependent on some biophysical control parameters that govern the coupling strength of cells within the multicellular ensemble. We thus note that, in our model, although $\mathcal{P}(x,y)$ can be considered as a prepatter that is responsible for the cell determination and differentiation on each particular area, it also directly depends on the communication between cells. Evidence for the existence of such a prepatter was already shown by Stern \cite{31} with genetic mosaics for bristle formation in \textit{Drosophila}. We shall refer to $\mathcal{P}(x,y)$ as the \textit{morphological attractor} or the \textit{target morphology} in tune with the works in which this idea has been suggested \cite{32–34}. Following those works, we assume here that $\mathcal{P}(x,y)$ is directly related to the $V_{\text{mem}}(x,y)$ landscape. This bioelectric-morphologic correspondence is realistic, since voltage reporter dyes have revealed gradients of $V_{\text{mem}}$ across the anterior-posterior (AP) axis of planarian flatworms showing that their head is depolarized while their tail is hyperpolarized \cite{28, 35}.

With these assumptions, we qualitatively model (at a coarse-grained level) the overall effect of complex intercellular interactions involved in regeneration. These are controlled by a diverse set of signals, including molecular pathways, gap junctional communication,
ion fluxes and nervous system signals [8]. On one hand, the model dynamics in the slow time scale is justified in terms of the wide applicability of percolation models to describe transport phenomena in complex porous media [36]. Continuum percolation processes are lattice-free, being appropriate to describe multicellular ensembles: Topological properties are not artificially constrained by rigid arrangements of nearest-neighbor configurations as in cellular automata or lattice maps. Continuous percolation is also a robust and universal means to model the building of a cellular long-range order which, we believe, is ultimately responsible for the regeneration of an organism. On the other hand, a similar assumption on the fast time scale has been invoked to justify the emergence of a non-local coupling governing the dynamics of slow variables in certain reaction diffusion systems in which fast diffusive variables are adiabatically eliminated [37, 38].

We briefly discuss how both time scales are connected in the model. Disks of radius $R$ with random centers, which are either close to or within a fragment of the organism after amputation (assumed bi-dimensional) are injected by means of a covering algorithm that constitutes our model. With these circular geometries we model the concerted action of neoblasts and the curvy interfaces formed by neoblast-derived mesenchymal cells in the blastema [25]. The disks roughly model the fact that signals propagate isotropically in the cellular environment starting from a random point and being received at points within a radius $R$ with a loss factor due to isotropic dispersion, noise and absorption in the environment. These limitations mean in practice that beyond a radius $R$ from the emitter, a signal can no longer be detected. If a signal emitted from a random point $(r_{1,t}, r_{2,t})$ is detected at time $t$ by cells at point $(x, y)$, the percolation model sets a value 1 at that point and a value 0 if the signal is not detected. Those cells at points with value 1 read then the positional information contained in $P(x, y)$ (a process that happens on the fast time scale that is being adiabatically eliminated). Boolean models of this kind are employed as useful first-order approximations in radio communication and wireless networks [39], and are biophysically justified in terms of diffusion and sensing of chemical species as well as the interaction of the cellular environment with endogenous electric fields. Although the parameter $R$ is here free, the dynamics of the model converges to the same attractor $P(x, y)$ in the infinite time limit (the regenerated structure) regardless of the value of $R$ (the convergence time being larger for smaller $R$). It is said that a Boolean model percolates if there exists an infinite connected component [40]. This is the case of our model, which yields at every time a
connected structure of overlapping disks, regardless of their radius $R$.

Our modeling of the target morphology $\mathcal{P}(x, y)$ makes use of recent mathematical methods \cite{41, 42} that provide a convenient means to work with both crisp and fuzzy sets and their algebra. All functions entering in our model are either compactly supported (i.e., they are nonzero only on a bounded domain of the plane), or display tanh-profiles, as ubiquitously found in reaction-diffusion systems, depending on a parameter $\kappa$ that is able to tune the support from compact (as $\kappa \to 0$) to the whole of $\mathbb{R}^2$ (as $\kappa \to \infty$). Examples of tanh-profiles are provided by Ising and Bloch walls \cite{43} formed by phase clusters in oscillatory media or trigger waves propagating in excitable media, as those described by the Fisher-Kolmogorov equation \cite{44}. These classes of functions allow to mathematically define regions and interactions within the organism, determining parts (organs) in a natural way. Most importantly, they also describe the action of experimentally tunable control parameters in the symmetry breaking structures that emerge when the attractor of the regeneration process is reached. Furthermore, an intriguing connection between weak intercellular coupling and the degradation of the positional information is revealed.

The outline of this article is as follows. In Section \textsc{II} we formulate the general theory of regeneration based on a continuum percolation process. In Section \textsc{III} we apply the theory to the specific case of planarian regeneration showing how our model reproduces a significant subset of experimental observations \cite{8}. Several limitations of our model and possibilities to overcome them are then outlined in Section \textsc{IV}.

\section{General Theory}

The theory depends on a morphologic function $P_t(x, y)$ that evolves on discrete time steps $t$ being iterated at each point $(x, y) \in \mathbb{R}^2$ and governing the polarization state of the cells that are concentrated at each point at time $t$. We assume that the function has compact support, i.e. it is nonzero only on a bounded domain of the plane. We define the support $\Omega_t$ of $P_t$ as the set of those points $(x, y)$ where $P_t(x, y) \neq 0$. The infinite time limit $P_\infty(x, y)$ exists and is also compactly supported.

