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BOUNDARY ELEMENT METHOD APPLICATION TO HEAT AND MASS TRANSFER DURING GROWTH OF BIOLOGICAL TISSUE

Growth of biological tissue is considered in the present paper. A mathematical model based on metabolism intensity conception is proposed. The proposed mathematical model gives an opportunity to consider multicomponent environmental media and to analyze an influence of every component on the growth process, based on its influence on metabolism process, known from some experimental research. As a result, the growth process is described as parabolic initial-boundary-value problem in domain with moving boundary. Since the growth process is, generally speaking, enough slow, the special methods, developed for slow phase transition calculation and based on small parameter method are applied to the problem. Using mentioned approach it is managed to build analytical solutions in one-dimensional (in space) case and numerical solutions are obtained in two- and in three-dimensional cases with additional application of boundary element method.

Key words: biological tissue growth, metabolism, heat and mass transfer, small parameter method, boundary element method.

Рассмотрены процессы роста биологических тканей. Предложена математическая модель на основе концепции интенсивности метаболизма, дающая возможность рассматривать многокомпонентную окружающую среду и анализировать влияние каждого из компонентов на процессы роста. Процессы роста описаны при помощи параболической краевой задачи в области с подвижной границей. Для решения данной задачи применен специальный метод, ранее разработанный для задач о медленном фазовом переходе и основанный на методе малого параметра. С помощью такого подхода возможно строить аналитические решения для одномерных по пространству случаев и получать численные решения с использованием метода граничных элементов для двумерных и трехмерных случаев.

Ключевые слова: рост биологической ткани, метаболизм, тепломассообмен, метод малого параметра, метод граничных элементов.

Розглянуто процеси росту біологічних тканин. Запропоновано математичну модель на основі концепції інтенсивності метаболізму, що дає змогу розглядати багатокомпонентне навколишнє середовище й аналізувати вплив кожного з компонентів на процеси росту. Процеси росту описано за допомогою параболічної крайової задачі в області з рухомою межею. Для розв'язання даної задачі застосовано спеціальний метод, раніше розроблений для задач про повільний фазовий перехід та заснований на методі малого параметра. Такий підхід уможливлює аналітичні розв'язки для одновимірних за простором випадків та отримувати числові розв'язки із застосуванням методу граничних елементів для двовимірних і тривимірних випадків.

Ключові слова: ріст біологічної тканини, метаболізм, тепломасообмін, метод малого параметра, метод граничних елементів.

Introduction. Problem of biological tissue growth [8] became very actual at the present stage of biological science development, because a lot of processes used in agriculture and biotechnology are determined by growth of biological tissue. Beside of that, problem of tumor growth is one of the most important in medicine [5; 8]. Two kinds of circumstances determine the growth process, the first one is genetic properties of tissue and the second one is environmental conditions, for example, nutrition, temperature and so on. The genetic mechanism is an object of very intensive investigations at the present stage, including mathematical modeling of genetics, and there are a lot of successes. However, the level of investigation is very far from complete description of biological

tissue growth on the base of genetic approach. As a result, most of investigations concerning a biological growth are based on phenomenological approach, considering biological tissues as a "black box" with experimentally determined properties. The growth is one of such properties of biological tissue. Nevertheless similar approaches have a lot of difficulties and disadvantages, in fact, they are only tool for solution of many problems and base for mathematical modeling on non-cellular level. Nevertheless the hard genetic determination of life cycle of any biological tissue, there is strong dependence of the tissue life functions on environmental conditions. This dependency has been known from an antiquity, and a lot of attempts were made to establish its general quantitative description, but their results were restricted by multiple of particular observations, conclusions and laws. The next step in this direction was mathematical modelling of the biological processes. Full review of mathematical modeling in biological sciences requires a separate investigations, which must be sufficiently more than the present paper. Since the growth of biological tissue is the object of the present work, consider specific features of the mathematical models of the given processes. General simplifying assumptions must be made to formulate a mathematical model.

Any biological tissue consists of cells. Process of cell reproduction is caution of multicellular tissue growth. The growth process consists of two parts: growth of individual cells and fission of cells, that is the growth process has evidently discrete behavior. Since cells are very small and number of them is very large, consideration of each individual cell is impossible and therefore some averaging is necessary. As a rule averaging process used in biology is similar to well-known continuos mechanics approach. According to this approach a multicellular biological tissue is assumed as continues media with distributed sources and some diffusive properties. In fact, cells create a porous media, but pressure difference enough for filtration flow is very seldom presence in the biological tissues, therefore transport phenomena in filtration flow can be neglected and diffusive properties of biological tissue are provided by some other specific mechanisms. Real transport phenomena in biological structures are very complex and difficult for simulation therefore the only way to build a mathematical model is to assume that transport phenomena has diffusive behavior and to use experimentally determined diffusive properties of media.

