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Mathematical modeling of critical phenomena in biomedical systems

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Abstract: According to the differential-topological approach, the spaces in which the conditions of stable and unstable phase are fulfilled are determined on the phase diagram of the existence of the CRISPR-systems, and the fulfillment of the conditions of the existence of the second-order critical space is investigated. The methods of mathematical modeling of critical phenomena in multicomponent systems, which have the prospect of use in modern biomedical and gene technologies, are applied. The proposed method involves modeling the states of the CRISPR-systems by systems of equations and inequalities containing potential functions of the system state that depend on several variables. The purpose of the modeling is to determine the stability spaces, bifurcations and spaces of simultaneous coexistence of several phases of the studied system. In the investigated area of the phase diagram of the CRISPR-systems, the existence of a stable and an unstable phase was determined. The position of the spaces of the phase diagram in which the conditions for the existence of a stable and unstable phase, i.e. bifurcation space, are fulfilled are found. It was found that there are no spaces of the phase diagram in which the condition of simultaneous coexistence of two phases is fulfilled. From this, it is concluded that in the studied space of the phase diagram, the system does not tend to disintegrate into two coexisting phases. The simulation results can be used to analyze the stability of the CRISPR-systems under different conditions of synthesis and operation.

Keywords: mathematical modeling, phase coexistence, differential-topological approach, spinodal decay, critical phenomena.

1. Introduction

Modern methods of mathematical modeling and software of computer algebra make it possible to approach the solution of practical problems of studying the stability of the states of multicomponent systems, which have the prospect of use in modern biomedical and gene technologies [1–7]. A special place in modern genetic engineering is occupied by the research of CRISPR systems, which are direct repeats and unique sequences in the DNA of bacteria and archaea dividing them, which, together with associated genes, provide cell protection from foreign genetic elements (bacteriophages, plasma) [1–5]. CRISPR cassettes are found in the genomes of many bacteria and most archaea. The repeats are separated by variable stretches of DNA, spacers, of approximately the same length. Spacers correspond to certain DNA fragments of foreign genetic elements (protospacers) by nucleotide sequence. In this regard, it was proposed and then shown that the sequences separating the repeats originate from the sequences of the genomes of bacteriophages and, accordingly, provide protection of cells against infections.

As a result of studies of the mechanism of action of the CRISPR-systems, it was assumed that it is a prokaryotic analogue of the RNA interference system of eukaryotes and provides bacteria and archaea with protection from bacteriophages [1].

Due to the emergence of prospects for the use of gene-based approaches in understanding system security, it is important to develop models that can be used to predict the states of CRISPR systems, to clarify the conditions of stable, unstable and critical phases of different orders, which has not been studied to date.

2. The aim of the study

The purpose of the study is to create a model and numerical modeling method that allow to study the spaces of the stable and bifurcation phase of the CRISPR system. The problems of researching the processes of the emergence of phase coexistence spaces in the CRISPR system remain unexplored, that is, the analysis of the possibility of the emergence of spaces of the phase space in the system under different conditions, where the conditions for the simultaneous coexistence of several stable phases are fulfilled. The purpose of the research in this paper is achieved by applying the provisions of Tom's theory of catastrophes and Landau's phase transitions [8 – 10]. A differential topological approach was used to find critical spaces [11 – 16]. In connection with the great complexity of finding analytical expressions of higher-order derivative determinants and analysis of their zero contours, computer modeling tools have been developed that provide effective solution of applied problems in the study and practical use of a wide class of technological processes of CRISPR system synthesis, as a multicomponent compound in biomedical technologies and predicting their behavior during operation under various external conditions.

To achieve the goal of the research, the following tasks were solved:

– analysis and systematization of existing experimental and theoretical data on the appearance of effects associated with the loss of stability in CRISPR systems and the appearance of spaces for the coexistence of phases of different orders [1–5] was performed;

— developed mathematical methods for predicting the appearance of critical spaces and spaces of phase coexistence in the CRISPR system in the investigated area of the phase diagram of the system's existence;

— software was developed that enables phase analysis of the studied CRISPR system.

