Model of morphogenesis with repelling signaling

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Abstract

The paper is devoted to a conceptual model of cell patterning, based on a generalized notion of epigenetic code of a cell determining cell states. We introduce the concept of signaling depending both upon the spatial distance between cells and the distance between their cell states (s-distance); signaling can repel cells in a space of cell states or attract them. The influence of different types of repelling signaling on cells evolution is considered. Stabilizing signaling, i.e., monotonically decreasing with s-distance signaling causes the restoring of cell states after perturbations; destabilizing signaling, i.e., a monotonically increasing one, causes the appearance of pairs of cells with alternating cell states (one close to “head” state and another to “tail” state) .The non-monotonic (in s-space) signaling splits the cells into groups. The model shows that different types of signaling may provide different types of cellular patterns. General principles for applying this model to complex cellular structures are discussed.

Introduction

Morphogenesis is a process of pattern formation in living organisms, which consists of multi-level cascades of regulatory signaling. There is a long history of modeling of pattern formation in morphogenesis, including continuum models, cell-based models (such as cellular automata and the agent-based models), and their combinations known as hybrid models (Hwang et al., 2009; Zhang et al., 2012; Lehotzky et al., 2019). The type of the modeling depends on the question adressed, which can be very precise or rather general, and on the goal of the modeling, which usually belongs to 3 main tasks: to test (or to generate) a scientific hypothesis, to make predictions on the outcome of the process(es), to test the influence of variation of the parameters on the stability of the system or its behavior.

A huge set of continuum models are based on the assumption that the body or its parts supports a gradient of the cell substances (morphogens), governing a formation of different patterns (Meinhardt, 2013, and references therein; Zhang et al., 2012; Prusinkiewicz, Lane, 2013). However, it is very difficult to describe the formation of many different structures with well determined morphology by morphogen gradients only. That is why, in the

current studies, authors supplement morphogen gradients theory with different types of additional effects for modeling pattern formation.

The continuum model in (Köthe, Marciniak-Czochra, 2013) proposes receptor-based model with multiple steady states, and shows how bistability and hysteresis in the kinetic system explain pattern formation.

The cell-based models which are based on the modeling of the behavior of individual cells, consider a finite set of determined cell states, a set of hypothesized rules for the transition of cell states, and a set of rules for cell-to-cell interactions. These models aim to explain how the behavior of individual cells governs the development of tissues. In these cases, the theoretical background for the suggested rules is taken from biological experiments or from published observations (Hwang et al., 2009; Zinovyev et al., 2013; Lehotzky et al., 2019). A vast set of these works model pattern formation based on the stem cells behavior. For example, (Tosenberger et al., 2015) proposes a model where stem cells influence the tissue growth by sending signals that ensure cell survival. These signals force the cells originating from the stem cell to inhabit a certain area around the stem cell, while the stem cells move according to the signals. This combination allows cells to form different tissues depending on the distances from the stem cells, assuming that the size of tissues also depends on the strength of the signal emitted by stem cells. The model explains the formation of different tissues, e.g., eyes, head and tail in simple organisms like Planaria. In the review (Lehotzky et al., 2019) one can find many examples of modeling of stem-cell-driven development of neural systems. For example, the simulations based on the model of neurosphere growth (Sipahi and Zupanc,2018; Zupanc et al.,2019), have predicted that the transformation of neural stem cell into a tumor stem cell is a major determinant of the brain tumorigenesis.

Finally, the hybrid models (Murray et al., 2013; Bessonov et al., 2013) demonstrate the power of such a research strategy by explaining the formation of various complex patterns.

However, it can be seen that different models based on completely different hypotheses for the same phenomena works equally well, thus leaving a question still open. One of the best illustrations is the modeling of the phenomena of regeneration. Thus, many works describe regeneration based on the morphogen gradient theory: the gradient increase on the boundary of the cut tissue governs cells to restore the original structure (Meinhardt, 2013). At the same time, the other studies, such as (Bessonov et al., 2015), explain how the cell patterns can regenerate themselves by proposing a mechanism dependent on cell

memory, allowing the cells to remember the former shape of the tissue and then to perform the morphogenesis dependent on the remembered signal.

In the present work we explore a model, which describes the pattern formation and regeneration using several basic assumptions that were stated in our previous works (Minarsky et al., 2017, Wang et al., 2020). The main proposed conjectures are:

1) the existence of an epigenetic code of a cell, which can be realized as a distribution of certain substances on the surface of the cell. Any distribution can be understood as some matrix $M=\left(m_{ik}\right)$, where one index refers to the position on the cell surface (for example, the sector number of its surface), and the other index refers to the type of substance. Elements of the matrix $\left\{m_{ik}\right\}$ refer to the number of molecules of type i in sector number k. A matrix $\boldsymbol{M}$ of a cell is also called its spectrum.

2) the existence of linear transformations of cell spectrum in a course of cell events which correspond to linear operators, the action of which corresponds to 6 proposed cell events. (Thus, the set $\{\boldsymbol{M}\}$ of possible states of the cell can also be considered as some space of state vectors on which these operators act).

3) the existence of an influence of the spectra of cells on their neighboring cells which we called epigenetic signaling (ep-signaling), manifested in a change in the spectrum M of a given cell under the action of the spectra of surrounding cells and leading to the appearance of the calculated spectrum M^S after signaling.

4) the existence of predetermined rules that allow given M and M^S to determine the particular cell event which will occur for a cell and to calculate (using the operators) the spectra of a cell (or 2 cells, in the case of division) that may arise as a result of this cell event.

Here we consider the application of this model to a simplified case of 1-dimensional cell tissue, meaning that it grows only along one axis, and discuss the influence of various types of ep-signaling (stabilizing and destabilizing monotonic, non-monotonic) and various strength of ep-signaling on the growth and development of the tissue. When belonging to the cellular automata models, our model enables considering a continuous range of cell states. Its main advantage is that it tests the concrete implementation of the epigenetic code hypothesis, which allows explaining several types of cell fate decisions (such as cell differentiation, tissue formation, cancer transformation, regeneration, cell death) and consequent processes of pattern formation in the frame of a unique model.

As a final point, we discuss the extension of this model to the multidimensional case, which will be able to provide a vast range of realistic patterns.

I Model description

Let us consider that the body of an organism is represented by one line of cells and that it grows only along one axe.

1.**Cell matrices (epigenetic spectra)**

An introduced epigenetic code of a cell is a complex matrix, corresponding to molecules distribution on the cell surface (Morozova and Penner 2015, Mynarsky et al. 2018, Wang et al. 2020). Here we consider some kind of linear characteristic of this matrix, which we call a vector of cell polarization. By this we obtain a vector ***m*** with two components (m_1, m_2). These components may correspond, for example, to the numbers of a fixed type of molecules on two halves of the cell surface (we calculated such characteristics in a paper devoted to morphogenetic software (Bessonov et al. 2019)); or they may be other parameters, obtained from surface molecules distribution.

Let us consider the norm of the vector ***m***: $|m|=|m_1|+|m_2|$.

We will assume that in all cell events $|m|=const$, which means that the total number of all coding molecules constituting the epigenetic code of any cell is the same. In this case the only parameter which changes at each cell event, is the v*alue of cell polarization* p:

$p = m_1 - m_2$. Thus, all possible cell states differ by p.

