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5 **A CELLULAR AUTOMATON TO MODEL  
 6 THE DEVELOPMENT OF PRIMARY SHOOT  
 7 MERISTEMS OF ARABIDOPSIS THALIANA**

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22 Development of organisms is a very complex process in which a lot of gene networks of  
 23 different cell types are integrated. Development of a cellular automaton (Ermentrout and  
 24 Edelshtein-Keshet, *J Theor Biol* **160**:97–133, 1993) that models the morphodynamics  
 25 of different cell types is the first step in understanding and analysis of the regulatory  
 26 mechanisms underlying the functioning of developmental gene networks. A model of a  
 27 cellular automaton has been developed, which simulates the embryonic development of  
 28 shoot meristem in *Arabidopsis thaliana*. The model adequately describes the basic stages  
 29 in development of this organ in wild and mutant types.

30 *Keywords:* Cellular automaton; mathematical model; development of shoot meristems;  
 31 parameters of model; period of division.

32 **1. Introduction**

33 Postembryonic development of the above-ground part of higher plants depends on  
 34 the functioning of the primary shoot apical meristem (SAM), a dynamic structure  
 35 that forms leafage, flowers, and scape. The formation of the primary SAM occurs at  
 36 the earliest stages of embryogenesis. Furthermore, the functioning of the promeris-  
 37 tem triggers development of the germ layers and at that time a complex meristem  
 structure is being formed (Fig. 1).<sup>2</sup>

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2 I. R. Akberdin et al.

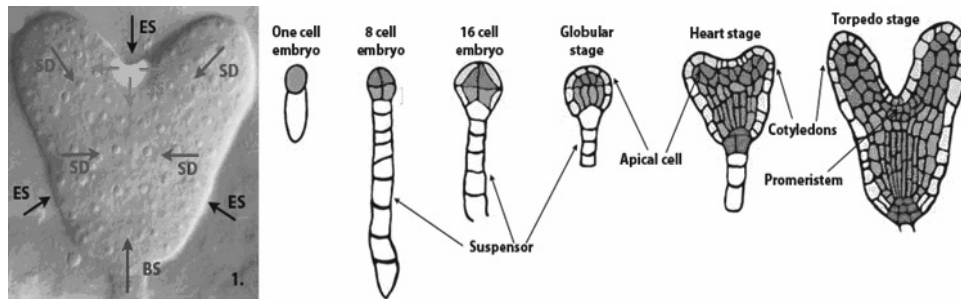


Fig. 1. (a) Directions of the model's hypothetical signal distributions in heart-stage embryo tissues: ES is External Signal, SS is Stem Signal, SD is Signal of Differentiation, and BS is Basal Signal. (b) Developmental stages of a plant embryo with the indication of organs and tissues significant to the model.

1 The cells of the apical and basal parts have different expression of different genes  
 in a 16-cell embryo. No further development of embryos is possible without SAM,  
 3 or at least their apical parts.<sup>3</sup>

4 Cellular automata have been extensively used to model a wide range of  
 5 processes.<sup>1,4</sup> In general, a cellular automaton is loosely defined as a collection  
 of cells with states that change their state depending on at least the states of  
 7 neighboring cells. The positional relationship of von Neumann<sup>5</sup> cellular automaton  
 is rectilinear in two dimensions; i.e. a two-dimensional (2D) grid, as formed by  
 9 the intersection of two sets of mutually perpendicular lines, producing cells. The  
 set of cells define a cell space, this space being of infinite size. The neighborhood  
 11 (a grouping function) is part of the state-transition function, and defines for any  
 cell, the set of other cells upon which the state of that cell depends. Biological  
 13 systems are particularly suitable for analyzing by cellular automata.<sup>1</sup> In particular,  
 cellular automata models have been used for a vascular tumour growth on a Voronoi  
 15 lattice,<sup>6</sup> to simulate the immune dynamics of particular diseases,<sup>7,8</sup> to model shape-  
 space interactions,<sup>9</sup> and finally for simulation of development of the multicellular  
 17 organisms known as morphogenesis.<sup>10</sup> The literature on modeling morphogenesis  
 is extensive. Held<sup>11</sup> provides a good summary. Most current models for morpho-  
 19 genesis are based on purely continuum approaches<sup>12</sup> or discrete cellular automata.  
 Here, the authors introduce cellular automaton to model for development of the  
 21 primary SAM in embryogenesis of the *Arabidopsis thaliana*. Modeling covers the  
 initiation of SAM, the formation of the SAM complex structure and its further  
 23 functioning. Here, the embryo is described as a 2D array of cells, the rates of divi-  
 sion of which depend on the cellular environment. The cells in the model may  
 25 receive and, depending on the cell type, produce signals that should be received by  
 other cells in the model. The biological meaning of signals is the concentration of  
 27 certain diffusing substances, or morphogenes, which provide a specific influence on  
 the cell.