3. Basic research materials

Modern studies show [1 – 5] that the properties of CRISPR systems, the so-called non-targeting rules of CRISPR-Cas, are related to the kinetics of hybridization, that is, they have a kinetic origin, and cleavage due to kinetically stopped hybridization is associated with it. It is believed that elucidating the properties of CRISPR systems can increase the specificity of engineered systems without losing efficiency. The repeats are 24 to 48 nucleotide pairs long; they have bivalent symmetry but are generally not true palindromes

In the work for modeling critical phenomena in CRISPR systems [1 –3], it is assumed that the dependence of the cleavage propensity on the position of mismatches in the guide-target hybrid originates from the kinetics of the targeting process, and the relative probability of cleavage for a sequence with a single mismatch (divergence, imbalance, heterogeneity) in position n compared to the probability of cleavage of the target sequence. This relative splitting probability is generally sigmoidal, that is, a continuously differentiable monotonic non-linear S-shaped function (S-curve or spline function) [1]:

$$P(n,T) = \frac{p_{\max}}{1+\exp\left[-1.7k_B T(n-n_s)\right]} \qquad (1)$$

with n_s giving the position where the splitting probability is half of the maximum p_{max} , and shifts are measured in units of $k_B T$. Here n_s is identified as the length of the kinetic seed space beyond which the mismatch will no longer strongly inhibit cleavage.

For the purpose of mathematical modeling of critical phenomena, the equations of state forming the basis of the model were built on some 2-dimensional space in coordinates (n,T) [1, 1 – 15]. A situation in which one stable state of the system coexists with another stable state was considered a criterion for determining the spaces of phase coexistence. The process of the emergence of such a space is a phase transition of the first kind according to Maxwell's principle. In this case, two or more global minima of the system state function will have the same depth. Within the investigated phase space, under certain conditions, bifurcation subspaces can appear in which a stable phase can become unstable. Critical spaces of order 2 can arise under conditions where two different phases become identical. Critical spaces of order 3 and 4 are formed, respectively, in the presence of three or four identical phases. Due to the insufficient amount of experimental data, modeling of critical spaces of order 3 and 4 has not been carried out in the work yet.

The search for spaces of the phase diagram in which the condition of a stable, unstable phase and the spaces of coexistence of phases of the CRISPR-system (1) are fulfilled was carried out in accordance with the provisions of Tom's theory of catastrophes and the generalization of the theory of phase transitions by Landau for the case of 2-dimensional space (n,T) [1, 9, 11 – 15]. To find the spaces of the phase diagram where the conditions of a stable phase are fulfilled, the analytical expression of the matrix of the partial first and second derivative functions $P(n,T)$ was obtained according to expression (1), i.e., in matrix form $\frac{dP}{dX}$ and $\frac{d^2P}{dX^2}$ where $X = X(n;T)$ is a vector, and the corresponding matrices were composed according to the rule:

$$\frac{d^2P}{dX^2} = \begin{pmatrix} \frac{\partial^2 P(n,T)}{\partial n^2} & \frac{\partial^2 P(n,T)}{\partial n \partial T} \\ \frac{\partial^2 P(n,T)}{\partial T \partial n} & \frac{\partial^2 P(n,T)}{\partial T^2} \end{pmatrix} \tag{2}$$