Let us assume that the norm $|m|=1$. Consequently,

$$m=½\cdot(1+p;1-p),-1\le p\le+1 \qquad (1)$$

For each two cells

$m_1-m_2=½\cdot(1+p_1;1-p_1)-½\cdot(1+p_2;1-p_2)=½\cdot(p_1-p_2;p_2-p_1)$ and

$¿m_1-m_2\vee¿¿p_1-p_2\vee.$

We will call a cell with $p>0$ a cell with right polarization, and a cell with $p<0$a cell with left polarization. The distance between cell states (polarizations),i.e., $|¿p_1-p_2\vee$, is called the s-distance.

Next we will assume that *a cell state* is defined by the polarization of its spectrum.

2. **Operators of cell events.**

According to the general conception of operators on cell events (Wang et. al 2019), let us consider a reduced form of these operators acting on vectors of cell polarization. As for all cell events the norm |***m***|=constant, we have $|Am|=¿m|$ for all operators A.

This means that the action of an operator A results in a *shift d* of the polarization of a cell:

$$Am=½\cdot(1+p+d;1-p-d). \qquad (2)$$

If ***m*** is written as a column, the operator A may be considered as a matrix:

$$¿1+d/2;d/2\vee¿$$
$$¿-d/2;1-d/2\vee. \qquad (3)$$

We suggest the existence of two operators of division $\boldsymbol{A}_1$ and $\boldsymbol{A}_2$ for right and left descendant of a cell, with the polarization shifts d_1 and d_2. We assume that d_1 and d_2 have opposite signs. Furthermore, for the time being, we assume $d_1=-d_2=d$.

In this case $A_1=A$, $A_2=A^{-1}$, where A has matrix (3), which means the symmetry of the two descendants.

It is convenient to measure the polarization of a cell in the units of the shift d, i.e., to describe it by the value $n=p/d$. The value of n(not an integer in the general case) is approximately equal to the number of divisions necessary for a non-polarized cell to acquire this polarization (or more precisely, to the number of applications of the operator A, the right or the left one, depending on the sign of n). As $¿p\vee\leq 1$, we have

$$¿n\vee\leq N \qquad (4)$$

where $N=1/d$ is the maximum possible value of polarization in the units of$n$ (numbers of cell divisions).

In the future, we will consider polarization in the units of n. The operators of the right (left) division change it by $+1(-1)$.

3. Signaling

In (Wang et al., 2020) we have presented three types of developmental model, namely, the minimal, normal, and direct models. Here we will discuss a direct model in which signaling directly changes the state of the cell and its descendants.

Since a change in spectrum means a change in polarization, the result of signaling in the general case will be:

$$n_i^S=n_i+\sum_k w_{ik}, \qquad (5)$$

where n_i^S is the polarization of the cell i after signaling, w_{ik} is the contribution to polarization of the i-th cell due to the influence of the k-th cell, and summation is carried out over all neighboring cells. Under the conditions of the one-dimensional problem n_i^S for each cell will be:

$$n_i^S=n_i+w_L+w_R, \qquad (6)$$

where w_L and w_R mean the influences of left and right neighboring cells on the i-th cell.

The *influence* w_{ik}depends on the states of the interacting cells, that is, the polarizations n_i and n_k, and on the distance between these cells. We will understand $|w_{ik}|$ as a *value of*

signal between the cells i and k. According to the direct model we assume zero influence on polarization in the absence of difference between states of the cells, i.e. zero s-distance. In this case the already mentioned symmetry of the left and right directions of polarization is respected. In particular, if we create a chain of absolutely identical cells, then this group does not start any changing under the influence of mutual signaling (due to the absence of a chosen direction of change). Therefore w_{ik} is an odd function of $(n_i - n_k)$.

Thus, we may write:

$$n_i^S = n_i + \sum_k h_i \cdot s_{ik} \cdot (n_i - n_k), \qquad (7)$$

where $s_{ik} = s(n_i - n_k, |r_i - r_k|)$ is an even function of the differences in cell polarizations $(n_i - n_k)$ and of spatial distance between cells $|r_i - r_k|$, which rapidly decreases with the growth of the latter. The value $h_i = h(n_i)$ is a positive constant corresponding to the *sensitivity* of the cell introduced in (Wang et al., 2020)

Equation (7) is a simplified analog of the equation presented in (Wang et al., 2020), namely:

$$M_i^S = M_i + \sum_k h_i \cdot s_{ik} \cdot (M_i - M_k), \qquad (8)$$

describing the cell spectrum M_i^S after signaling.

Note all terms in (7), which are proportional to $(n_i - n_k)$ do not give input to the norm $¿ m_i^S \vee ¿ \vee m_i \vee ¿$.

Next we will make an important assumption that the signaling should be a repelling one. This means that the term w_{ik} leads to the increasing of $(n_i - n_k)|$, that is, of the s-distance between the corresponding cells. Thus, we assume that the coefficients $h_i \cdot s_{ik}$ in (7) are positive.

4. Rules of cell response to signaling

We propose the following set of rules for the cell response to the signaling.

Rule 1 (signaling implementation rule)

A cell under the action of signaling passes from a state with polarization n to a state with polarization n^S, according to (7). If $|n^S| > N$, then the cell passes into the closest final state, corresponding to $n^S = +N$ or $-N$.

Rule 1 guarantees for a cell at every step the occurrence of an internal cell event, that is, a change of its spectrum, produced by signaling.

Rule 2 (division restriction rule)

If signaling exceeds a certain threshold value E:

$$¿ m^S - m \vee ¿ \left| p^S - p \right| = ¿ n^S - n \vee \cdot d > E, \qquad (9)$$

then the cell cannot divide.

The value of the positive constant E will be specified later (see (20), (24)).

Given (7), the condition for the restriction on division can be written in the form:

$$\left| \sum_k h_i \cdot s_{ik} \cdot \left(n_i - n_k \right) \right| > e \ , \qquad (10)$$

where $e = E / d$.

However, this restriction rule does not account for the case of possible mutual compensation of the strong effects from two neighbor cells. We can make the condition (10) (which may be called the *weak restriction rule*) more stringent:.

$$\sum_k ¿ h_i \cdot s_{ik} \cdot \left(n_i - n_k \right) \vee ¿ e \ . \qquad (11)$$

Condition (11) may be called the *strong restriction rule*.

Note that for the application of a weak restriction rule the cells should be receiving stronger asymmetric signaling than in the case when a strong restriction rule is considered.

Rule 3 (rule of arrest in a boundary state).

We say that a cell is near the boundary state, if:

$$\left| n^S - N \right| < 1 \quad \text{or} \quad ¿ n^S + N \vee ¿ 1 \qquad (12).$$

In this case the division does not occur.

Rule 3 corresponds to the fact that a totally differentiated cell or a cell in the final state is usually unable to divide. Later we will show that within the framework of the model the boundary state of a cell is the final one.

Rule 4 (rule of apoptosis)

A cell undergoes apoptosis if the following rule is fulfilled

$$\left| \sum_k h_i \cdot s_{ik} \cdot \left(n_i - n_k \right) \right| > a, \qquad (13)$$

where $a > e$ is a chosen constant.

This is a *weak rule* of apoptosis. Analogous to (11), there is a *strong rule* of apoptosis:

$$\sum_k ¿ h_i \cdot s_{ik} \cdot \left(n_i - n_k \right) \vee ¿ a. \qquad (14)$$

Rule 4 reflects the fact that a cell will apoptize if its environment emits too strong signaling.

