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Research Article

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Matrix Modeling of the Artificial Cell / Protocell Division with "ARTCELL DIVISION SIMULATOR-2009/2010": from Computer Simulation to Experimental Multispectral Investigations Based on Multi-Channel DPSSL Microbeam Setup

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Abstract

A model of the artificial cell / protocell division is proposed, which al-lows achieving similarity to different forms of cell division and emer-gence of the cell colonies by rearrangement of the parameters. The most characteristic features of cell division reproduced in this model are: cytotomy with a constriction (separatrix); cytokinetic processes after cytotomy; asynchronous nature of cell division; surface dispro-portionation during the cell division (as a consequence, the presence of both symmetrical cytotomy and budding); formation of the topological distortions; the possibility of colonial cell association; the presence of fixed cells and groups of cells (reproductive generators) like CFU and their coordinated operation. Cytokinetic processes are recorded in the systems of undifferentiated artificial cells. Such variability in the artificial cell "cultures" is observed in the form of reversible processes depending on the environmental conditions. Such instability of the regimes, probably, could have taken place in the course of evolution at the first stages of development of reproductive systems in protobionts, when mechanisms of genetic or other structural biochemical stabilization did not yet exist, but was developed during the division of the score for the future selection of these pathways.

Keywords: Artificial Cell Modeling, Protocell Modeling, Cytotomy, Cytokinesis, Budding, Cell Division, Matrix Visualization, Isoline Mapping, Isophots, CFU.

1. Introduction

Different models of the cell division based on nonlinear phenomena in cell metabolism are cur-rently known. Early developments in this area (long before the Turing model) considered the cell as a metabolic sys-tem with the substance flows induced by the diffusion forces directed both inside and outside the cell [1,2]. For this, the Hamiltonian principle was used, which is rather common in nonlinear physics. Subsequently, the theory was improved by the introduction of the so-called "prin-ciple of the maximum energy metabolism" [3]. In general case, instabilities emerging in the cell under the action of reaction-diffusion processes lead to the cell division when the critical specific surface area of the plasmalemma is reached.

Nonequilibrium thermodynamic effects underlying the cell division lead to the restoration of the cell integrity after cytotomy [4]. In animal cells, this is performed by the non-equilibrium mechanism of the cytoskeleton functioning [5]. The latter, including actomyosin complexes and motor proteins, can be considered as an analogue of the active gels that underlie the artificial muscle operation. Non-equilibrium mechanical phenomena in living cells and active gels are highly similar [6]. The latter are activated by an electrochemical action, i.e. by changing the redox potential Eh (mV), ion concentrations, specific electrical conduc-tivity of the medium, or by applying low voltages. Therefore, in the model case, cytotomy can be induced in the synthetic cells by varying the charge parameters of their medium. As a result of the above varia-tions, the properties of the electric double layer on the cell surface will also change. As a correlate of hydrophobicity, the surface tension will also be changed, re-sulting in the increased mechanical instability of

the shell. As a consequence of a change in the diffusion regime and heat and mass transfer, an ionic disproportion between the medium and the synthetic cell interior will arise, leading to the changes in the osmotic pressure. Combination of the above factors will lead to the synthetic cell division occurring in accordance with the model of the critical specific surface area.

Nowadays, there are known applications of the diffusion-metabolic model to the description of self-reproducing vesicular metabolic sys-tems – the so-called "protocells", considered as the adequate models of protobiological systems that satisfy Turing's metabolic conditions (re-action and diffusion) [7,8]. Meanwhile, a similar model is known which is also applicable to Dose and Fox proteinoid microspheres, which, in addition to the simple binary division, are also characterized by bud-ding [9,10]. Despite this fact, the transition between budding and binary division has not practically been ad-dressed in the existing cell division models, although it is obvious that they are in fact the limiting cases of each other from a morphometric point of view. In this work, an attempt is made to illustrate this transition using isolinear mapping.