According to the obtained analytical expressions of the matrix of derivatives, the zero contours of the determinant of the matrix of the first derivatives were found and the signature of the determinant of the matrix of the second derivatives was investigated (Fig. 1a,b). The position of the spaces of the phase diagram that meet the conditions for the existence of spaces of a stable phase was obtained by the system of equations and inequalities:

$$\det\frac{dP}{dX} = 0; \quad \det\frac{d^2P}{dX^2} > 0, \tag{3}$$

by the method of superimposing the topology of the obtained zero contour of the determinant of the matrix of the first partial derivatives of the investigated function (1) and the spaces on the diagram of the existence of the investigated CRISPR-system, in which the conditions of positive values of the determinant of the matrix of the second partial derivatives are fulfilled. To find analytical expressions of derivative matrices and zero contours of their determinants, the free Maxima computer algebra system was used. To find out the condition $\det\frac{d^2P}{dX^2} > 0$, that is, the positive signature of the determinant of the matrix of components of the second partial derivative of the function under study (1), the position of the zero contours of the determinant was first found, and then the value of the determinant around the found zero contour was investigated by direct calculation. The found space of the phase diagram, in which the conditions for the existence of spaces of a stable phase are fulfilled, is shown in Fig. 2.

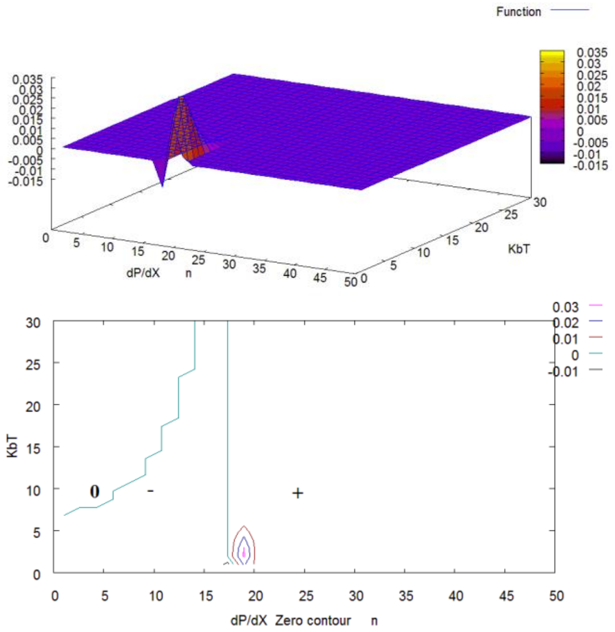


Fig. 1a. Three-dimensional surface and zero contours of the determinant of the matrix of first derivatives of the $\det\frac{dP}{dX}$.

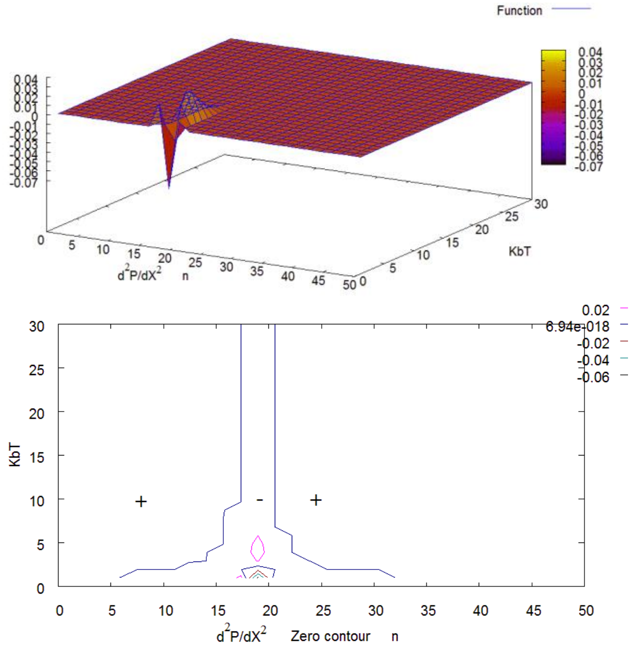


Fig. 1b. Three-dimensional surface and signature of the determinant of the matrix of the second derivatives of the $\det\frac{d^2P}{dX^2}$.