Rule 5 (division rule)

In all situations that do not fall under the rules of 2,3,4 *the cell divides, and the right and left descendants acquire the vectors* $A_1 m^S$ *and* $\boldsymbol{A}_2\boldsymbol{m}^S$ *and polarization:*

$$n_R = n^S + 1, n_L = n^S - 1. \qquad (15)$$

5. Evolution of one-dimensional chain of cells (growing "worm")

Next, we will consider the application of the above scheme to the description of the evolution of some cellular system. For that, we will choose some parameters of the model. First, for simplicity, we assume that the cell sensitivity does not depend on its state (polarization of its spectrum), that is, we take h (n) = constant = 1.

Second, we consider interaction only between neighboring cells, that is, w_{ik} and s_{ik} are either equal to zero or to the largest possible absolute value, and are independent of the distance between the cells $|r_i - r_k|$. Thus, we consider that all non-zero signals $w(x)$depend only on the s-distance between neighboring cells:

$$w(x) = s(x) \cdot x, s_{ik} = s(x), w_{ik} = w(x), \qquad (16)$$

where $x = n_i - n_k$. The absolute value $|x|$ is the s-distance between interacting cells, $s(x)$ is a positive even function. And thus $w(x)$ is an odd function: for each pair of cells $w_{ik} = -w_{ki}$.

Let an isolated cell have a polarization n_0, which is far enough from the boundary values N or $-N$. According to change of polarization by ± 1 after division and formulas (7) (16), the first two rounds of signaling and divisions will cause the following changes:

$$n_0 \to n_0 = (n_0 - 1; n_0 + 1) \to (n_0 - 1 - w(2); n_0 + 1 + w(2)) \text{ ¿}$$

$$\text{¿ } (n_0 - 2 - w(2); n_0 - w(2); n_0 + w(2); n_0 + 2 + w(2)), \qquad (17)$$

where → means signaling and ¿ means division (Figure 1).

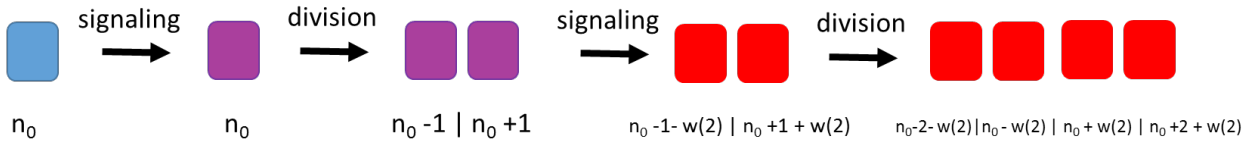


Figure 1. Scheme of the first 2 steps of development of the cell chain.

Now let us suppose that the first two divisions generate an equidistant chain, with distance between neighbors $x = 2$, i.e.

$$(n_0 - 3; n_0 - 1; n_0 + 1; n_0 + 3). \qquad (18)$$

Comparison with (17) gives:

$$w(2)=w(x=2)=1. \qquad (19)$$

It makes also sense to assume that the signaling between two daughter cells of an initial single cell does not stop division according to rule 2. Hence $w(2)\le e$, and we get a necessary condition for the division threshold:

$$e\ge 1. \qquad (20)$$

Let us consider, taking into account (19), the action of signaling on (18):

$$(n_0-4\,;n_0-1\,;n_0+1\,;n_0+4). \qquad (21)$$

Note that the signals on internal cells from their neighbors is compensated. If we assume the condition of weak restriction on division (10), after the next division we obtain:

$$(n_0-5\,;n_0-3\,;n_0-2\,;n_0\,;n_0+2\,;n_0+3\,;n_0+5¿. \qquad (22)$$

Note that every cell in a chain (21) is divided. If the condition of strong restriction (11) is assumed, then, depending on the division threshold e, we obtain the same situation as in (22) or the division of internal cells is prohibited and we obtain:

$$(n_0-5\,;n_0-3\,;n_0-1\,;n_0+1\,;n_0+3\,;n_0+5¿. \qquad (23)$$

Thus (compare with (18)) we again obtain an equidistant chain that has grown because a shift in the polarizations was caused by signaling (s-shift) and the boundary cells got divided.

Let us find a necessary condition for the division threshold. Each inner cell receives a signal w_L+w_R (see(6)), where both signals have module equal to $w(2)=1$. For division to be prohibited, according to (11), it is necessary that $¿w_L\vee+|w_R|>e$, or, given (20):

$$1\le e<2. \qquad (24)$$

Thus, if the threshold for signaling e lies between the values of the module of one and two “normal signals”, then the models with weak and strong restriction rules have explicit different behaviors. The “normal signal” refers to the signal that occurs between two neighboring descendants of a cell, that is, $w(2)=1$.

We will assume that condition (24) is satisfied and analyze the models with both weak and strong restrictions on division. The model with strong restriction rule does stop the division of inner cells and provides a growing “worm” due to the division of terminal cells. Thus, one gets a chain of cells with normally equidistant spectral positions (s-positions), like (18) or (23), which is extended by 2 after each step (signaling + division) (Fig 2). The model with weak restriction rule does not stop the division of inner cells (Fig 3). This process will continue until the terminal cells will stop changing or dividing

due to the rules 1 and 3, that is, they will acquire boundary states close to $n=\pm N$. The entire length of the chain will have a fixed number of cells, approximately equal to N.

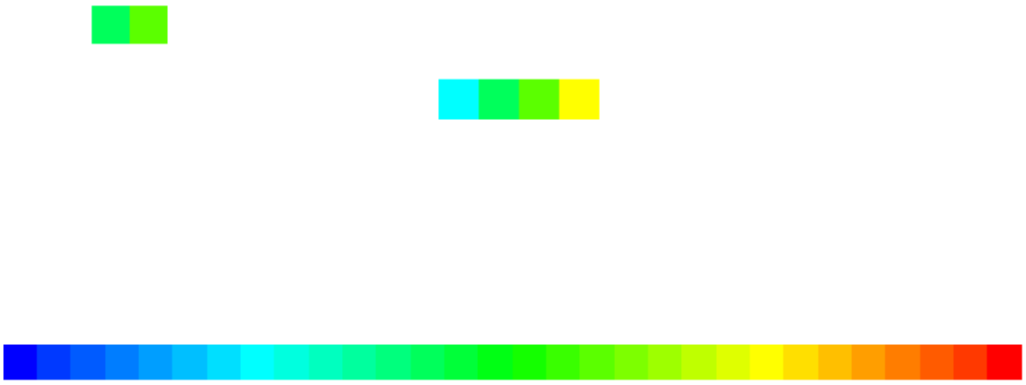
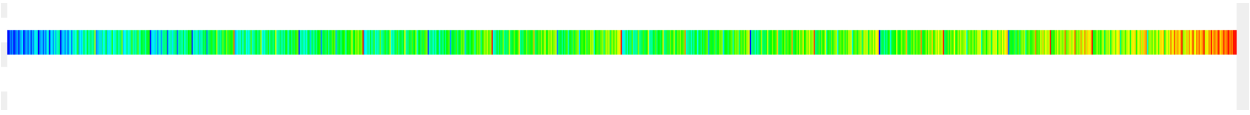


Figure 2. The normal “worm” (with strong division restriction rule) which has grown up to the final states on both edges, with equidistant cell s-positions along the chain. Parameters: $e=1.8, a=6, N=30, w(2)=1$. Number of steps (signaling +division) from initial cell S= 15. A changing of color corresponds to a changing of polarization of a cell. Deep red color corresponds to $n=+N$,deep blue color corresponds to $n=-N$ (which can be understood as a “head” and a “tail” correspondingl