Since $P_t$ is compact at every time, we consider that the dynamics takes place on a square region $M$ of the infinite plane $\mathbb{R}^2$ of side $L$ so that $\Omega_t \subseteq M, \forall t$. The origin $(0, 0)$ is placed at the center of $M$. The dynamics starts from an arbitrary initial condition $P_0(x, y)$ that
is non-zero in a finite compact spatial region $\Omega_0$, satisfying $\Omega_0 \subset M$. This initial condition constitutes a fragment of the organism to be regenerated and is centered at the point $(a, b)$ ($|a| < L_0$, $|b| < L_1$ and $(a, b) \in P_0$). Then, the function $P_t(x, y)$ evolves according to the map

$$P_{t+1}(x, y) = \left[ H \left( P_t(x, y) - \frac{1}{2} \right) + D_t(x, y) - H \left( P_t(x, y) - \frac{1}{2} \right) D_t(x, y) \right] P(x, y)$$ (1)

where $H(x)$ is the Heaviside step function ($H(x) = 0$ if $x < 0$, $H(0) = 1/2$, $H(x) = 1$ if $x > 0$) and

$$D_t = B \left( [x - r_{1,t}]^2 + [y - r_{2,t}]^2, R^2 \right)$$ (2)

Here, we have introduced the compactly-supported $B$-function of real arguments $x, y$ [15–17]

$$B(x, y) = \frac{1}{2} \left( \frac{x + y}{|x + y|} - \frac{x - y}{|x - y|} \right) = \text{sgn}(y) H (|y| - |x|)$$ (3)

By definition, $B(-x, y) = B(x, y)$ and $B(x, -y) = -B(x, y)$. In Eq. (2) $r_{1,t}$ and $r_{2,t}$ are the real numbers given by

$$r_{1,t} = a + \left( \eta_t + \frac{R}{\sqrt{2}} \text{sgn}(\eta_t - a) - a \right) H \left( P_t(\eta_t, \xi_t) - \frac{1}{2} \right)$$ (4)

$$r_{2,t} = b + \left( \xi_t + \frac{R}{\sqrt{2}} \text{sgn}(\xi_t - b) - b \right) H \left( P_t(\eta_t, \xi_t) - \frac{1}{2} \right)$$ (5)

where $\eta_t$ and $\xi_t$ are random numbers taken from the uniform distribution in the interval $[-L, L]$. The initial condition $P_0(x, y)$ in Eq. (1) is explicitly given by

$$P_0(x, y) = B (x - a, R_X) B (y - b, R_Y) P(x, y)$$ (6)

where $R_X$ and $R_Y$ are parameters that satisfy $0 \leq R_X \leq L$, $0 \leq R_Y \leq L$.

The function $P(x, y)$ in Eq. (1) is also compactly supported, with support denoted by $\Omega_\infty$, and encodes the positional information of the cells within the regenerated planarian in terms of the cell membrane potential $V_{\text{mem}} < 0$ as

$$P(x, y) = \frac{V_{\text{mem}}(x, y) - V_{\text{hyp}}}{V_{\text{dep}} - V_{\text{hyp}}} \max P, \quad (x, y) \in \Omega_\infty$$ (7)

where $V_{\text{hyp}}$ and $V_{\text{dep}}$ denote the hyperpolarized and depolarized potentials respectively ($V_{\text{hyp}} \leq V_{\text{mem}} \leq V_{\text{dep}}$) and $\max P$ is the maximum value of $P(x, y)$.

Eq. (1) governs the random injection, at each time step $t$, of a fully penetrable disk $D_t$ of radius $R$ and center $(r_{1,t}, r_{2,t})$, so that the body of the organism at time $t$ is the set formed
FIG. 1: (Color online) Sketch (not to scale) of the geometry of the insertion of a random disk $D_t$ of radius $R$ through Eq. (1), clarifying the meaning of the parameters in Eqs. (4) and (5). The newly injected disk $D_t$ overlaps with the regenerated fragment $P_t$ at time $t$. by the union of all the disks and the support $\Omega_0$ of the initial condition $P_0$. At each iteration step, the newly injected disk overlaps with the previously regenerated fragment. We now prove this statement. Let the random point $(\eta_t, \xi_t)$ do not belong to $\Omega_t$. Then, from Eqs. (4) and (5) $(r_{1,t}, r_{2,t}) = (a, b)$ and hence, a disk with radius $R$ and center $(a, b)$ is injected. But the intersection of this disk and $\Omega_0$ is non-empty, because $(a, b) \in \Omega_0$. This represents a random signal within the organism that does not trigger a growth of the blastema. If the random point is close to or belongs to the boundary of $\Omega_t$ (the blastema), the newly generated disk of radius $R$ is a distance $R$ away and, therefore, it either partially overlaps with $P_t$ or intersects $P_t$ tangentially at the contact point $(\eta_t, \xi_t)$. Thus the injected random disk, represents a signal triggered in the blastema and leading to its growth. The geometry of this growth process and the different parameter parameters entering in it through Eqs. (4) and (5) are sketched in Fig. 1. In this way, a connected structure of disks is obtained which is typical of a continuous percolation process of fully penetrable disks in the plane [36] (well above the percolation threshold [26, 27]).

To better grasp Eq. (1), let $\Delta_t$ denote the compact support of the newly added disk as given by the function $D_t$ in Eq. (2). The dynamics of the supporting sets for all functions entering in Eq. (1) is, consistently with that equation, obtained as

$$\Omega_{t+1} = (\Omega_t \cup \Delta_t) \cap \Omega_\infty$$

(8)

where, as indicated above, $\Omega_\infty$ is the compact support of the function $\mathcal{P}(x,y)$ in Eq. (7). This latter function is the stable attractor of the map Eq. (1) since, as $t \to \infty$, the support
\(\Omega_\infty\) of \(\mathcal{P}(x,y)\), being bounded, is fully covered by the disks. Therefore, since \(\Omega_0 \subseteq \Omega_\infty\), we have

\[
\Omega_0 \subseteq \Omega_1 \subseteq \ldots \subseteq \Omega_t \subseteq \Omega_{t+1} \subseteq \ldots \subseteq \Omega_\infty
\]

(9)

Note also that, because of Eq. (9), we have \(\Omega_t \cap \Omega_\infty = \Omega_t\), \(\forall t\). Therefore, although the attractor of the dynamics is somehow present at each iteration step of Eq. (1) as a 'driving force' constraining the dynamics, \(P_t\) is generally different to the attractor \(P_\infty = \mathcal{P}(x,y)\).