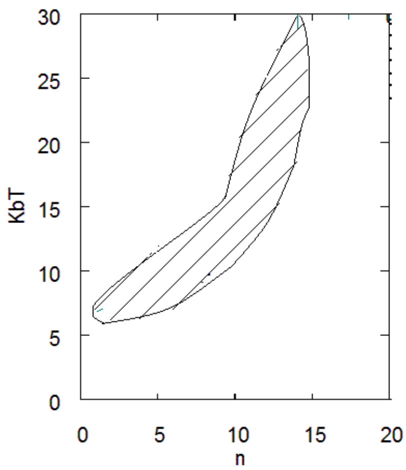


Fig. 2. The space of the phase diagram in which the conditions for the existence of stable phase spaces are met (shaded space on the diagram).

To find spaces of the phase diagram in which the conditions of first-order instability or bifurcation spaces are fulfilled, similarly to the above-mentioned method, a system of differential equations and inequalities was solved [9, 11 – 14]:

$$\det\frac{dP}{dX}=\det\frac{d^2P}{dX^2}=0;\quad \det\frac{d^3P}{dX^3}>0\,. \tag{4}$$

where the $\frac{d^3P}{dX^3}$ is the matrix of partial third derivatives on the $X=X(n;T)$ of the function (1), and the $\det\frac{d^3P}{dX^3}$ is the determinant of the matrix of the third partial derivative of the function under study. By the method of directly superimposing the topology of the determinants of the matrices of the first, second, and third derivatives and the zero contours of the determinants of the matrices of the first and second derivatives of the function under study, the spaces of the phase diagram were found in which conditions (4) are simultaneously fulfilled. In order to find out the sizes of the obtained spaces, numerical studies were additionally carried out, that is, the values of determinants (4) were directly calculated near the found zero contours of the determinants of the matrices of the first and second partial derivatives of the function (1) with respect to variable $X = X(n;T)$. First, the spaces in which the conditions of $\det\frac{dP}{dX} = \det\frac{d^2P}{dX^2} = 0$ are simultaneously fulfilled were left on the phase diagram of the existence of the CRISPR system (9), that is, the spaces of the phase diagram along which the determinants of the matrix of the first and second partial derivatives are equal to zero, and then the fulfillment of the condition of $\det\frac{d^3P}{dX^3} > 0$ for the left spaces was checked. To study the signature of the determinant of the matrix of the third partial derivative, the location of the zero contours of the investigated determinant was obtained, and then the value of the determinant at points near the found zero contours was determined by direct calculations.

The results of the study of the signature of the determinant of the partial derivatives of the matrix of the third derivative and the spaces found in which the conditions of instability of the first order are fulfilled are shown in Fig. 3a and Fig. 3b. The found space of the phase diagram, in which the conditions of first-order instability, or bifurcation spaces, are fulfilled, is shown in Fig. 4.

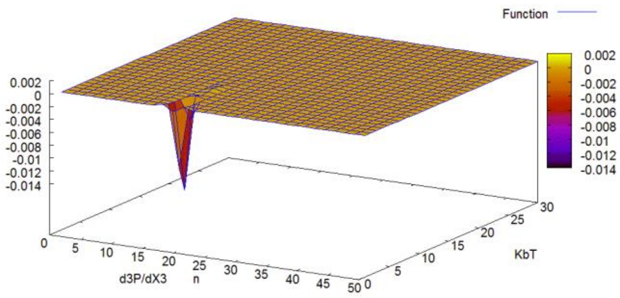


Fig. 3a. Three-dimensional surface of the determinant of the matrix of the third derivatives of the $\det\frac{d^3P}{dX^3}$.