A

B

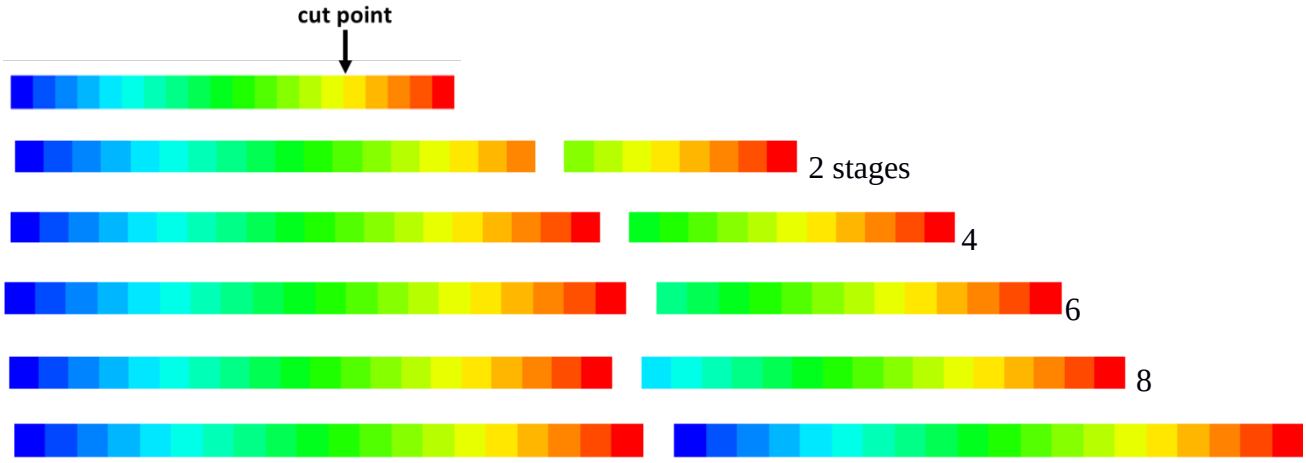


C

Figure 3. The abnormal growing “worm” with weak division restriction rule, allowing divisions of inner cells. Parameters: $e=2, a=6, N=12, w(2)=1$. The following steps are shown: $A¿5; B¿6; C¿12$.

Also it can be noted that if the chain of cells is cut, that is two inner neighboring cells are spatially separated at a distance annihilating their mutual signaling, then these cells will become the “head” and “tail” of two new partial chains (Fig 4). This means they will become the right and left dividing terminal cells, from which the chains of cells will grow to the required final length N with terminal cells with polarization $+N$ and $-N$

respectively.



The two full size “worms”

Figure 4. The development of two parts of the “cut worm”. The left part is restoring by rebuilding its “head”, the right side – by rebuilding its “tail”.
Parameters: $e=1.8, a=6, N=20, w(2)=1$.

II. Analysis of the stability of the model.

Cells in Final State and Stem-Like Cells

All cells in the stabilized "worm" stagnate, that is, they do not divide and do not change due to signaling. However, cells in the boundary state cannot be modified under any change of external conditions, that is, it is impossible to create a signaling that pushes them out of this boundary state. Thus, these cells are analogues of the most specialized cells in the final state. The remaining cells of the “worm”, being inside, stagnate (remain unchanged), but, when being placed on the edge (for example, by cutting the “worm”, Fig 4), they begin to divide, producing a cell in the same state (thus reproducing themselves) and a more differentiated one (closer to the edge). This behavior is consistent with the behavior characteristic of stem cells. Thus, all cells of the “worm”, except the boundary ones, can be considered as different types of stem-like cells: when they are placed inside a spectrally ordered (s-ordered) chain they are governed by “normal” signaling (leading to stagnation), while, when they are at the boundary, signaling at the edge provokes their division.

Stabilizing and Destabilizing Signaling.

Let us consider a normal s-ordered chain and an inner cell k within it. Let us define the s-distances $x=n_k-n_{k-1}>0$ and ¿$n_{k+1}-n_k>0$. The cell k receives the total signal $s=w(x)-w(y)$. If the cell is in equilibrium, the signal s is 0, and a strong rule of division restriction forbid the cell to divide: $|w(x)|+|w(y)|>e$.

Let us consider different variants of cell position violations.

1. Spatial violation.

If a distance to a neighbor cell increase, the value of a signal from it will decrease. This means (due to our assumption of repelling nature of signaling) that the original cell will begin a s-shifting under the action of total signal towards the distant cell. As soon as the prohibition of division is removed due to a decrease in value of the received signal, the cell will begin division in the direction towards the farthest neighbor.

2.S-distance violation.

Suppose now that neighbor cells are located at minimal possible spatial (normal) distances, but $x \neq y$. If we take into account only the signaling on the given cell, then after it the s-distances between the cell and its neighbors will become:

$x' = x + w(x) - w(y)$ and $y' = y + w(y) - w(x)$.

If w(x) is an increasing function, the sign of the signal $w(x) - w(y)$ coincides with the sign of $x - y$, and the cell will begin to decrease its s-distance to a closer neighbor and increase it to a more s-distant one. Next, the s-repulsion from a more s-distant neighbor can shift the cell from the region between the states of neighbors. The opposite situation of decreasing w(x) means that a shift of s-position leads to equalization of s-distances to neighbors.

Finally, $w(x) = const$ means zero total signal $(w(x) = w(y))$ and absence of changes in cells s-positions. So, we can conclude that:

if the odd function $w(x)$ characterizing signaling (see (16)) is a decreasing one (while positive for $x>0$) , then the non-dividing s-ordered chain of cells

$\ldots n_{k-1} < n_k < n_{k+1} < \ldots$ *tends to be equidistant under the action of signaling.*

We call the decreasing of $w(x)$ the phenomenon of *stabilizing* signaling.

Note that this is quite natural, since the s-repulsion between spectrally close cells is greater than between s-distant ones.

If $w(x)$ is increasing, then the s-ordered chain first demonstrates a pairing, that is, the system is grouped into pairs of cells with a small s-distance inside the pair, and then the chain loses ordering and exhibits complex unstable behavior in the state space and s-shift of cells till the final conditions is observed.

We call the increase of $w(x)$ a *destabilizing* signaling (Fig 5).