The dynamical evolution of the map builds the union of randomly injected disks and the initial condition, the growth of the structure being constrained by the support of the function \(\mathcal{P}(x,y)\). This process is sketched in Fig. 2. Starting from an initial condition, \(P_0\) a series of disks are randomly injected so that there is always a nonempty intersection of the new disk with the union of the previously inserted ones. The whole process is constrained by the support \(\Omega_\infty\) (an ellipse in the figure) of the function \(\mathcal{P}(x,y)\). In the figure, the region shaded green is the already regenerated organism and the region shaded orange becomes regenerated at time \(t + 1\).

The field \(\mathcal{P}(x,y)\) codifies the positional information in terms of the morphologically-relevant landscape of membrane voltages \(V_{\text{mem}}(x,y)\) [29]. We give a simple heuristic argument to suggest how this function may arise from adiabatic elimination of fast degrees of freedom. Let us consider this function as time-dependent \(\mathcal{P}(x,y,t)\). This would correspond to a situation where there is a non-zero average net current through the cells at \((x,y)\) so that the electric potential \(V(x,y,t)\) is different to the stationary value at zero current \(V(x,y,t) \neq V_{\text{mem}}(x,y)\). Then, Eq. (7) would generalize to

\[
\mathcal{P}(x,y,t) = \frac{V(x,y,t) - V_{\text{hyp}}}{V_{\text{dep}} - V_{\text{hyp}}} \max \mathcal{P}, \quad (x,y) \in \Omega_\infty
\]

(10)

The possible stationary values of \(V_{\text{mem}}\) at each location are responsible for the cell dif-
ferentiation. It is reasonable to assume that there can be many such possible stationary values for $V_{\text{mem}}(x,y)$, although finite in number, and including $V_{\text{hyp}}$ and $V_{\text{dep}}$ as the most hyperpolarized and most depolarized stable states, respectively. Thus, let us assume that there are $2N + 1$ fixed points for $V_{\text{mem}}$ labelled as $V_k$ with $k \in [0,2N]$ so that $V_0 \equiv V_{\text{hyp}} < V_1 < \ldots < V_{2N} \equiv V_{\text{dep}}$. This situation corresponds to a multistable regime that can be phenomenologically modeled with the following dynamics

$$C \frac{dV}{dt} = - \prod_{k=0}^{2N} (V - V_k) \equiv g(V) \quad (11)$$

where we have introduced the effective capacitance $C$. It is clear from this equation that all values for which $V_{\text{mem}} = V_{2m}$ ($m \in [0, N]$) are stable, while those for which $V_{\text{mem}} = V_{2m-1}$ ($m \in [1, N]$) are unstable. This is obtained from a linear stability analysis close to any stationary value $V_{\text{mem}}$ which leads to the expression

$$C \frac{d(V - V_{\text{mem}})}{dt} \approx - \frac{V - V_{\text{mem}}}{Z} \quad (12)$$

where the effective impedance $Z(V_{\text{mem}}) \equiv [df(V)/dV|_{V=V_{\text{mem}}}]^{-1}$ is positive for $V_{\text{mem}} = V_{2m}$ ($m \in [0, N]$) and negative for $V_{\text{mem}} = V_{2m-1}$ ($m \in [1, N]$). The linearization, Eq. (12), is valid for small perturbations close to any stationary value of $V_{\text{mem}}$ and also for more general nonlinearities than $g(V)$ above (involving, possibly, the concentrations of some chemical species as well [48]). It is then clear that if the stationary state $V_{\text{mem}}$ is stable, then $V$ relaxes to $V_{\text{mem}}$ as $V \propto \exp(-t/\tau_{\text{ch}})$ ($\tau_{\text{ch}} \equiv ZC$, $Z > 0$) and thus, for $\tau_{\text{ch}}$ sufficiently small, the time scale involved is faster than the one of $P_t$ in Eq. (1). Therefore, it can be adiabatically eliminated so that $V = V_{\text{mem}}$ in Eq. (10) and, thus, $P(x,y,t) = P(x,y)$ as in Eq. (1). This is reasonable, since the update $t \to t + 1$ in Eq. (1) proceeds on a time scale that corresponds to the growth of the blastema, and this can be viewed as a much slower process than the evolution of $V(x,y,t)$ to the rest potential $V_{\text{mem}}(x,y)$.