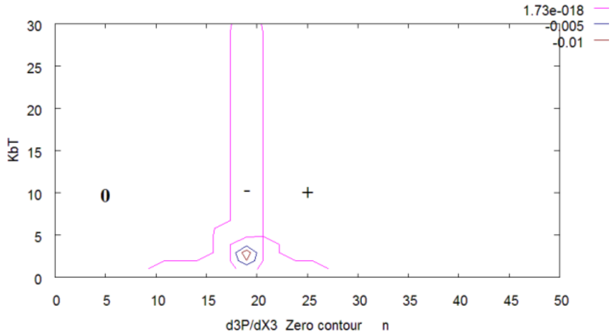
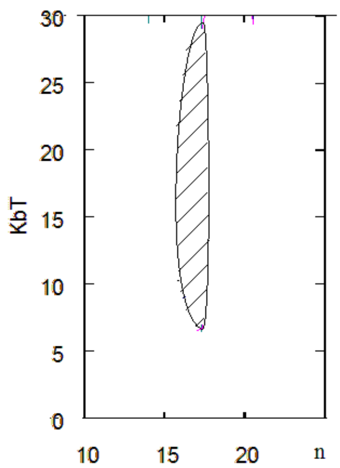


Fig. 3b. The zero contour and the signature of the determinant of the matrix of third derivatives $\det\frac{d^3P}{dX^3}$.



]**Fig. 4.** The space of the phase diagram in which the first-order instability conditions are fulfilled (shaded space on the diagram).

The search for spaces in which the condition for the existence of a second-order critical space is fulfilled, i.e. the conditions for the simultaneous occurrence of two coexisting phases of the CRISPR system (9), was carried out by searching for the solution of the system [9, 11 – 14]:

$$\det\frac{dP}{dX} = \det\frac{d^2P}{dX^2} = \det\frac{d^3P}{dX^3} = 0; \quad \det\frac{d^4P}{dX^4} > 0, \tag{5}$$

where the $\det\frac{d^4P}{dX^4}$ is the determinant of the matrix of the fourth partial derivatives of the function (1). Similarly to the method of finding stable and unstable phases, a search was made for the space of the phase diagram in which conditions (5) are simultaneously fulfilled by directly superimposing the topology of the determinants of the matrices of the first, second, and third derivatives and the zero contours of the determinants of the matrices of the first, second, and third derivatives of the investigated function. First, spaces were left on the phase diagram of the existence of the CRISPR system (9) in which the conditions of $\det\frac{dP}{dX} = \det\frac{d^2P}{dX^2} = \det\frac{d^3P}{dX^3} = 0$ are simultaneously fulfilled, that is, spaces of the phase diagram along which the determinants of the matrix of the first, second, and third partial derivatives are equal to zero, and then the fulfillment of the condition of $\det\frac{d^4P}{dX^4} > 0$ for the left spaces. To study the signature of the determinant of the matrix of the fourth partial derivative, the location of the zero contours of the investigated determinant was obtained, and then the value of the determinant at points near the found zero contours was determined by direct calculations.

The $\frac{d^3P}{dX^3}$ and $\frac{d^4P}{dX^4}$ matrices are block matrices. Yes, the $\frac{d^4P}{dX^4}$ matrix has the structure [16]:

$$\frac{d^4P}{dX^4} = \begin{pmatrix} \begin{pmatrix} \frac{\partial^4 P(n,T)}{\partial n^4} & \frac{\partial^4 P(n,T)}{\partial n^3 \partial T} \\ \frac{\partial^4 P(n,T)}{\partial n^2 \partial T \partial n} & \frac{\partial^4 P(n,T)}{\partial n^2 \partial T \partial T} \end{pmatrix} & \begin{pmatrix} \frac{\partial^4 P(n,T)}{\partial n \partial T \partial n^2} & \frac{\partial^4 P(n,T)}{\partial n \partial T \partial n \partial T} \\ \frac{\partial^4 P(n,T)}{\partial n \partial T^2 \partial n} & \frac{\partial^4 P(n,T)}{\partial n \partial T^3} \end{pmatrix} \\ \begin{pmatrix} \frac{\partial^4 P(n,T)}{\partial T \partial n^3} & \frac{\partial^4 P(n,T)}{\partial T \partial n^2 \partial T} \\ \frac{\partial^4 P(n,T)}{\partial T \partial n \partial T \partial n} & \frac{\partial^4 P(n,T)}{\partial T \partial n \partial T^2} \end{pmatrix} & \begin{pmatrix} \frac{\partial^4 P(n,T)}{\partial T^2 \partial n^2} & \frac{\partial^4 P(n,T)}{\partial T^2 \partial n \partial T} \\ \frac{\partial^4 P(n,T)}{\partial T^3 \partial n} & \frac{\partial^4 P(n,T)}{\partial T^4} \end{pmatrix} \end{pmatrix} \tag{6}$$