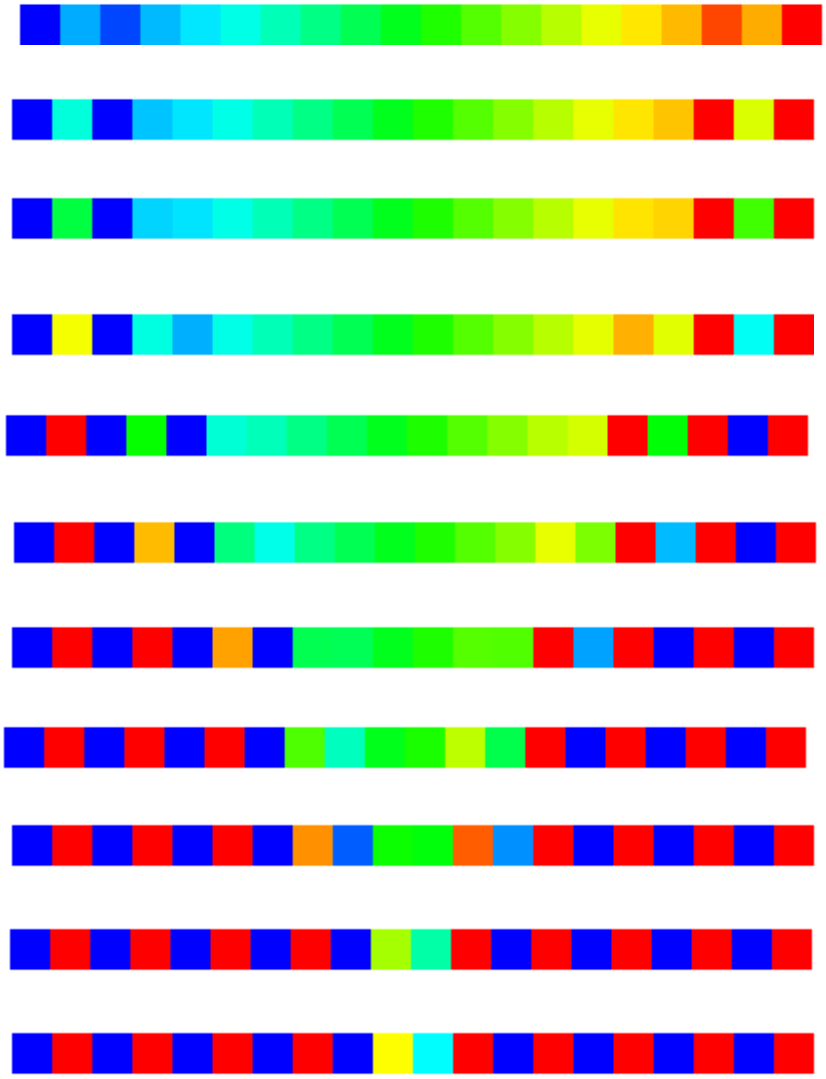


Figure 5. The evolution of the grown chain under destabilizing signaling. As a result of a spectral non-equidistance in any concrete place, the sequence of cells gets into alternative terminal positions (head and tail). In this example a small initial non-equidistance appears at the ends of the grown "worm" because N is not an integer. Parameters: $e=1.8, a=6, N=20, w(2)=1, w(x)=w(2)+k\cdot(x-2), k=+0.05$.

For the case of constant signaling (more precisely, $w(x)=const\cdot sign(x)$, and if we follow (19), then $const=1$), any non-dividing s-ordered chain of cells demonstrates stagnation, that is, the invariance of the polarizations of all (at least inner) cells.

Now we find out whether the normal s-distance between the cells (that is, $|x|=2$) is stable. Of course, this question makes sense only for stabilizing signaling, leading to the equidistance of the s-ordered chain.

3. An equidistant s-ordered chain with abnormal s-distance x between cells.

The *total* signaling on inner cells is equal to zero, and therefore either these cells divide with a decrease of their mutual s-distance (until $|x|$ is large enough and $|w(x)|<e/2$), or the cells do not change their state. Consider now the terminal cell (for definiteness, the right

one). If it is not close to the boundary position, then under the action of signaling it will shift to $w(x)$, and then its two descendants will be in s-position shifted by $w(x)-1$ and $w(x)+1$ with respect to the initial maternal cell polarization.

The intercellular s-distances will be $x'=x+w(x)-1$ and 2. Note that if $x>2$then $w(x)<w(2)=1$ and therefore $x'<x$; similarly, if $x<2$, then $x'>x$. Thus, the average s-distance in a chain as a result of division of the terminal cells, shifts to normal, that is, to 2. Summing up:

if cell divisions occur in an s-ordered chain of cells with stabilizing signaling, the chain tends to acquire equidistant distribution of cell states with normal s-distance between neighbor cells.

The state of a system with a normal s-distance between all cells is an attractor in stabilizing signaling, but it does not necessary occur. If the terminal cells have already reached the boundary state and are not dividing, the s-distances can be stabilized at a constant value $x\neq 2$, (if $|w(x)|>e/2$ and no inner divisions occur). This means that the total number of cells in such an established chain is different from N(namely, approximately $2N/x$). However, there seems to exist no natural mechanism for the occurrence of a "too rarefied" (in the s-space) or "too compressed" "worm".

A cell with impaired spectrum inside an s-ordered chain of cells

Let us consider the situation of a cell that violates s-ordering; for example, $n_k>n_{k-1}$ and $n_k>n_{k+1}$. Such a situation can be created, for instance, by planting a "head" cell from the right-polarized part of a chain in its left- polarized "tail". This situation can occur spontaneously during destabilizing signaling, when, due to s-repulsion from a more s-distant neighbor, the polarization of the cell k will get outside the interval $[n_{k-1};n_{k+1}]$. In such a situation, the sign of the signaling from both neighbors is the same, therefore there is *no difference* in the effect of the weak and strong conditions on the arrest of division (the absolute value of the sum of signals is equal to the sum of the absolute values). The state of the cell continues to be pushed out and away from the environment (the cell planted in the "tail" becomes more and more "head").

In the case of destabilizing signaling, the absolute values of both signals from cell neighbors increase and the process stops only when the cell reaches the final state. In the case of stabilizing signaling, the absolute value of these (pushing out) signals decrease, and (if the condition $w_L+w_R<e$ is achieved), the planted cell will begin to divide inside its environment.

Note that the right neighboring cell (with index $k+1$) is itself in a position that violates the order ($n_{k+1}<n_k$ and $n_{k+1}<n_{k+2}$) and it will be pushed by signaling to the position of the final "tail" state. Possible ongoing divisions and shifts due to signaling will lead to *the appearance of* 2 *consecutive "worms" as a result of planting: from the left "tail" cell to the newly formed "head" (initially planted cell) and from the new "tail" (right neighbor of the planted cell) to the right "head"*(Fig 6).

The lengths (number of cells) of the two stabilized "worms" depend on the ratio of the threshold of division $e$with the rate of decrease of the signaling function $w(x)$. In particular, if $w(x)$ decreases quickly enough, then the formation of two "full-grown" "worms" is possible: the length of each chain is equal to the length of the initial chain before planting of a cell inside it.