The modeling of $P(x,y)$ makes use of compactly supported functions, as the Heaviside function $H(x)$ and the $B$-function defined in Eq. (3). To understand why this class of functions are necessary in this context, let $\text{Body}(x,y)$ be a compactly-supported function that is equal to 1 if $(x,y)$ belongs to the set of points occupied by the body of an organism and 0 otherwise. Let $\text{Head}(x,y)$ be defined similarly for the head of the organism. Since the support of $\text{Head}(x,y)$ is a subset of the support of $\text{Body}(x,y)$, it is clear that the function $P(x,y) = \text{Body}(x,y) (1 + \text{Head}(x,y)) = \text{Body}(x,y) + \text{Body}(x,y)\text{Head}(x,y)$ returns 0 if $(x,y)$
does not belong to the interior of the organism, 1 if it does belong to the body but not to the head, and 2 if it belongs to the head. In this way, we have obtained a function taking values on a finite subset of the natural numbers with the nice property that the larger the value of the function, the higher the number of subsets to which \((x, y)\) belongs. Remarkably, with the connection made in Eq. \(\text{(7)}\) between \(\mathcal{P}(x, y)\) and \(V_{\text{mem}}(x, y)\), it is seen that \(V_{\text{mem}}(x, y)\) corresponds to a depolarized value for the membrane voltage \(V_{\text{dep}}\) if \((x, y)\) is in the head of the organism, and to a more polarized value \(V_{\text{mem}} < V_{\text{dep}}\) if \((x, y)\) belongs to the body but not to the head. Thus, we have an order relationship obtained by inclusion and trees (analogous to Hasse diagrams) can be drawn to describe hierarchies of spatially extended morphological elements within an organism, from the body down to parts, tissues, organs, etc., each branch of the tree following a different chain of inclusions. This mathematical order relationship matches the experimental scale of \(V_{\text{mem}}\), from more hyperpolarized to more depolarized values.

We elaborate on some further technical mathematical details that are needed in the mathematical modelling of the target morphology \(\mathcal{P}(x, y)\). Let \(C(x, y)\) denote a compactly-supported function and \(f(x, y)\) a continuous function that does not have compact support but is bounded, satisfying \(|f(x, y)| \leq K\) (for some \(K \in \mathbb{R}^+\)) everywhere. Then, the function \(G(x, y)\) defined by the product

\[
G(x, y) = C(x, y) f(x, y)
\]

has also compact support. Furthermore, as we have seen above, the sum of any two compactly supported-functions \(C\) and \(G\)

\[
S(x, y) = G(x, y) + C(x, y)
\]

is also compactly supported. These elementary mathematical properties can be fruitfully exploited, and their power is made apparent if \(f(x, y)\) has some further “nice” properties. In the following we shall deal exclusively with combinations of \(\mathcal{B}_\kappa\)-functions as models for \(f(x, y)\) in Eq. \(\text{(13)}\). The \(\mathcal{B}_\kappa\) function of real variables \(x\) and \(y\) \(^{[41, 42]}\) is defined as

\[
\mathcal{B}_\kappa(x, y) \equiv \frac{1}{2} \left[ \tanh \left( \frac{x + y}{\kappa} \right) - \tanh \left( \frac{x - y}{\kappa} \right) \right]
\]

in terms of the parameter \(\kappa \in \mathbb{R}\). For small \(\kappa\) \((\kappa \to 0)\), this function is approximately equal to 1 for \(|x| < |y|\) and approximately equal to 0 for \(|x| > |y|\). The function is always positive
for positive \( y \) (as considered in this work) and its maximum \( (\approx 1) \) is attained at \( x = 0 \), its minimum \( \sim 0 \) being found at \( |x| \to \infty \). Therefore,

\[
0 = \lim_{x \to \infty} B_\kappa(x, y) \leq B_\kappa(x, y) \leq B_\kappa(0, y) \quad \forall y > 0
\]  

For all finite values of \( x \) and \( y \), the \( B_\kappa \)-function satisfies the limits \[41\]:

\[
B_\infty(x, y) \equiv \lim_{\kappa \to \infty} B_\kappa(x, y) = 0 \quad \frac{B_\infty(x, y)}{B_\infty(0, y)} = 1 \tag{17}
\]

\[
B_0(x, y) \equiv \lim_{\kappa \to 0} B_\kappa(x, y) = B(x, y) \tag{18}
\]

and one also has, furthermore, \( B_\kappa(-x, y) = B_\kappa(x, y) \), \( B_\kappa(x, -y) = -B_\kappa(x, y) \). The interest of \( B_\kappa \)-functions is that, because of Eqs. \[17\] and \[18\] the parameter \( \kappa \) can tune the support from compact (at \( \kappa = 0 \)) to uniformly distributed over infinite domains (as \( \kappa = \infty \)) being always bounded \[42\].

### III. APPLICATION: A MODEL FOR PLANARIAN REGENERATION

We now consider a specific explicit expression for \( P(x, y) \) in Eq. \[1\] to describe some experimental features observed in planarian regeneration. We consider that the function \( P(x, y) = P(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E) \) depends on four control parameters \( \kappa_0, \kappa_1, \kappa_2 \) and \( \Delta E \) that can be experimentally accessed. Parameters \( \kappa_0 \in [0, \infty) \), \( \kappa_1 \in [0, 1] \) and \( \kappa_2 \in [0, \infty) \) correspond to different intercellular coupling strengths: the larger any of these parameters are, the weaker the corresponding coupling strength \[41, 49\]. Parameter \( \kappa_0 \geq 0 \) denotes the coupling between cells in the planarian body, as mediated by gap junctions. An increased value of this effective parameter models an experimental weakening of the intercellular coupling, obtained, e.g. by blocking the gap junctions of the planarian cells with octanol. The parameter \( \kappa_1 \) denotes the coupling strength (connectivity) between cells in the nervous system and is taken here as \( 0 \leq \kappa_1 \leq 1 \). This parameter is increased by, e.g. amputating the nerve cords of the planarian, thus disabling a proper connectivity between cells of the nervous system. The parameter \( \kappa_2 \) denotes the coupling strength of the (depolarized) cells in the head of the planarian. Therefore, \( \kappa_2 \approx 0 \) models the membrane depolarization of the blastema (endogenously regulated by hydrogen and potassium flux through membrane ion translocator proteins) which is required for head regeneration \[8\]. This parameter can be experimentally increased by means of the drug SCH-28080, which disturbs the ion pumps in the worm cells,
altering their membrane voltage and leading to trunk fragments that regenerate into worms with no heads [8]. Finally \( \Delta E \in \mathbb{R} \) denotes any external voltage drop applied between head and tail of the planarian thus affecting the AP polarity. Besides these control parameters, the lengths \( L_0 \) and \( L_1 \) denote major and minor axis of an ellipse governing the dimensions of the regenerated planarian. These can be experimentally varied by controlling the food supplied to the planarian [8] (we shall keep \( L_0 \) and \( L_1 \) fixed throughout). The function \( \mathcal{P}(x, y) \) in Eq. (1) is then given by