## 1      2. Methods and Algorithms

3      The model assumes that the stage and rates of division of an individual cell depend  
 5      on the influence of signals that are coming from other cells of embryo. Under the  
 7      model, four biologically meaningful signals, which unambiguously simulate the mor-  
 9      phodynamics of cell tissues at the generally accepted level of abstraction, were  
 11     selected (Fig. 1). They are the following: the External signal, the Basal signal, the  
 13     Stem signal and the Signal of differentiation. The External signal is an equivalent  
 15     of real substances produced by cells of epidermis. In the real embryo apical-basal  
 17     pattern of development is controlled at the early step by a special organ, a sus-  
 19     pensor. It is likely that the suspensor has an influence on the cells of embryo  
 21     through certain signals; and in the model this influence is defined by the basal  
 23     signal. The Stem signal formed in pluripotent cells of the meristem is a biological  
 25     analog of the cytokinin hormone.<sup>13</sup> This signal influences on the rate of division.  
 27     Lateral differentiated cells produce signal of differentiation. A biological analog of  
 29     the differentiation signal influencing on the rate of division is such hormone as  
 31     auxin.<sup>13</sup>

33     All the embryo cells in the model can be classified according to the type of the  
 35     signal they produce:

- 19     (1) *Null*. These cells mean empty space that neither produce signals nor divide.
- 21     (2) *NullEx*. Cells of the epidermic layer. They produce External Signal (ES) and  
 23     are represented around the entire perimeter of the embryo. They do not divide,  
 25     but they are supposed to surround cell embryos in the model.
- 27     (3) *NullSus*. Cells of the suspensor. They produce Basal Signal (BS) and are con-  
 29     fined to the lower part of the embryo. There are two NullSus cells in the model.
- 31     (4) *Lateral*. These cells imitate “differentiated” cells, which produce Signal of Dif-  
 33     ferentiation (SD).
- 35     (5) *Promeristem*. Cells of the embryo meristems. These cells produce Stem Signal  
 (SS) and are confined to the upper part of the embryo. During development,  
 they change into L2meristem and L3meristem type cells.
- (6) *Transit*. Cells near the meristem. They also produce SD, but have the highest  
 rates of division.
- (7) *L2meristem*. Cells of the meristem. They are situated in second layer from  
 the epidermic layer of the upper part of the embryo. These cells produce SS.
- (8) *L3meristem*. Cells located one layer down from the L2meristem type cells.  
 These cells produce SS.

Each cell has a set of internal parameters to characterize its state:

- 37     (1) Type. Cell type.
- 39     (2) ES0, BS0, SS0, SD0 are the values of the signals produced by the cell.
- (3) ES, BS, SS, SD are the values of the signals accepted by the cell.

4 *I. R. Akberdin et al.*

- 1 (4)  $K_{ij}$  is the characteristic of cell state at position  $(i, j)$  calculated as the ratio of  
 2 SS to SD. Each type of cell has own range of  $K$ . At the current point of time,  
 3 the cell is influenced in the state characterized by the parameter:

$$K_{ij} = \frac{\text{StemSignal}_{ij}}{\text{DifferentSignal}_{ij}}.$$

- 5 (5)  $T_{ij}$  is the period of cell division, which depends on the current value of the  
 6 characteristic  $K_{ij}$ .  
 7 (6)  $Tp_{ij}$  is the number of iterations after the last division of the cell at position  
 8  $(i, j)$ .