First attempts to describe biological processes by chemical reactions took place in first half of XIX century. As a result of almost two hundred years of science development, the chemical mechanisms of life are quite clear for understanding at the moment, but correspondent theory is very complex and sophisticated. Details of this theory are not concerned the object of the present work. Note only, that there isn't single quantitative measure of metabolism, because a lot of chemical reactions mutually interact. However the simplest way to formulate a mathematical model for metabolism process is to introduce some numerical value called metabolism intensity and to assume, that any chemical reaction and consequently heat and mass transfer process rate is determined by (in the simplest case it is proportional to) metabolism intensity. As a rule, metabolism intensity is connected by linear relation with velocity of tissue growth. This rule is almost always right for simplest organisms, but metabolism of highest animals is more complex. All mathematical models, which will be developed in the present paper below, will be based on the assumption that there exist single value, described the metabolism intensity. Of course, it is phenomenological approach and relation function connecting metabolism intensity and consuming of nutrient substances (excrement production) must be determined experimentally. An evident advantage of such mathematical models (so-

called one-parametrical models) is their flexibility and opportunity to take into account different number of concentration fields on different level of consideration.

There are two possible mechanisms of biological tissue growth. The first one is the surface growth and the second one is the volume growth. The kind of growth depends of kinds of tissue. The intensive cell fission takes place in relatively thin layer near the tissue surface in the case of surface growth. Cells situated inside the tissue have stable metabolism without intensive fission in this case, then their total volume remains constant. Reproduction of all cells takes place in the case of volume growth, although the most intensive fission, as a rule, takes place near the surface.

All considered above mathematical models are reduced to initial-boundary-value problems for system of diffusion equations with non-linear sources in moving boundary domain. Motion of the domain boundary is caused by tissue growth.

Phase transitions are well known from ancient times, because they are very widespread as in nature, as in many technologies. Physical theory of phase transformations on microscopic and macroscopic levels were developed and, as a result, there are not sufficient unsolved questions, what can arise during solution of most of applied heat and mass transfer problems including phase transition [11]. However, there is not so good situation from the point of view of computational mathematics, because phase transition problems contain specific kind of non-linearity connected with motion of phase transition boundary, because the solution for the field, caused the phase transformation, depends on the domain shape, but the domain shape depends on the solution (as the boundary shape depends on it). And more than that it depends on history of the field development. Since the considered non-linearity cannot be represented as some function (excluding the simplest cases), different implicit linearizations are used for solution of such problems. As a rule, time-stepping algorithms are used for numerical solution of phase transition problems and the domain shape is fixed on the time step, that is, there is an implicit splitting of the process by the field evolution and interphase boundary motion. Thus such algorithms provide «jumping» domain shape and time step must be enough small to guarantee small domain shape «jump» and high accuracy of the field calculation. Both given requirements may be used as criteria of time step choosing in dependence on particular problem. In any case, beside of additional time step restriction, there is an additional error source, concerning the domain boundary motion. Any full review of numerical methods of Stefan problem solution requires a special investigation and cannot be included in restricted length of the present paper. However the following general conclusion can be made: all mentioned numerical algorithms of Stefan problem solution, based on finite element or finite difference approaches, are rather directed to fast phase transformations, because under restricted time step they require a lot of time steps for slow phase transformations. Then they are found non-effective in the case of slow phase transformations.

The described situation in numerical method of Stefan problem solution is quite natural, because fast phase transformations are base of most technological processes, including phase transformations and attract serious interests in industrial designs. Slow phase transitions often occur in natural processes. The quasi-stationary approximation (called Leybenzon approximation in Russian literature) is used to apply for numerical calculation of such processes [11]. However, number of similar works were very restricted and they mostly were devoted to engineering design, nevertheless this approach become popular in problems of freezing (meeting) of soil, for investigation of phase transitions in solid body, in some evaporation (condensation) problems. The situation in