\[
\mathcal{P}(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E) = \left[ 1 - B \left( \sum_{n=0}^{1} B \left( \frac{x^2}{L_n^2} + \frac{y^2}{L_{1-n}^2}, 1 \right) \frac{B_{\kappa_0 \kappa_1} (n, \frac{1}{2})}{B_{\kappa_0 \kappa_1} (0, \frac{1}{2})} \right) \right] \times (19)
\]

\[
\times \left[ 1 + \sum_{m=0}^{1} \sum_{j=0}^{1} \sum_{k=0}^{1} B_{\kappa_2} \left( (x - (-1)^j L_m f)^2 + (y - (-1)^k L_{1-m} f)^2, \rho^2 \right) \frac{B_{\kappa_0} \left( \Delta E - 2j, \frac{3}{2} \right)}{B_{\kappa_0} \left( 0, \frac{3}{2} \right)} \right]
\]

We first note that Eq. (19) is of the type \( \mathcal{P}(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E) = \) Body\((x, y; \kappa_0, \kappa_1) (1 + \text{Head}(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E)) \) described in Section II where

\[
\text{Body}(x, y; \kappa_0, \kappa_1) \equiv 1 - B \left( \sum_{n=0}^{1} B \left( \frac{x^2}{L_n^2} + \frac{y^2}{L_{1-n}^2}, 1 \right) \frac{B_{\kappa_0 \kappa_1} (n, \frac{1}{2})}{B_{\kappa_0 \kappa_1} (0, \frac{1}{2})} \right) \quad (20)
\]

and

\[
\text{Head}(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E) \equiv \sum_{m=0}^{1} \sum_{j=0}^{1} \sum_{k=0}^{1} B_{\kappa_2} \left( (x - (-1)^j L_m f)^2 + (y - (-1)^k L_{1-m} f)^2, \rho^2 \right) \frac{B_{\kappa_0} \left( \Delta E - 2j, \frac{3}{2} \right)}{B_{\kappa_0} \left( 0, \frac{3}{2} \right)} \quad (21)
\]

For simplicity we have reduced the head morphology of a regenerated planarian to the presence of the two eyes whose relative positions within the planarian and radii are, respectively, governed by the parameters \( f \in [0, 1] \) and \( \rho \).

The function \( \mathcal{P}(x, y; \kappa_0, \kappa_1, \kappa_2, \Delta E) \) is compactly supported, its support being equal to the one of the Body\((x, y) \) function (which is also compactly supported). Therefore, this latter function establishes the overall shape of the regenerated structure.

Eq. (11) together with the initial condition Eq. (6) and the morphogenetic field given by Eq. (19) constitutes our model for planarian regeneration. We now discuss the model for different parameter regimes substantiating the results with numerical simulations of Eq. (1). In all cases, the process converges to a regenerated organism, generally before 10000 time steps of the map.
Although finite values for the parameters are always considered in the numerical simulations, we mathematically describe the model for parameter values that are asymptotically large or small. For finite $\kappa_0$, $\kappa_1$ and $\kappa_2$ the behavior abruptly interpolates between the ones found in these asymptotic limits, which, therefore, accurately characterize the structures found in the different parameter regimes of the bifurcation diagram.

A. All control parameters vanishingly small: normal regeneration of the planarian

We model normal regeneration of the planarian by taking small values for all control parameters. This corresponds to a situation in which all cells within the planarian are strongly coupled and there are no externally applied voltages. In the limiting case describing this situation (where all parameters are zero) Eq. (19) simplifies to

$$P(x, y; 0, 0, 0, 0) = B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) \left[ 1 + \sum_{k=0}^{1} B \left( (x - L_0 f)^2 + (y - (-1)^k L_1 f)^2, \rho^2 \right) \right]$$

where we have used Eqs. (17) and (18) together with the fact (as can be proved by exhaustion) that $1 - B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) = B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right)$. We have also used that $B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) B \left( (x - L_1 f)^2 + (y - (-1)^k L_0 f)^2, \rho^2 \right) = 0$ because the intersection of the supports of the functions $B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right)$ and $B \left( (x - L_1 f)^2 + (y - (-1)^k L_0 f)^2, \rho^2 \right)$ is the empty set. We see that in this asymptotic regime, the function $\text{Body}(x, y; \kappa_0, \kappa_1)$ in Eq. (20) reduces to

$$\text{Body}(x, y; 0, 0) = B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right)$$

Thus the regenerated organism has the shape of an ellipse with radii $L_0$ and $L_1$.

We note that $P(x, -y; 0, 0, 0, 0) = P(x, y; 0, 0, 0, 0)$ i.e. the normally regenerated planarian has a reflection axis on the line $y = 0$ which corresponds to medial-lateral symmetry [8]. Note however that $P(-x, y; 0, 0, 0, 0) \neq P(x, y; 0, 0, 0, 0)$ and this establishes the natural AP polarity of the regenerated planarian. It is an experimental fact that a worm trunk fragment resulting from the removal of head and tail, will always regenerate its head in the same orientation as the original worm, thus maintaining its AP polarity [8]. This is captured by Eq. (22) above.