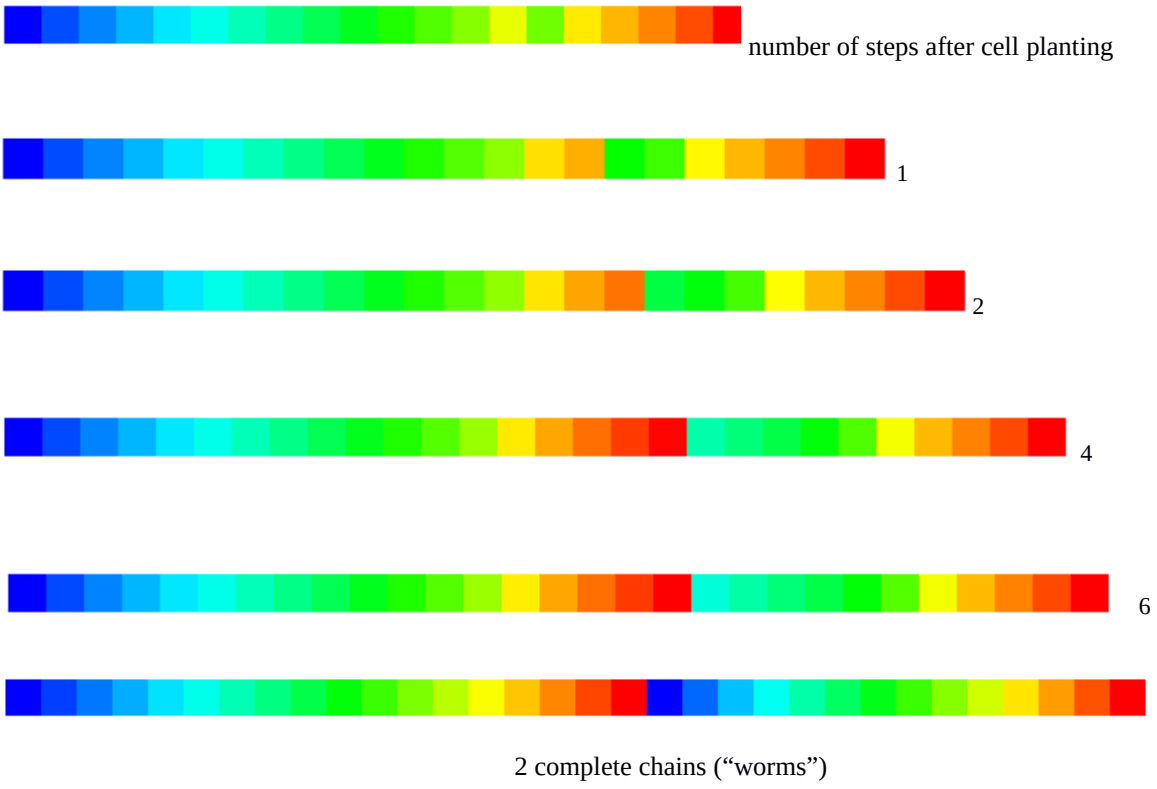


Figure 6. A cell with impaired spectrum is planted inside an ordered chain. The more "tail-shifted" cell being planted in a "head" part of a "worm", undergoes s-shifts and divisions and eventually forms a tail of the right "worm". The left neighbor of the planted cell forms a head of the left "worm". Parameters:
$e=1.9, a=6, N=20, w(2)=1, w(x)=w(2)+k\cdot(x-2), k=-0.05$

An example which illustrates this situation is the experiment with micromeres of an embryo of sea urchin (Gilbert, 2013). When these cells are inserted into the embryo in out-of-order position, they initiate the neighboring cells to form an entoderm, and later a mesoderm.

Discussion

The significance of simplifying assumptions

Now we will discuss how significant are the simplifying assumptions which were made, and their influence on the outcome of the model.

1.A signal value

The choice of $w(2)=1$, which ensured the equidistance of a chain of 4 cells (see (18)), is not obligatory. Let us consider an arbitrary $w(2)$. A polarization of terminal cell that appeared after division have s-distance 2 from its neighbor and next will be shifted by $w(2)$ under signaling. After the next division, a new terminal cell will acquire s-position which differs from the polarization of previous terminal cell by $w(2)+1$. Thus, as a result of each division of a terminal cell, the chain is spectrally extended by $w(2)+1$ and increases by 1 cell. The average intercellular s-distance thereby tends to the value $x_S=w(2)+1$. It is established by the stabilizing signaling as the same distance between cells throughout the chain, if no internal divisions occurred during chain growth. In general, *in the stabilized "worm" the established average distance will be*

$$x_S \le w(2)+1 , \qquad (25)$$

where strict inequality means the absence of internal divisions during growth. The condition for this absence is:

$$w(2) \le e < 2\,w(x_S) . \qquad (26)$$

The left inequality in (26) allows the division of (non-final) terminal cell, while the right one in the case of strong restriction rule (11) prohibits division within a stabilized chain. Condition (26) generalizes the condition (24). A comparison of (25) and (26) gives the necessary condition on w(x) for prohibiting the divisions of inner cells of a chain in the case of stabilizing signaling:

$$w(2) < 2\,w(w(2)+1). \qquad (27)$$

2. Cell sensitivity and signal strength

It is clear that the assumption that cell sensitivity is constant ($h(n)=const$) is not very significant unless it affects division. If $h(n)$ varies smoothly enough along a chain, this will influence a value of s-shift produced by signaling, and will affect only the rate of establishment of the equidistance in the case of stabilizing signaling. But if the sensitivity changes strongly enough to allow divisions of inner cells (see (11)) in an ordered chain, then the following subsequent steps will occur:

1)In the regions with the smallest $h(n)$the divisions take place.

(Note that the cells with an abnormally low sensitivity may represent analogues of cancer cells: they continue to divide in any environment, since they perceive a signal below the threshold for division arrest).

2) In these areas where divisions occur, the average s-distance between cells decreases**.** It is important to note that *a decrease in the average s-distance always occurs when internal cells divide.* This is explained by the fact that s-positions of the marginal cells of a group do not change (or change slightly due to signaling), while the number of cells within a group increases.

3) The inhomogeneity of s-distances generated by cell divisions will be gradually compensated by stabilizing signaling, which leads to a redistribution of s-distances and to the establishment of equidistance over the entire chain with a lower overall average x.

(It is important to note that *the mechanism of stabilizing signaling does not depend on the non uniformity of the sensitivity* $h(n)$.)

4) As a result, a longer chain (i.e. a chain with more cells) stabilizes at a decreasing average s-distance$x$ such that the increased value of the signal $w(x)$ will stop divisions everywhere (regardless of the value of n and the corresponding sensitivity $h(n)$).If x_S is an average s-distance, the condition for the establishing of the steady-state is:

h_{min} ¿)¿ $e/2$. (28)

We may propose an additional change in the model by introducing a concept of *intrinsic intensity of the emitted signal* $I(n)$. In this case, the resulting signaling will depend not only on the sensitivity of a receiving cell and the function w(x) of the mutual s-distances of this cell and its neighbors, but also on the neighbor's state, expressed as $I(n)$.

For this case, instead of equations (5) and (7), we will have the equation:

$$n_i^S = n_i + \sum_k h(n_i)\cdot I(n_k)\cdot w(n_i - n_k) \quad (29)$$

As it was already shown, the movement to equidistance means the alignment of the s-shifting signals for inner cells from the left and right sides.

If $I(n)=const$, then setting $x=const$ follows from $w(x)=const$.

If $I(n)$ changes from cell to cell, then the intercellular s-distances should satisfy

$$I(n)\cdot w(x) = const \quad (30)$$

for the equality of signal values from cell neighbors and chain stability.

Since the signaling is stabilizing (w(x) is a decreasing function), we obtain the statement: *The ordered chain of cells is stabilized in such a way that in the region of the cell states with more intense repulsive signaling, the s-distance between cells will be greater.*

Naturally, the intensity $I(n)$ may change not smoothly; in such cases several thresholds of signal intensity $I(n)$ may exist and influence cell differentiation and the formation of tissues or organs. It is clear that even a little change in n may cause the significant change in I(n), with the consequent strong changing of s-distances. Among many facts illustrating such thresholds of signal intensity $I(n)$ we can cite, for example, the influence of anchor cell of C.elegans on the line of its neighbor cells in the process of vulva formation: the cell closest to the anchor cell undergoes specific division with production of inner vulva cells, the two cells neighboring to the first one (and thus being little farther from the anchor cell) undergo different set of divisions resulting in formation of extra vulva cells, while the other cells in the line of the cells-ancestors become hypodermal cells (Gilbert, 2013).