We calculate the overall influence of all the cells on the cell at position  $(i, j)$  by the following formulas:

$$\text{ExternSignal}_{ij} = \alpha_{ij}^E \sum_{k,m} \text{ExternSignal0}_{km} e^{-n/R_E},$$

$$\text{BasalSignal}_{ij} = \alpha_{ij}^B \sum_{k,m} \text{BasalSignal0}_{km} e^{-n/R_B},$$

$$\text{StemSignal}_{ij} = \alpha_{ij}^S \sum_{k,m} \text{StemSignal0}_{km} e^{-n/R_S},$$

$$\text{DifferentSignal}_{ij} = \alpha_{ij}^D \sum_{k,m} \text{DifferentSignal0}_{km} e^{-n/R_D}.$$

9 The summation is performed over all the cells of a particular tissue, including the  
 10 epidermis layer and the suspensor;  $(k, m)$  is the position of the cell, the influence of  
 11 which was taken into account;  $n = \text{abs}(k-i) + \text{abs}(m-j)$ , where  $i, j$  are the consid-  
 12 ered cell coordinates,  $k, m$  are the affected cell coordinates;  $R_E, R_B, R_S, R_D$  are the  
 13 constants which characterize penetrance for ES, BS, SS, and SD, respectively. The  
 14 model assumes that time in which a distribution of signals reaches steady state is  
 15 much less than characteristic time of cell cycle. In this sense we can say that system  
 16 reaches steady state instantly. Also this model assumes that while generated signal  
 17 by the cell achieves to other cell located on the distance “ $n$ ”, this signal will lose  
 18 part of the own power in each cells between them. In general it can be showed with  
 19 this equation  $\frac{d}{dn}S = -\lambda S$ , where  $S$  is the concentration of the signal. Solution of  
 20 the equation is  $S = S_0 e^{-\lambda n}$  that we show in above formula, where  $\lambda$  replaces by  
 21  $\lambda = 1/R$ .  $\alpha_{ij}^E, \alpha_{ij}^B, \alpha_{ij}^S, \alpha_{ij}^D$  are the constants which characterize the sensitivity of the  
 22 cell to a certain type of signal. This constant expresses cells receptivity to signal,  
 23 in other words the model assumes that signals have secondary transmitters that  
 24 increase or decrease effect. This constant depends only on the type of the cell.

25 The qualitative behavior of the function  $T_{ij}$  is shown in the Fig. 2 according to  
 the biological position:

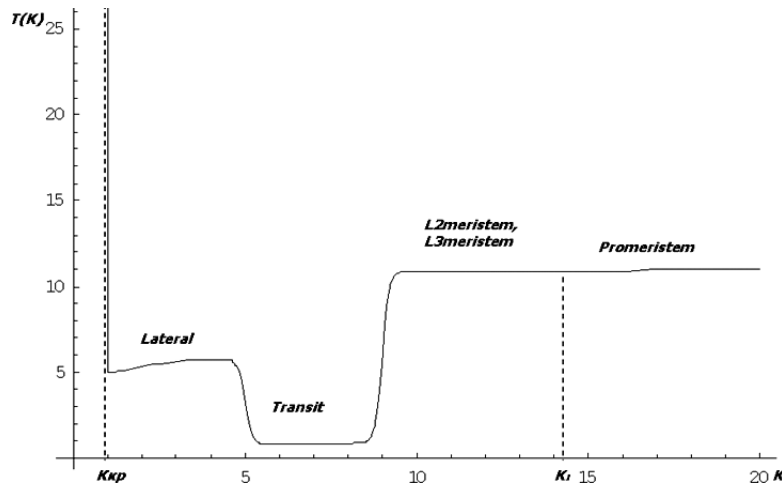


Fig. 2. Dependence of division periods on the parameter  $K$  for different cell types.