In Fig. 3 five snapshots of $P_t(x, y)$ at different times $t = 0, 100, 1000, 2000, 10000$ are shown for three different initial conditions involving a portion of the trunk (a), the tail (b)
FIG. 3: (Color online) Snapshots of $P_t(x,y)$ obtained from iterations of Eq. (1) for the values of $t$ over the panels. Parameter values are $\kappa_0 = \kappa_1 = \kappa_2 = 0.01$ and $\Delta E = 0$, for three different initial conditions consisting of a planarian fragment taken from (a) the trunk, (b) the tail (b) and (c) the head. Other parameter values are: $L_0 = 5$, $L_1 = 4$, $R = 0.6$, $h = 0.001$, $f = 2/3$ and $\rho = 1/5$. Shown is the square region of the plane $\mathbb{R}^2$ comprised between points $(-5.5,-5.5)$ and $(5.5,5.5)$.

and the head (c) of the planarian. Normal regeneration of the planarian with the original AP polarity is observed in all three cases. We observe that the infinite time limit of the dynamics is well defined and attained after a certain long transient $\tau < 10000$, even when the process obtained from Eq. (1) is stochastic. Thus, the model correctly describes the experimental fact that regeneration usually results in the formation of a whole worm regardless of the injury that initiated it, preserving the AP polarity of the original [8].

B. Externally applied voltages $\Delta E \neq 0$ perturbing the AP polarity of the planarian

The planarian AP polarity is also regulated by bioelectric signals resulting from applying external fields [50, 51]. We model any applied external voltage drop by means of the parameter $\Delta E$. In Fig. 4 we show the impact of an $\Delta E$ in the regeneration process. If $\Delta E \in [-1,1/2)$ the natural polarity is reinforced and the planarian regenerates normally. For example, as shown in the figure, for $\Delta E = -1$ a normal regeneration of the planarian takes place, as in Fig. 3. However, if $\Delta E \in (1/2,3/2)$ the natural AP polarity is compen-
sated and double-headed worms arise as shown in Fig. 4 for the case $\Delta E = 1$.

Let us consider the limiting case in which all control parameters are zero except $\Delta E \in (1/2, 3/2)$. We have, from Eq. (19) by applying Eqs. (17) and (18) and the same mathematical facts that led us to Eq. (22) that Eq. (19) now reduces to

$$P(x, y; 0, 0, 0, 1) \equiv$$

$$= B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) \left[ 1 + \sum_{j=0}^{1} \sum_{k=0}^{1} B \left( \left( x - (-1)^j L_0 f \right)^2 + \left( y - (-1)^k L_1 f \right)^2, \rho^2 \right) \right]^{(24)}$$

Note that together with $P(-x, -y; 0, 0, 0, 1) = P(x, y; 0, 0, 0, 1)$ we have also the symmetry $P(-x, y; 0, 0, 0, 1) = P(x, y; 0, 0, 0, 1)$ i.e. there are two reflection symmetry axes on the lines $y = 0$ and $x = 0$, respectively. This corresponds to a regenerated planarian with two heads. The AP polarity is lost and the thus degraded positional information leads to a more symmetrical morphological attractor where, together with the medial-lateral symmetry, the regenerated planarian also has AP symmetry.

If $\Delta E > 3/2$ the natural AP polarity of the planarian is reversed and the head appears now in the posterior part and the symmetry leading to a two-headed worm is again broken as shown in the Figure for $\Delta E = 2$. Note that in this case, Eq. (19) reduces to

$$P(x, y; 0, 0, 0, 2) = B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) \left[ 1 + \sum_{k=0}^{1} B \left( \left( x + L_0 f \right)^2 + \left( y - (-1)^k L_1 f \right)^2, \rho^2 \right) \right]^{(25)}$$

In this equation we note that $P(-x, y; 0, 0, 0, 2) \neq P(x, y; 0, 0, 0, 2)$ so that again the AP polarity is regained, although in the reverse direction.

These observations fully capture the observations of classical experiments [50, 51]: Applying a external voltage drop leads to a compensation of the natural AP polarity of the planarian giving rise to double-headed worms and, when sufficiently high, to its reversal [8]. Thus, regeneration proceeds normally when the anterior cut faces the cathode (negative), while double-headed worms arise when the anterior cut faces the anode (positive). With the application of higher voltage drops, morphologically normal worms are generated, but whose AP polarity is reversed.
C. Gap junctions blocked with octanol ($κ_0$ large) or hyperpolarized with drug SCH-28080 ($κ_2$ large)

Proper gap-junctional communication ($κ_0$ small) has been shown to be a necessary requirement for keeping the AP polarity of the planaria during regeneration [8]. Let us now consider $κ_0$ large. Increasing $κ_0$ means in our model that the coupling/connectivity between planarian cells is weakened. Typically, for $κ_0 > 5$ the behavior is already similar to making $κ_0 \rightarrow \infty$ because of the saturation properties of the $B_κ$-function. This can be experimentally achieved by blocking the gap junctions of the planarian cells with octanol [8]. Then, regardless of the value of $ΔE$ (i.e. of the AP polarity), Eq. (19) reduces in this situation to

\[
\mathcal{P}(x, y; \infty, 0, 0, ΔE) \equiv \\
\mathcal{B} \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right) \left[ 1 + \sum_{j=0}^{1} \sum_{k=0}^{1} \mathcal{B} \left( (x - (-1)^j L_0 f)^2 + (y - (-1)^k L_1 f)^2, \rho^2 \right) \right]
\] (26)

This equation has the same form that Eq. (24) with the peculiar feature that it is here independent of $ΔE$. 