3. The spectrally shifted cell division

In the model, the polarization shifts for the left and right descendants were chosen equal modulo d (and thus, $A_1 = A_2^{-1}$). The removal of this assumption and the choice $d_L \neq d_R$ leads to *shifted division*, that is, after appropriate normalization, the descendants will diverge by s-distance 2, but both will be s-shifted by an equal value n_D. The division rule (see (15)) is replaced by:

$$n_R = n^S + 1 + n_D, n_L = n^S - 1 + n_D. \qquad (31)$$

Shifted division leads to different growth rates (in the spectral space) of the ends of the chain. The “head” and “tail” grow to final states in a different number of steps and have a different average s-distance between cells, which is gradually leveled off by stabilizing signaling (Fig 7). After a considerably long duration of development with s-shifted division the chain will acquire both head and tail terminal states (Fig 8).

The only "danger" in a shifted division is a possible violation of the s-order in the chain. To prevent this, the shift n_D should not be too large. Namely: let us consider that the shift n_D goes to the left, and x is the current s-distance from the right terminal cell to its neighbor. After a shift due to the signaling, this distance becomes $x + w(x)$, and after division, the distance from the left descendant to the left neighboring cell will be: $x + w(x) - 1 - n_D$. The condition for non-violation of the s-order will be:

$$|n_D| < x + w(x) - 1. \qquad (32)$$

For the case of $n_D$shifting to the right, the same condition is obtained by analyzing the division at the left end. The fulfillment of (32) for all positive x provides a sufficient condition for non-violation of the order. A necessary condition is the fulfillment of (32) for $x = x_S$. Considering (25) we obtain:

$$|n_D| < w(2) + w(w(2)+1) \qquad (33)$$

as a necessary condition for non-violation of the order in the absence of inner cells divisions.

a)

b)

Figure 7. The cell chains with *spectrally shifted cell* division. Strong division restriction rule, parameters $e=1.8, a=6, N=40, w(2)=1, w(x)=w(2)+k(x-2), k=-0.05$, number of steps $S=20$. a) left shift $n_d=-0.9$, only left edge is formed. b) right shift $n_d=+0.9$, only right edge is formed. Deep blue color corresponds to $n=-N$, deep red color corresponds to $n=+N$.

number of stages S= 1500

S= 3000

S= 6000

S= 10 500

Figure 8. Slow evolution of grown asymmetric "worm" to the s-equidistant final state as a result of stabilizing signaling. $N=20, k=-0.05, n_d=-1.8, a=6, e=1.5$.

4. Non-monotonic signaling

Until now, we assumed the monotony of the function $w(x)$, which led either to the stabilization of cells at equidistant positions (decreasing $w(x)$), or to instability (increasing $w(x)$). Of course, the dependence of signaling on the s-distance between cells can be more complex. Let us consider the following interesting case of non-monotonic signaling: in the region of s-distance after division ($x=2$) and in the region of established average values x_s

(see (25)), the cells have a signaling slowly growing with s-distance (destabilizing); next when the s-distance between cells decreases, the signaling begins to increase significantly (Fig.9).

Since the timing of increasing instability is long (because of the slow growth of w(x)), the situation will develop as follows:

first the chain grows to a maximal length, having an average s-distance x_S; next the cells in the region of destabilizing signaling are compressed into groups (clusters) with a small distance x_{int} between cells and a large external distance x_{ext} between groups, until the system as a whole is stabilized at distances and signals such that the signal is leveled off for all cells: $w_i = w_j$ (Fig 10).

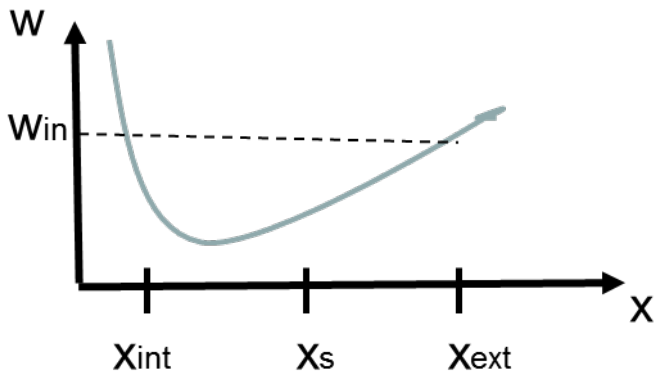


Figure 9. Nonmonotonic signaling leading to the formation of cell clusters with an internal distance between cells x_{int} and an external distance between clusters x_{ext}. In this case, intercellular signaling is set at the level $w_i = w(x_{int}) = w(x_{ext})$.

The numbers of cells in the resulting clusters depend on the details of the occurrence of instabilities in the growing chain. They can be regulated partly by variable signal intensity $I(n)$ (see (29) and (30)).

200 steps

800 steps

1600 steps

After 15000 steps.

Figure 10. The groups formed under non-monotonic signaling. $N=30; e=1{,}5;$ $w(x)=w(2)+k(\exp(2-x)-2)(\exp(2-x)-1); k=0{,}05; w(2)=1; a=12.$ The initial groups have size 2, then size 4, and then they merge in bigger groups. The groups are quasi-stable.

Note that signaling inside the group $w¿$ stabilizes the group. Though the signaling between groups is a destabilizing one, big size of these groups makes them quasi-stable. The time of a group stability exponentially increases with the group size.Also, it can be seen that if the number of cells in the cluster is redundant and their intercellular distances are small, the signaling in the group will lead to apoptosis when $w¿$ (Fig.9), if the strong condition of apoptosis (14) is chosen.

However, if a cell with sufficiently distant spectrum is planted in the cluer, it violates the order, and apoptosis occurs even under the weak condition (13). If the formed cluster groups can be considered as analogues of tissues, then the model illustrates a possible signaling mechanism of tissue protection from those cells of a body which are “strangers” to a given tissue.

5. *Pulling signaling*

Let us briefly consider the situation for a model with pulling signaling, that is, w(x) has the opposite sign to x and $¿x+w(x)\vee¿\vee x\vee$. The general properties of this model will be as follows:

1) Lack of final states.

There is always an attracting (pulling) signaling that pulls a cell from a boundary state.

2) A tendency of spectral contraction. If

$$w(2)\leftarrow 1, \qquad (34)$$

then the system of cells is pulled together into a group with continuously decreasing s-distance; the distance between the terminal cells decreases after each step (signaling+division).

3)The properties at stabilizing signaling. In the case of attracting signaling, the criterion for stabilization is the opposite to the situation with the repulsing one. If $¿w(x)\vee¿$ increases with the growth of s-distance$¿x\vee¿$(the variant of strictly linear signaling $w=-s\cdot x$ also belongs to this case), then the signaling stabilizes the inner cells in equidistant positions. In this case, the right end cell is shifted by signaling by $w(2)<0$, then, after division, the right end is in position $1-¿w(2)\vee¿$ and the process repeats. If the condition (34) is not satisfied, then the “worm”, comprised of such signal-attracting cells, can grow in the right direction until its “head” will be at a boundary s-position near $n=N$. However, the division

process does not stop there. After some time, the cell that reaches the right edge and stops dividing will be pulled by signaling to the left, the conditions for the applicability of rule 3 of stopping the division will be violated and hence new cells will appear. The conclusion is that:

Attracting stabilizing signaling creates a chain of equidistant cells that continues to divide throughout the chain. When condition (34) is satisfied, this chain will contract in the space of states into a growing set of identical cells. If this condition is violated, the chain will be uniformly filled by the cells within the entire set of states from $n=-N$ *to* $n=+N$*; as the number of cells grows, the s-distance between neighboring cells decreases*.

Signaling between cells will decrease.

4) The properties at destabilizing signaling. If $¿w(x)\vee¿$ decreases with the growth of the s-distance $¿x\vee$, the system is unstable and cells are pulled together into groups of identical cells. At the same time, the values of signaling between them increase, and if the apoptosis threshold is overtaken (condition (13) or (14)), then these cells will undergo apoptosis.