Since such reproduction mechanisms underlie the population dynamics of microbiological systems, control and regulation of the number of bacteria in colonial communities can be described within the framework of a non-equilibrium approach [11]. Modern theoretical biology is based on a statistical-mechanical approach however, the problem of asynchronous cell division can be satisfactorily resolved only in the presence of synchronization or control using a nonlinear oscillator [12,13]. The principle of synchronization by periodic disturbances and mapping of the equipotential lines (as in the interference visualization) adopted in this work partially solves the problem of asynchronous divi-sion, at least for non-conjugated dividing cells, and also allows one to predict the cell growth by the nature of curvatures and numerical values of the boundary equipotential lines.

2. Methods

To simulate the cell division configurations a Bolkhovitin-ov's-Verkhovtsev's algorithm (ARTCELLDIVISIONSIMULA-TOR-2009/2010) was compiled, described earlier in according to which a 3x3-fold matrix was subjected to periodic disturbanc-es causing changes in the values. The results were output as a dat-file and imported into the SigmaPlot 8.0 software, in which, based on the results of stochastic modeling, isolinear mapping (with variable discreteness) of the matrices obtained was per-formed. Equipotential line parameters displayed on the maps were normalized to a single range in order to simplify data anal-ysis [14]. To visualize budding configurations, matrices A were transposed into AT. Then the data process-ing was carried out, similar to the processing of the non-transposed matrices A. The values of the matrices displayed on the isolines in both the first and second cases belonged to the range [1;130]. Scale parame-ters were chosen based on the data visualization requirements.

The contextual interpretation of the simulation results was carried out by comparative morpho-logical analysis of the graphical images ob-tained and cytological micrographs of the cell reproduction stages. Pre-diction of the vegetative dynamics of the daughter cells was carried out based on the numerical values of the finite contour envelopes (isolines) characterizing the cell morphology. Due to the fact that an open trajec-tory cannot be self-limiting, trajectories with an open contour do not belong to the cell topology and hence, cannot be indicators of its possi-ble growth. For this reason, such trajectories were omitted as non-informative ones during the simulation process.

The method described does not allow one to simulate ultrastructural phenomena, being in fact a contour morphometric analysis. However, within the framework of the critical specific surface theory, its applica-tion turns out to be quite appropriate. Reading the contour diagram from the minimum finite values allows one to reconstruct the process of cell division in dynamics.

Thus, the model proposed, without taking into account the physical vegetative cell growth, makes it possible to distinguish between the stages of interphase and cytotomy only according to the topological criteria (the appearance of topological nonequivalences is associated with the disturbances) without reference to the actual lengths of the equipotential lines.

In some cases, there is an overlap of several elliptical trajectories corre-sponding to the reproductive groups. In this case, reading of the dia-grams is carried out in two stages, which is due to the fact that under the given conditions, each reproductive unit is delimited from the oth-ers by its own separatrix. When modeling the cell colonies, such a pro-cedure can be difficult, since the number of the nested separatrices can be rather large.

3. Results

Let us consider the elementary case of cell division, in which two groups of cells located in the perturbed region divide asynchronously under quasi-equilibrium conditions. It is possible to simulate the fol-lowing forms or types of the cell division:

(a) Cytotomy with a constriction (Fig. 1-a)
(b) Cytotomy and cytokinesis (Fig. 1-b)
(c) Budding with deformation (Fig. 1-c, Fig. 1-d)
(d) Transitive (intermediate) variant between budding and division (Fig. 1-e)
(e) A colony-forming unit with a "sessile" cell attached to the surface (Fig. 1-f, Fig. 1-g).

In this case, interpreting the diagram (Fig. 1) in accordance with the above stated principles, for the first group of cells... At the same time, for the cells that undergo cytokinesis after cytotomy and, as a result, move away from the cell generator, common finite isolines with the cell generator do not exist, since the front of equipotential values propagates (and is distorted) in an inhomogeneous planar system.