FIG. 4: (Color online) Snapshots of $P_t(x, y)$ obtained from iterations of Eq. (1) for the values of $t$ over the panels. Parameter values are $κ_0 = κ_1 = κ_2 = 0.01$ and the three different values of $ΔE$ indicated on each row. Other parameter values are: $L_0 = 5$, $L_1 = 4$, $R = 0.6$, $h = 0.001$, $f = 2/3$ and $ρ = 1/5$. Shown is the square region of the plane $\mathbb{R}^2$ comprised between points $(-5.5, -5.5)$ and $(5.5, 5.5)$. Note that other initial conditions lead to the same structures at $t$ large.
FIG. 5: (Color online) (a) Snapshots of $P_t(x,y)$ obtained from iterations of Eq. (1) for the values of $t$ over the panels. Parameter values are (a) $\kappa_0 = 10$ and $\kappa_1 = \kappa_2 = 0.01$ and (b) $\kappa_0 = \kappa_1 = 0.01$ and $\kappa_2 = 0.01$. ($\Delta E$ is taken as zero in both (a) and (b) although other values lead to the same regenerated pattern). Other parameter values are: $L_0 = 5$, $L_1 = 4$, $R = 0.6$, $h = 0.001$, $f = 2/3$ and $\rho = 1/5$. Shown is the square region of the plane $\mathbb{R}^2$ comprised between points $(-5.5, -5.5)$ and $(5.5, 5.5)$.

In Fig. 5 (a) we observe that for a large value of $\kappa_0$, keeping all other parameters small and $\Delta E$ arbitrary, a two-headed worm is regenerated. This, again captures experimental observations: regardless of the AP polarity, blocking the gap junctions of the body cells of a planarian fragment with octanol leads to two-headed worms [8, 52–54].

If a planarian fragment is exposed to drug SCH-28080, the depolarized cells of the planarian head become hyperpolarized [8]. This means that those cells become indistinguishable from that of the body and, therefore, trunk fragments regenerate into worms with no heads. This is achieved in our model by lowering the connectivity of the cells that are specific to the head, which is equivalent to increasing $\kappa_2$. In this case, in the limit $\kappa_2 \to \infty$, Eq. (19) reduces to

$$P(x, y; 0, 0, \infty, \Delta E) = B \left( \frac{x^2}{L_0^2} + \frac{y^2}{L_1^2}, 1 \right)$$

which is just the planarian body, Eq. (20) with no heads.

In Fig. 5 (b) we observe that a worm with no heads is regenerated when $\kappa_2$ increases keeping all other parameters small and $\Delta E$ arbitrary.
D. Gap junctions blocked with octanol ($\kappa_0$ large) and ventral nerve cords cut ($\kappa_1$ nonzero)

In all above situations the support of the function $P$, i.e. the function Eq. (20) has been reduced to just an ellipse, Eq. (23), by which we have modeled the shape of the body of a normally regenerated planarian. However, if the ventral nerve cords of the planarian are cut, thus reducing the connectivity of cells in the nervous system, this can be modeled by an increased value of $\kappa_1$. Furthermore, if the gap junctions of the cells are blocked with octanol, so that $\kappa_0$ is large, the cells lose positional information and, as a consequence, the planarian can grow along two orthogonal axis giving rise to a more symmetrical four-headed planarian after regeneration. This is shown in Fig. 6. We see that the support of the function $P(x, y)$ now consists of two ellipses intersecting orthogonally. Indeed, in the limiting case describing this situation we have that Eq. (19) reduces to

$$P(x, y; \infty, 1, 0, \Delta E) = \left[1 - B \left(\frac{x^2}{L_n^2} + \frac{y^2}{L_1^{-n}}, 1, \frac{1}{2}\right)\right] \times (28)$$

$$\times \left[1 + \sum_{m=0}^{1} \sum_{j=0}^{1} \sum_{k=0}^{1} B \left((x - (-1)^j L_m f)^2 + (y - (-1)^k L_1^{-m} f)^2, \rho^2\right)\right]$$

We now note that, besides the symmetries $P(x, -y; \infty, 1, 0, \Delta E) = P(x, y; \infty, 1, 0, \Delta E)$ and $P(-x, y; \infty, 1, 0, \Delta E) = P(x, y; \infty, 1, 0, \Delta E)$ we also have the symmetry $P(-y, x; \infty, 1, 0, \Delta E) = P(x, y; \infty, 1, 0, \Delta E)$ as well.

It is suggested from experiments that the ventral nerve cords transmit information along the planarian AP axis during regeneration [52]. It is also observed that a post-pharyngeal fragment treated with octanol and with the nerve cords partially amputated regenerates into a quadruple-headed worm [8]. Our model captures this experimental observation, both
in the above asymptotic limit and in the numerical simulation of the model, as shown in Fig. 6.

IV. DISCUSSION

We observe that increasing the $\kappa_0$ and $\kappa_1$ parameters, positional information is degraded, AP polarity being lost together as well as the lateral-medial-lateral axis (in the four-head case). Degradation of the positional information contained in $\mathcal{P}(x, y)$ occurs for weakened intercellular couplings: Individual cells have more freedom to choose between possible arrangements as reflected by the increased symmetry of the target morphology on the plane.

Fig. 7 summarizes the morphologies found in the simulations for the respective variations of the parameters. We see how symmetry is gradually increased with parameters $\kappa_0$, $\kappa_1$ and $\kappa_2$ from structures with just only a reflection symmetry axis (symmetry group $Z_2$) to others with four reflection symmetry axes (or two reflection symmetry axes and a fourfold rotation axis orthogonal to the plane, through the planarian center) with the dihedral symmetry group $D_8$ of the square. This is consistent with interpreting the parameters $\kappa_0$, $\kappa_1$ and $\kappa_2$ as 'thermal parameters' that weaken the coupling between cells: There is here an analogy with critical phase transitions in which the most symmetric phases are found at high temperatures, symmetries been broken at low temperatures. Symmetry breaking is associated in this work to having more detailed positional information, which constrains the cells to a less symmetrical target morphology.