The application of the differential topological approach to the solution of system (5) showed that the system has no solutions in the studied phase space, that is, the condition for the appearance of spaces in which the condition for the existence of a second-order critical space is fulfilled is not fulfilled. In addition, the methods of direct calculations of the signature of the studied space were applied, which also confirmed the lack of fulfillment of conditions (5). The results of the study of the signature of the determinant of the matrix of the fourth derivatives of the function (1) and the results of the search for zero contours of the studied determinant are shown in Fig. 5a and Fig. 5b.

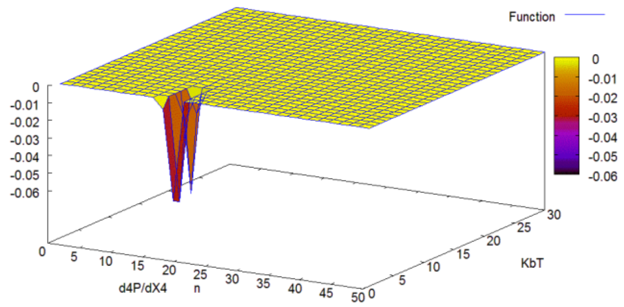


Fig. 5a. Three-dimensional surface of the determinant of the matrix of fourth derivatives $\det \frac{d^4P}{dX^4}$

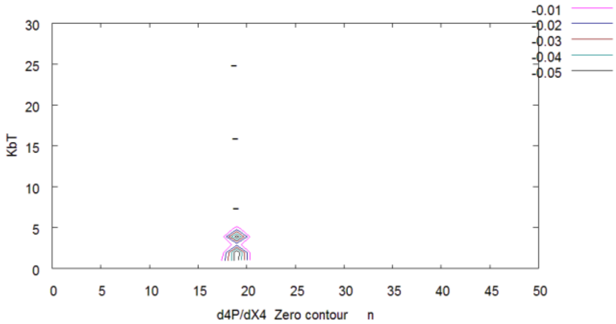


Fig. 5b. Signature of the determinant of the matrix of fourth derivatives $\det \frac{d^4P}{dX^4}$

4. Conclusion

According to the provisions of Tom's theory of catastrophes, as well as the generalization of Landau's theory of phase transitions to the case of 2-dimensional phase space, a mathematical model of critical phenomena in the CRISPR system was built [1].

In accordance with the proposed mathematical model of critical phenomena and on the basis of a differential topological approach, a method was developed and its algorithm for predicting the occurrence of critical spaces and spaces of phase coexistence of order two in the studied CRISPR system was implemented.

Using the differential-topological approach and direct calculation, the existence of spaces of the phase diagram of the studied system, in which the conditions of stable and unstable phase are fulfilled, was determined, and the position of the identified spaces on the diagram of the existence of the studied system was also found.

Based on the analysis of the conditions for the occurrence of a second-order critical space, in which there is a probability of simultaneous coexistence of two phases, it was found that such conditions are not fulfilled in the studied area of the phase diagram. Hence, it can be concluded that the system in the studied space of the phase diagram does not tend to spinodal decomposition into two coexisting phases.