The cell generator is a system of isolines centered at the zero of the ab-scissa, converging to the reproductive cleavage separatrix (constriction) $I_{fl} \rightarrow I_S$. The generator can have infinite isolines outside the zero ordi-nates, but only columns ≥ 1 are visualized within the framework of the 3x3 matrix model. Thus, in the first

case considered (Fig. 1-a), the un-provability of the cytotomic connection between the cells with $I_{max} > 30$ is associated with the absence of coordinates beyond the 3x3 matrix

Let us consider an example of operation of such a generator, shown in Fig. 1-b. The structure of isolines with $I_S = 34$ and $I_{max} = 40$, located at zero abscissas (ordinate 2), is a classic example of a generator on the separatrix. It follows from the diagram that the cell is under division, and, in contrast to the case shown in Fig. 1-a, no loss of connection / bonding occurs at the visualized stage of the process. In addition, the generator cell is deformed, and the product of generation can rather be characterized as a result of budding than a result of cytotomy, since with a dimensional imbalance between the generator and the generated cell (isolines with the same $I > I_S$ values delimit the areas of the phase space with different area) they are characterized by the common $I < I_S$. The generator cell always remains stationary: its center on the ordinate is obligatory in the center of symmetry (budding occurs along the symmetry line), and on the abscissa - at the initial point of coordinates (in other words, in the central row of the first column of a 3x3-fold ma-trix).

The same illustration shows an example of symmetric cytotomy fol-lowed by cytokinesis (the symmetry is incomplete, since, without hav-ing a common separatrix line, which gives a contour to the cytotomy link, as in the diagram in Fig. 1-a, the cells which are the the results of cytotomy do not have their own mechanisms of growth synchroniza-tion). In this regard, it is logical that when the disturbances are brought to the extreme values at which the deformation is maximum, it is possi-ble to visualize the process of cell differentiation and morphological variations (aberrations) of the cell division, which can be caused in this way. Figs. 1-c and 1-d show two variations obtained in the course of a computational experiment using the above method. When the dispro-portion between the “generator” and the daughter cell is small, and vis-ualization of the separatrix, with the other things being equal, is unat-tainable, the resulting structure is closer to the product of the ordinary cell division than to the result of budding. Meanwhile, for the second reproducing structure shown in Fig. 1-d, the reduction of the budding structure is obvious, which is the result of the matrix perturbation. With a twofold increase in disturbances (Fig. 1-c: $I_{max} = 45$; Fig. 1-d: Imax = 91), their result changes dramatically. With the growth of Imax induced by them, the line contours are narrowed. At the same time, the spatial disproportion between the sizes of the “generator” and the prod-ucts of its activity is growing. This trend suggests that with extreme disturbances and, as a consequence, an increase in the model nonlinear-ity, the probability of non-equilibrium division and / or budding in-creases.

It should be noted that in a system consisting of more than one repro-duction unit, the influence of the cells on the processes that are a result of the extreme disturbances is indicated. When the load is doubled, the equipotential contour of the budding generator is deformed and shifted relative to the previous position. Thus, the state and evolution of the model structures depend on the environment and the forces that directly affect them. In the presence of mutually conjugated cells in the model, there is an interaction leading to the synthesis of new biosimilar (in terms of cell division) forms.

By minimizing the inhibition or by inactivating one of the model gen-erators (removing the trajectories of the separatrix region), it is possible to observe not only regeneration of the structure corresponding to the reducing bud region, but also “activation” of the generator located on the back side. The result of this manipulation is shown in Fig. 1-e. Un-der certain conditions of exposure, the generator begins to operate as a colony-forming unit (Fig. 1-f). It is advisable to consider this structure in the transposed form of A^T, since such an approach is convenient for comparison with the biological prototypes (see Fig. 1-g).

By transposing A into A^T, duplicating the generator and complicating the nature of the perturbations in the A^T plane, one can achieve the sim-ilarity between the model and its biological prototype, where not single cells, but their communities exist, which have different division rates and different sizes of the initial units. Fig. 1-g shows a map of equipo-tential surfaces for a doubled number of generators in the transposed matrix AT with a correspondingly changed form of disturbances.

The map in Fig. 1-g lacks functional contours and topological "liga-ments" / connections. (The infinite isolines that played a role in identi-fication of the cellular structures and interpretation of the previous maps have been removed from this map for better visualization of the morphological similarity with the prototype). In this regard, it is possi-ble to easily compare color gradient images to the maps of equipotential surfaces, obtaining visualization in the dynamics of the budding process or a cell division. The latter example is shown in Fig. 2.