1 As can be seen from Fig. 2, the embryo meristem cells (Promeristem,  
 2 L2meristem, L3meristem) in the tissue divide slower than the others; the  
 3 Transit type cells divide very quickly; the rates of division of the Lateral  
 4 type cells are medium. When the parameter  $K$  takes on the value  $K_{kp}$ , the period of division  
 5 becomes infinity and the cells will not divide anymore. When the parameter  $K$   
 6 takes on the threshold value  $K_1$ , the Promeristem type cells divide into L2meristem  
 7 and L3meristem cells. This dependence was revealed by using the function:

$$f(x) = \frac{1}{1 + e^{\frac{x-\mu}{\sigma}}},$$

8 where  $x$  is a value of  $K_{ij}$ ,  $\mu$  is equals to critic values of  $K_{ij}$  and  $\sigma$  equals to 0.1. If  $T_{ij}$   
 9 is not an integer, the function  $T_{ij}$  is rounded in accordance with the standard rules  
 10 of adjustment. To ascertain whether or not a cell is undergoing division,  $Tp_{ij}$  and  
 11  $T_{ij}$  are compared. At the next iteration, the value  $Tp_{ij}$  is increased by one for each  
 12 non-dividing cell. If  $Tp_{ij} > T_{ij}$ , division into two daughter cells is ascertained. For  
 13 each daughter cell,  $Tp_{ij}$  is equal to zero. Noteworthy, if  $T_{ij}$  increases more rapidly  
 14 than  $Tp_{ij}$ , the cell will not divide. The model is used pseudo parallel simulation  
 15 for calculation of signal concentration, selection of cell type and for selection of  
 16 division direction, but directly procedure of division occurs in series and sequence  
 17 of division is selected in a random way.

### 19 3. Results

20 The developed cellular automaton adequately describes the developmental mor-  
 21 phodynamics of primary shoot meristem of *Arabidopsis thaliana* in embryogenesis  
 (Fig. 3).

6 *I. R. Akberdin et al.*

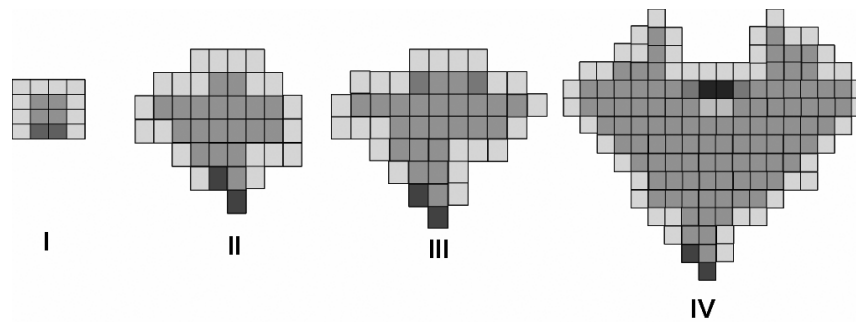


Fig. 3. Developmental stages of plant embryo modeled by the cell automaton: I — 16 cell embryo; II — globular stage; III — heart stage; IV — torpedo stage.

1 By varying the parameters of the cellular automaton, we have successfully mod-  
 2 eled the following mutations described in the literature:

- 3 (a) the meristem forms but cannot cope with the auxin flowing in from the germ  
 4 layers, and so it differentiates. This leads to formation of the joined germ layers  
 5 and as a consequence to the stoppage of the plant development;<sup>14</sup>  
 6 (b) the meristem forms, and so do germ layers, but no regulation is exerted on the  
 7 meristem cells population. As a result, the meristem cells differentiate and the  
 8 meristem zone shrinks.<sup>2,15</sup>