For any type of attracting signaling, any planted cell, regardless of its initial state, is drawn into the set of cell states of the system, described above.

6. Different rate of division and displacement due to signaling. Non-discrete time

Until now, our model has considered that cell events *division* and *signaling* have equal duration, but this requirement is not necessary. The s-positions of all cells in a cell chain can noticeably change during a time period coinciding with a division of one cell. Mathematically, this can be taken into account, for example, by introducing a fixed interval of division time and continuous s-shift due to the signaling. This can be done by taking a rate of this s-shifting instead of the values of the s-shift (as it was done before) in the corresponding formulas.

Thus, if we assume that:

a) the cell that began to divide continues this process until completion, regardless of changes in external signaling,

b) the time duration of one division is taken per unit of time,

c) in these units, the speed of motion in the state space caused by signaling is expressed by the function w(x) used earlier, as:

$$\frac{dn_i}{dt}=\sum_k h_i\cdot w_{ik}(n_i-n_k). \quad (35)$$

Then it is possible to process all further calculations as in the discrete case, and all the results of the model will remain qualitatively valid. The differences concern only the

details of the continuous change of the cells spectra (states) due to the signaling, and, possibly, slight changes in some inequalities containing w(x). For example: the rates of s-shifts caused by signaling should be selected as the average ones over the time of cell division(s).

Moreover, it is necessary to take into account that:

d) during the division, the s-positions of the dividing cell changes: its signaling towards the left neighboring cell monotonously changes from signaling of the n_0 s-position at the beginning of division ($t=t_0$) to the signaling of the n_0-1 s-position at the end of division ($t=t_0+1$); and towards the right neighboring cell, from signaling of the n_0 s-position at the beginning to signaling of the n_0+1 s-position at the end.

In fact, paragraphs a), b) c) and d) describe a method for constructing a continuous model that yields approximately the same results as the discrete model does.

The extension of the one-parameter model to the multidimensional case

We can consider different parameters that encode a cell by its position in different chains of s-states. Some of these parameters can be linked to the spatial directions of cell polarization (i.e., the uneven distribution of some substances on a cell surface involved in signaling), while others can be independent on cell geometry (however, signaling by such "scalar" parameters can be included in the rules determining a direction of division).

One can also notice the possibility of dependence of cell signaling upon time. For example, a stabilizing signal in a chain may switch on at a particular stage of development thus fixing the states of cells inside the order.

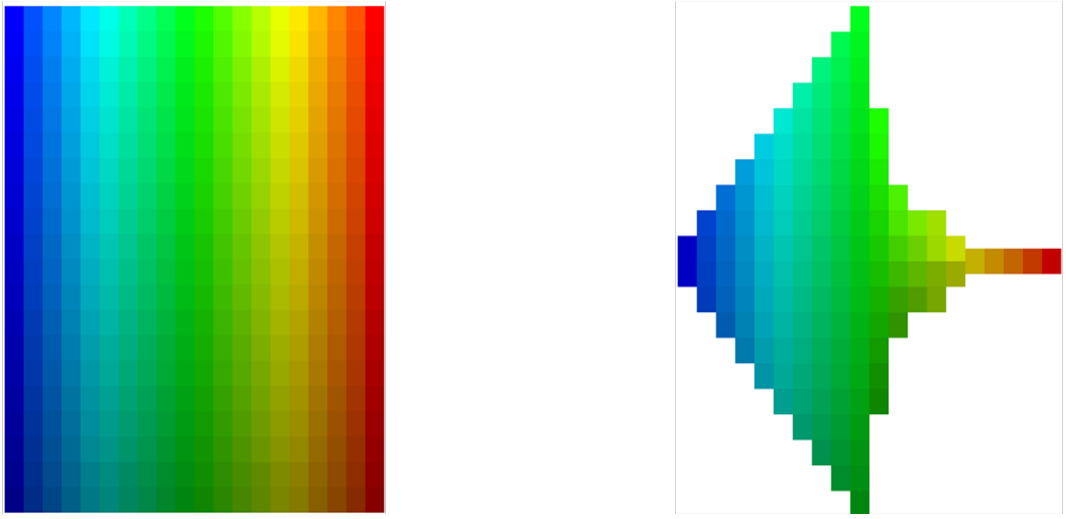
As a conclusion, we can propose the following principles for a multiparametric model describing morphogenesis:

1. A process of development (morphogenesis, embryogenesis) may be considered as the simultaneous or sequential acquisition by the cells of states in different spectral chains.
2. The total state of a cell is determined by its positions in many one-parameter spectral chains corresponding to the changes in the state of the cell by each parameter.
3. Mutual linkage of developmental chains is possible: that is, a change in the position of a cell in a one-parameter chain can affect the signaling and different threshold values in another chain. For example, the achievement of a final state by a cell within one chain may influence its evolution in other parameters and chains. In the illustration, presented on Fig.11, the threshold of division is influenced (lowered) in cells coming close to a tail.
4. The signal received by the cell influences its division. Signaling on different parameters provides different contributions to this effect; in particular, each of these contributions can

have different effect on cell division in different spatial directions. Each cell division may change the position of a cell in a given one-parametric chain of development in a certain way.

5. The absence or presence of an influence between chains results in this or that pattern of a set of cell states in the space of parameters. If the divisions in different 1-parametric chains occur correspondingly in different spatial directions, different spatial cell patterns will appear.

An example of two 1-parametrical chains with and without interaction is represented in Fig11, A, B.



A **B**

Figure 11. The illustrations of 1-parametric signaling in a 2-dimentional model.

For the 1st parameter, the red and blue colors mark fully specialized cells in the final states (e.g., “head” and “tail” correspondingly), while yellow and green cells can be viewed as analogous to stem cells or cells in intermediate states. The darker or lighter color mark the states of cells in the chain of the vertical dimension (e.g., cells on the dorsal or ventral sides of the organism). A) A case without interaction between two 1-parametrical chains. B) A case with interaction between two 1-parametrical chains. On the left side the threshold of maximal lightness is influenced (lowered) in the cells coming close to a head, while on the right side the threshold of division is influenced (lowered) in cells coming close to a tail. Parameters for two chains: $e_1=1; e_2=e_1+c'\cdot n; a_1=a_2=12; N1=20; N_2=N_1-¿\ c\cdot n; w2+k\cdot(x-2); k=-0.05; c=c'=0$ (in A); $c=1, c'=0.1$(in B).

Conclusions

We present and analyze the conceptual model based on the epigenetic code hypothesis which combines the discrete changes of cell states in a course of cell division with continuous change of cell sates under signaling (epigenetic signaling). This 1-parametric model enables to reach the outcome of various patterns for various cases, which may be understood as various types of cell fate decisions, together with the capabilities of a self-tuning of the stabilized order of cell states in each particular case after small perturbations. At the same time, in the situation of strong perturbations of an order of cell states the model displays a biologically relevant behavior of a tissue (chain of cells), for example, the process of regeneration.

Because of these properties of the model, its concrete realizations with appropriately chosen set of parameters can be used for examining several types of cell fate decisions (such as cell differentiation, tissue formation, regeneration, apoptosis (cell death) and, probably, cancer transformation) influencing pattern formation.

We show the avenue for constructing the multiparametric (in a space of cell states) and three-dimensional model as a combination of mutually influencing 1-parametric 1-dimensional chains.

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