With the mathematical methods presented in this paper, we can attempt theoretical answers to challenging experimental questions. The following one has been recently posed in [8]. We quote that reference: Take one planarian from each of two species with clearly different morphologies: S. mediterranea with a rounded head, and P. felina with a hammerhead. In this experiment, the neoblasts are killed off (by irradiation) in half of the S. mediterranea worm. Subsequently, live neoblasts from the P. felina worm are transplanted into the irradiated worm. If this chimeric worm is now cut, forcing it to regenerate its head, which head shape will be regenerated (round or hammer, or perhaps a hybrid, or perhaps regeneration will never cease as each set of neoblasts works to remodel the head)? [8]. We can adventure an answer to this question. Let $\mathcal{P}_0(x, y)$ and $\mathcal{P}_1(x, y)$ denote the target morphologies of the S. mediterranea and the P. felina worms respectively. Now, let $\kappa_2$ denote
the connectivity of the neoblasts of the S. Mediterranea worm. The limit $\kappa \to 0$ denotes optimal connectivity of the S. Mediterranea neoblasts and, hence, it leads to the robust regeneration of the S. Mediterranea worm. However, as $\kappa$ is increased, the connectivity of the neoblasts of S. Mediterranea is weakened and, in the regenerating organism those of P. felina have an increased connectivity for increased $\kappa$. In case that almost all neoblasts of S. Mediterranea have been replaced by those of the P. Felina, the connectivity of the former is infinitely weakened ($\kappa \to \infty$) since they become scarce in the organism. Reasonably, it can then be expected that the target morphology $\mathcal{P}(x, y)$ of the regenerating organism may have the form

$$\mathcal{P}(x, y) = \mathcal{P}_0(x, y)B_\kappa\left(0, \frac{1}{2}\right) + \mathcal{P}_1(x, y)B_{1/\kappa}\left(0, \frac{1}{2}\right)$$

From this expression we note that in the limit $\kappa \to 0$, we have, by using Eqs. (17) and (18), $\mathcal{P}(x, y) = \mathcal{P}_0(x, y)$ (S. mediterranea worm), while in the limit $\kappa \to \infty$ we obtain $\mathcal{P}(x, y) = \mathcal{P}_1(x, y)$ (P. felina worm). At finite, intermediate $\kappa$ values, we would obtain a small family of hybrid worms with the morphology given by Eq. (29). By our conclusions in Section II we see that $\mathcal{P}(x, y)$ is compactly supported and, therefore, it is a valid definition of the target morphology of the hybrid worm (i.e., it can be unambiguously said whether
the point \((x, y)\) belongs or not to the spatial region occupied by the worm). Note that many other expressions like Eq. (29) are possible. The mathematical methods described in this paper can be used in the mathematical modeling of these possibilities to adventure hypotheses that experiments may validate/falsify.

Our model for planarian regeneration has some obvious limitations:

- The functions appearing in the target morphology \(P(x, y)\) are not familiar ones, and the details of the microscopic mechanism giving rise to these compactly supported functions is unknown. In spite of some heuristic arguments given in Section II, the model describes the multicellular ensemble on a coarse-grained dynamical scale and it is explicitly assumed that there exists an underlying target morphology stored in the cells that the cells can somehow read. Thus, rather than describing this morphology as an emergent property [20], our approach is more in tune with recent proposals [33].

- The minimalistic model presented here for planarian regeneration is a mere caricature of what is actually observed. Although it qualitatively captures a subset of the most prominent experimental observations, many exceptions are not taken into account. For example, it is known [8] that very thin cut fragments sometimes regenerate with double heads although never double tails [16] and that very long worms sometime spontaneously produce two heads after fissioning [55]. These possibilities are not yet described by the model. We believe, however, that, with some ingenuity, the model can be extended to account for these observations as well.

- The model is two-dimensional and, therefore, the dorsal-ventral polarity [8] is not taken into account. We note however, that the model can be extended to account for this situation (at the cost of more computational resources) by injecting random spheres rather than disks and by extending the elliptic shapes here considered to ellipsoids.

V. CONCLUSIONS

In this work we have solved the problem of how an arbitrary target morphology \(P(x, y)\) [32] [34] can be obtained as a robust attractor in the long-time limit of a continuum percolation process, so that a connected, compact structure, is obtained at every time step. We believe that this result constitutes a viable general theory for epimorphic regeneration in
biology in which an organism replace damaged parts of their body by exact replicas of the
original with help of a mediating blastema, whose growth is here modeled by the percolation
process.

We have applied our theory to the qualitative modelling of planaria regeneration [8–
15]. Our model is lattice-free and, therefore, does not assume any specific topology of the
multicellular ensemble, although the strength of the connectivity between cells is explicitly
taken into account by means of effective control parameters that can be experimentally
operated. In turn, these parameters have an impact on the target morphology: When the
connectivity is weakened, the emerging attractor has a different structure, reflecting, in
some cases, the degradation of the positional information as the freedom of the multicellular
ensemble is increased. For example, if the gap junctions of the cells are blocked and the
connectivity of the cells in the nervous system is weakened, four-headed planaria can be
formed out of a trunk fragment. The model also describes AP polarity and its loss or even
its reversal by acting on a fragment of the planarian trunk through externally applied fields.

The theory may also be generalized to describe some experimental morphallactic phe-
nomena. For example, if $\mathcal{P}(x,y)$ is made to depend on the slow time variable $t$ as well, but
the compact support of the function remains constant at every time, dynamical processes
of reorganization and rescaling of organs within an organism can also be described without
changing its overall external shape.

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