9 Visualization of the cellular automaton (Fig. 4) was created that allows simulating  
 of the process of development.

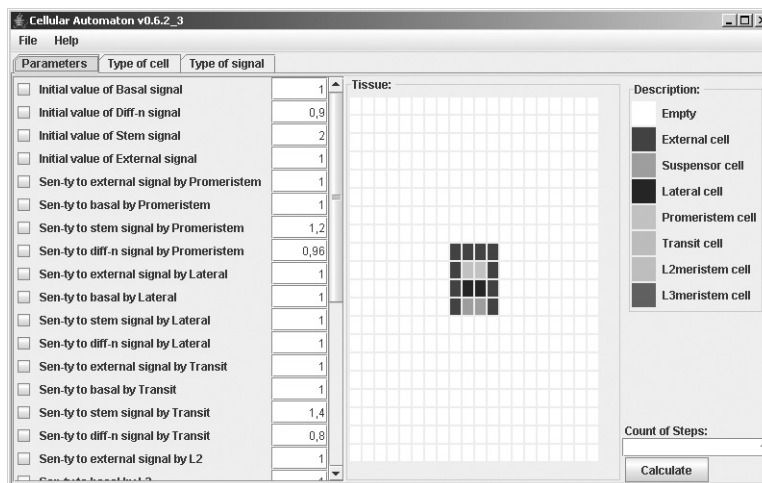


Fig. 4. Visualization of developed cellular automaton.

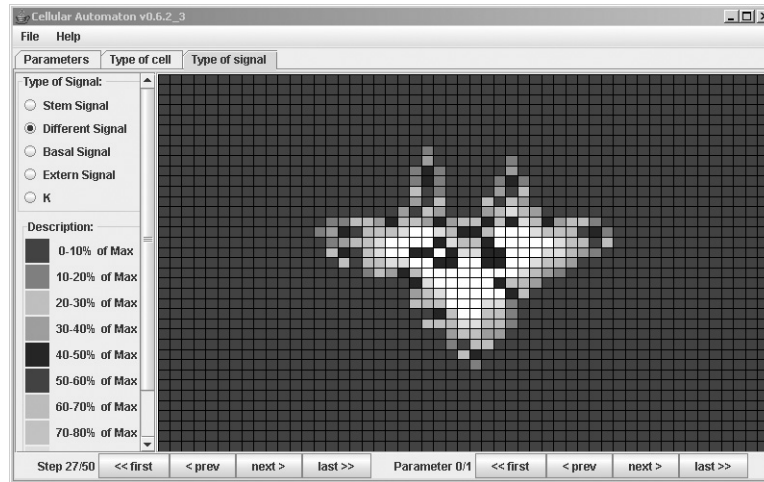


Fig. 5. Visualization of differentiation signals distribution.

1 Also, the visualization of cellular automaton model allows estimating distri-  
 2 bution of four biologically meaningful signals, which unambiguously simulate the  
 3 morphodynamics of the cell tissues (Fig. 5).

#### 4. Discussion

5 Creation of a cellular automaton that imitates morphodynamics of embryo devel-  
 6 opment by means of regulation of signals produced by different embryonic cells is  
 7 a first step in modeling the process of development in general and in modeling the  
 8 gene network for morphogenesis in particular.<sup>16</sup> The formation of plant meristems  
 9 in embryogenesis is characterized by a combination of a violent development of dif-  
 10 ferentiating tissue and a stable development of its stem cells. Both processes were  
 11 modeled in the cellular automaton being reported. Not only is this automaton a  
 12 tool for predicting the dynamics of the division process and the cell differentiation  
 13 process which underway in the systems being considered, but also for the exami-  
 14 nation of how real mutations influence the system. As a progression of this work,  
 15 we plan to develop a cellular automaton, which will enable modeling of various  
 16 experimentally induced mutations. Sophistication of characteristic cell definitions  
 17 will be added for a more adequate description. Also, in the future work, we plan to  
 18 use the cellular automaton model introduced here to investigate the development of  
 19 primary shoot meristem of the *Arabidopsis thaliana* in embryogenesis under differ-  
 20 ent initial parameters of the model. It allows recognizing of significant parameters,  
 21 which greatly influence on behavior of dynamic system and determining the stable  
 22 state of this biological system by variation parameters. The created visualization  
 23 of the model will be essential helper in decision of the problem and clear helper for  
 biologists.

8 I. R. Akberdin et al.

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*The Development of Primary Shoot Meristems of Arabidopsis Thaliana* 9

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10 *I. R. Akberdin et al.*

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