References:

1) Uddin, F. CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future / F Uddin, C. M. Rudin, S. Triparna // Front. Oncol., 07 August 2020 Sec. Cancer Genetics Volume 10 - 2020 – https://doi.org/10.3389/fonc.2020.01387

2) Ran, F. Genome engineering using the CRISPR-Cas9 system / F. A. Ran, P. D. Hsu, J. Wright / Nature Protocols – 2013. – Vol. 8. – P. 2281–2308

3) Matthew G. Mathematical modeling of selfcontained CRISPR gene drive reversal systems/Matthew G. Heffel, G. C. Finnigan // Scientific Reports. – 2019 9:20050. https://doi.org/10.1038/s41598-019-54805-8 10

4) Yuanyuan X. CRISPR-Cas systems: Overview, innovations and applications in human disease research and gene therapy / Yuanyuan Xu, Zhanjun L // Computational and Structural Biotechnology Journal – 2020. – Vol.18. – P. 2401–2415

5) Klein, M. Hybridization Kinetics Explains CRISPR-Cas Off-Targeting Rules / Misha Klein, Behrouz Eslami-Mossallam, Dylan Gonzalez Arroyo, Martin Depken // Cell Reports – 2018 – 22, February 6, P. 1413–1423

6) Shapovalov H. Mathematical modeling of critical phenomena in biomedical systems / H. Shapovalov, A. Kazakov, I. Berber // Proceedings of the II International Scientific and Technical

Conference “MODERN TECHNOLOGIES OF BIOMEDICAL ENGINEERING” – 2023. – P. 218 – 222

7) Соловйов С. Математичне моделювання як сучасний інструмент прогнозування ефективності протиротавірусних вакцин / С. О. Соловйов // медична інформатика та інженерія – 2011. – № 2. – С. 59 – 63

8) Cahn, J. On spinodal decomposition [Текст] / J.Cahn // Acta Met. — 1961. — Vol. 9. — P. 795 — 801.

9) Okada, K. Classical calculations on the phase transition I. Phase diagram in four-dimensional space for the system with one order parameter / K. Okada, I. Suzuki // J. Phys. Soc. Jap. — 1982. — Vol. 51, № 10. — P. 3250 — 3257.

10) Laugier, A. Thermodynamics and phase diagram calculations in II-VI and IV-VI ternary systems using an associated solution model [Текст] / A. Laugier // Revue De Physique Applique. — 1973. — Vol. 8, № 9 — P. 259–26.

11) Kazakov, A. Computer simulation for stability of quaternary solid solutions [Текст] / A. Kazakov, I. Kishmar // J. Crystal Growth. — 1991. — Vol. 110. — P. 803 — 814.

12) Kazakov, A. Stability analysis of quaternary alloys including the lattice mismatch strain energy [Текст] / A. Kazakov, I. Kishmar // J. Crystal Growth. — 1992. — Vol. 125. — P. 509 — 518.

13) Shapovalov G. Calculation of the phases coexistence spaces in the system Hg-Mn-Te-Se [Текст] / A. Kazakov, D. Burtnyi, G. Shapovalov // Proceedings of Odessa Polytechnic University. — 2018. — Т. 54, № 1. — С. 69 — 73.

14) Kazakov, A.I. Computer simulation for formation of critical spaces in II–VI solid solutions / A.I.Kazakov, G.V.Shapovalov, P.P.Moskvin // Journal of Crystal Growth. — 2019. — V. 506 — P. 201 — 205.

15) Moskvin, P. P. Spinodal decomposition and composition modulation effect at the lowtemperature synthesis of $A_x^3 B_{1-x}^3 C_x^5$ semiconductor solid solutions / Pavel P. Moskvin, Sergii I. Skurativskyi, Oleksandr P. Kravchenko, Galyna V. Skyba, Hennadii V. Shapovalov // Journal of Crystal Growth. — 2019. — V. 510 — P. 40 — 46.

16) Traat, I. Matrix calculus for multivariate distributions / I.Traat // State University of Tartu — 1986. — V.733. — P. 64 — 85.