As a rule, the "generators" are either sedimented or adhered to a planar surface, therefore the use of the rectangular Cartesian coordinate sys-tem in this case can be justified as a model simplification. As the com-putational experiment shows, the character of the separated secondary "cells" depends on the attachment or non-attachment of the "generator" cells to the "surface" (i.e. on the boundary conditions) and can be com-pared to the phenomena of adhesion of the native cells to the surfaces with different wettability. Formation of the "shell" (finite trajectories-isolines pull) of the newly formed cells occurs in all cases from the similar equipotential lines of the generator, due to which the isolines of the shells of the daughter and mother cells coincide. It is theoretically possible to complicate the model and study the interference of multiple protocellular generators "sources".

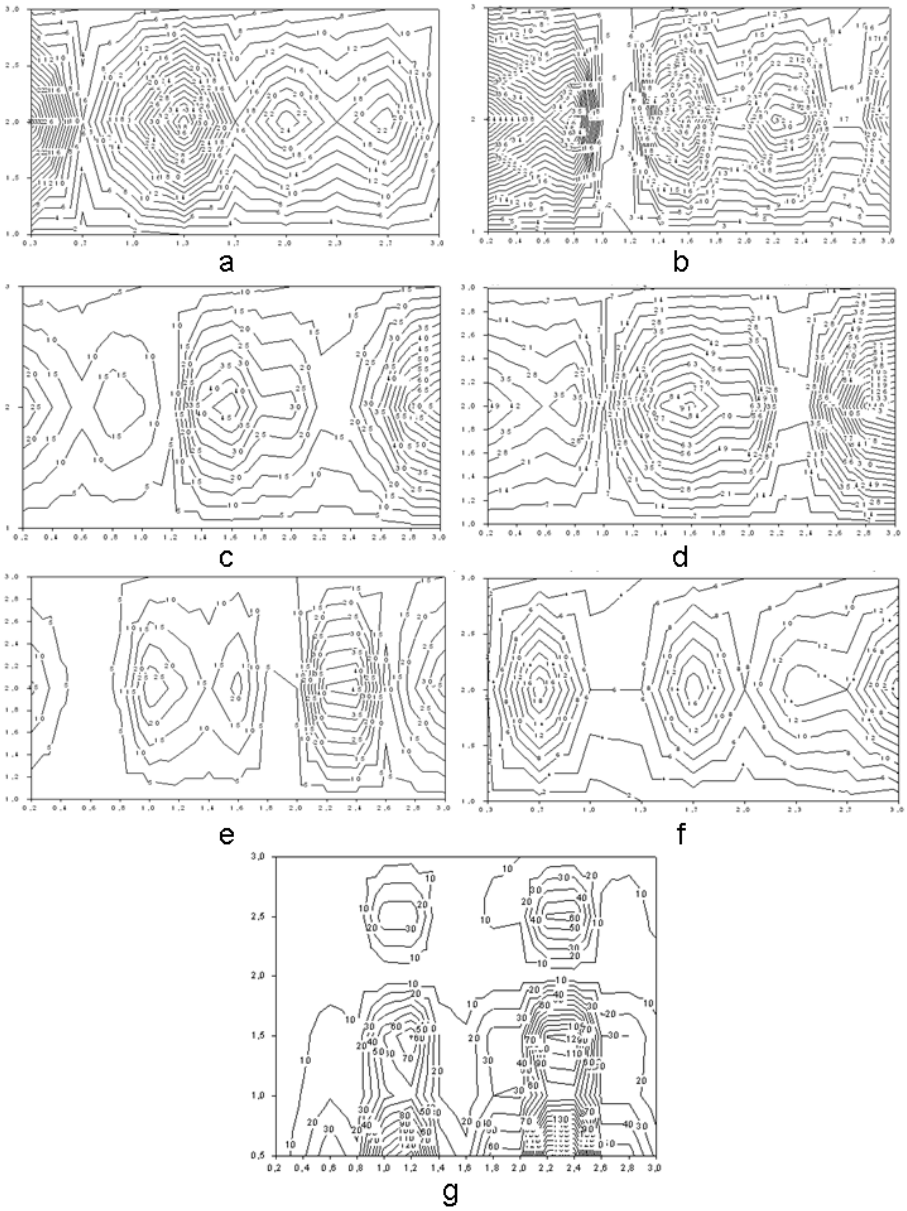

Figure 1: a - Binary division by a constriction; b - Cytotomy and cytokinesis; c - Bud-ding with deformation; d - Budding with deformation (variant of development); e - Transition from the inhibited budding to the cell division; f - Transition to budding from the attached (at the level of the 30-th column) cell; g- A colony-forming unit during the budding process.

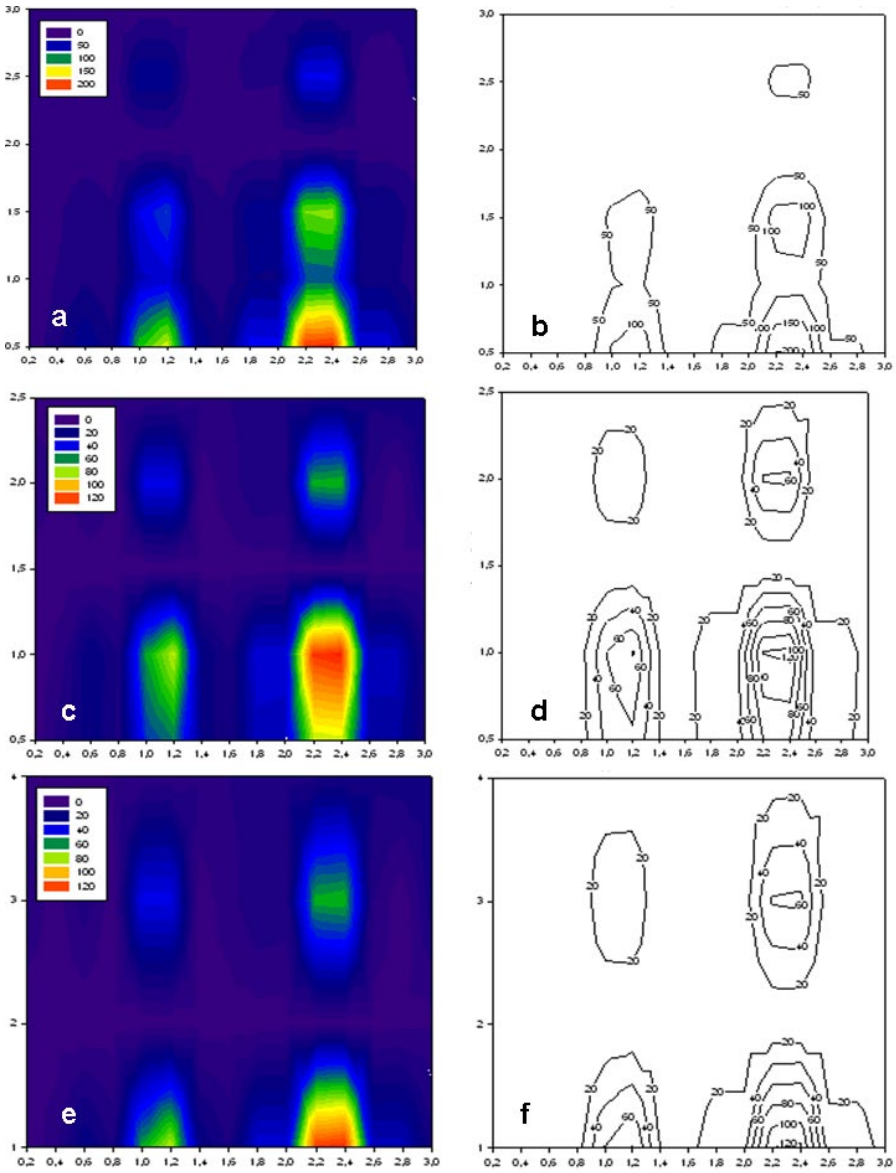

Figure 2: Three types (forms) of budding of the cell generator fixed in the medium.

At present, high discrete and precise model is being developed with the possibility of simultaneous counting of 100 generators. By iterating the exponentiation (the number of generators) and increasing the frequency to a certain limit, the multicellularity of the colony increases. In this case, the size of the cells depends on the wavelength.

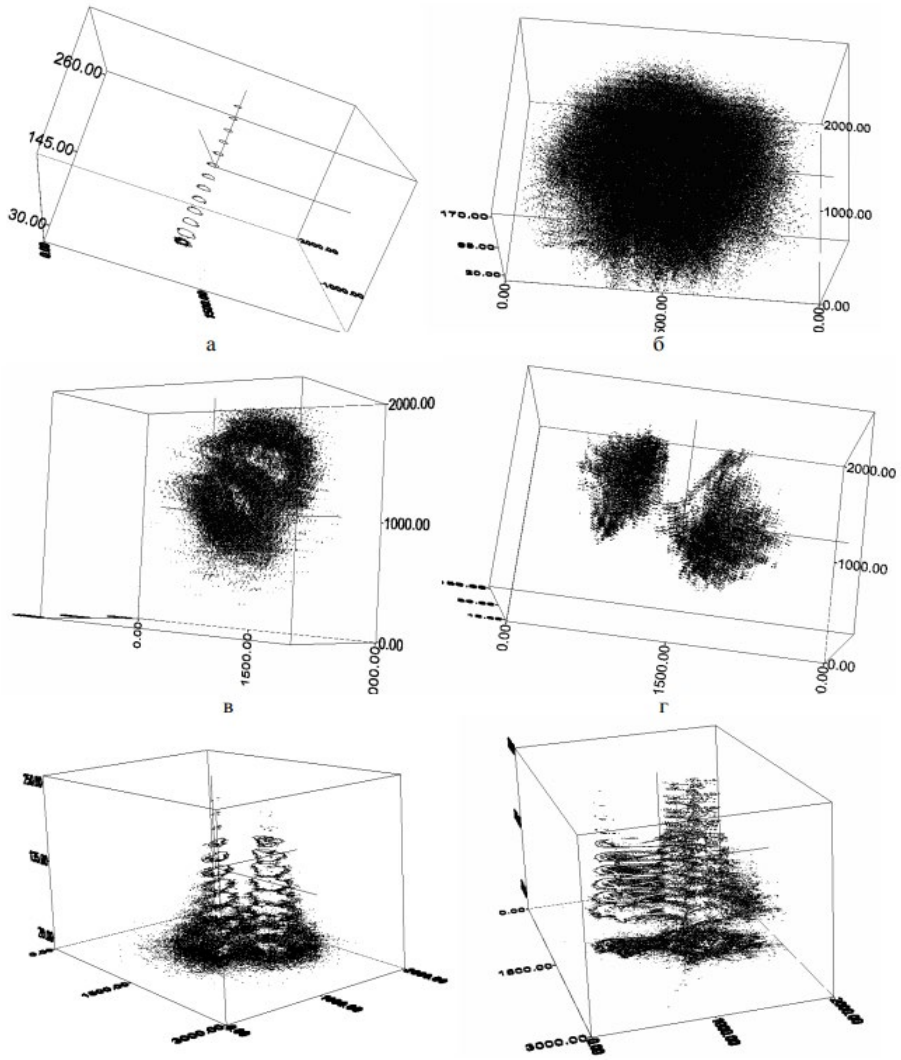

Figure 3: Experimental data for illustration of similarity between compu-tational models and real cell division / protocell division types (equiva-lent for the Fig. 1, Fig. 2).

4. Conclusion

The results obtained by such computational methods are in good agreement with the experimental visualizations of the cell and protocell division that we obtained using bordance analysis of microscopic imag-es (see Fig. 3) early proposed in for dynamic (time-lapse) lens-less mi-croscopy and multi-angle laser-assisted (multi-channel DPSSL) projec-tion microscopy [15-19].

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