numerical modelling of slow phase transition was sharply changed in connection with three new problems. The first problem was simple attempt to build more accurate mathematical models for environment processes, for example, in meteorology or soil investigations. The second problem is phase transition in microgravity condition, which became important with starting of intensive space exploration. And finally the third problem was connected with attempts to obtain a material with minimal residual stresses, what was important in material sciences. An experience of application of traditional finite difference and finite element approach to the mentioned problems was rather unsuccessful, nevertheless a lot of problems were solved, because their numerical solution required huge computer resources and therefore their research opportunities were strongly restricted. Beside of that, the traditional methods often could not provide necessary accuracy of the numerical solution. On the other hand the quasi-stationary approximation had difficulties too, because it is related to asymptotically slaw processes and doesn't take into account initial conditions. Beside of that, elliptical boundary-value problems, which must be numerically solved at every time step of quasi-stationary problem solution, are rather inconvenient for finite difference method. In addition, grid rebuilding is necessary for quasi-stationary approximation at the every time step, as for other time-stepping algorithms for full Stefan problems. As a result, using of quasi-stationary approximation was very restricted last decades.

After the first original works of Y. P. Chuang and J. Szekely [6; 7] a lot of papers were devoted to boundary element method application to Stefan problem. And certain success had been achieved in this field, because there isn't so strong restriction on time step, connected with differential operator, and boundary element method more precisely approximates the phase transition boundary and gives an opportunity to realise more exact time integration algorithm. However general effectiveness of boundary element method for parabolic problems is less than similar effectiveness of finite difference method, what was shown in many paper, see, for example, [9]. Of course, using of some special boundary element method algorithms can improve the situation, but any time-stepping numerical method cannot completely solve the problem of slow phase transition.

Let explain the conclusion made above. First of all, it is necessary to determine the term «slow phase transition». As it will be shown below, velocity of phase transition is described by dimensionless parameter called Stefan number. Usually the Stefan number is interpreted as relation of thermal energy, spent in heating (cooling) of some phase, to energy spent in phase transformation process, correspondingly. Authors of the present work propose another treatment according to which the Stefan number is relation of two times characterising heating (cooling) and phase transition, correspondingly. Nevertheless the Stefan number is determined by the same formula, the last treatment is better, because it clear explains several phenomena difficult for understanding, such as phase transition in small drop surface, a phase transition near a state of phase equilibrium. The term «slow» means that the Stefan number is small and therefore there are two different time scales in the problem. The «fast» time is connected with the temperature field, and the «slow» time describes the phase transformation process. Traditional methods based on field discretization and time-stepping algorithm cannot overcome this difficulty because they require a stepping of «fast» time, as a result, too many steps of «fast» time in necessary to consider a process in «slow» time. More than that, even algorithms, based on different transformation in time domain (such as integral transformation with respect to time, are serial expansions) cannot provide desirable effectiveness. Only analytical or approximate analytical approaches, which present a temperature field solution in explicit form, are

suitable here, but an area of such method application is very restricted and, in fact, they can be used only for some one-dimensional (in space) problems. Thus to create an effective algorithm for the considered problem is necessary to move the «fast» time from solution procedure. Asymptotic approaches give an opportunity to build a mathematical model with required properties. The first work in this direction was paper [10], where the small parameter method was applied to Stefan problem. However the proposed algorithm had not become popular, by almost the same reasons, what quasi-stationary approximation had not become popular. Beside of that, nevertheless the requirement of Stefan number smallness took place in the paper [10], slow phase transitions were not determined as a field of effective application of the developed method.

Boundary element method [1;4] has become powerful tool for numerical solution of boundary-value problems. It is especially effective in comparison with traditional finite difference method and finite element method for elliptical problems in domain of complex geometrical shape. The main idea of the present paper, concerning the numerical approach, is using of boundary element method for solution of elliptical boundary-value problems, which arise for every approximation on every time step. As a result, an effective computational algorithm is developed, because of well-known advantages of boundary element method such as discretization only boundary alone and high accuracy of computations.

Nevertheless there are a lot of problems, concerning a taking into account of the initial conditions, infinite and semi-infinite domains, in the proposed method. However high computational effectiveness for considered kind of problems makes it practically the best for computational solution of given problems.

Governing equations. Let consider D_1 filled by some biological structures (in the simplest case by homogeneous or non-differentiated cellular mass). Let restrict the following consideration by the case of homogeneous cellular structures. The tissue in the domain D_1 is porous media where cells form a frame and intercellular space is porosity. Let assume that pores are filled by same liquid, which is complex solution of nutrient substances and excrements of cells. There is an intensive heat and mass transfer between the frame and the liquid in pores, what is very important specific feature of the described structure. Let the domain D_1 is partially or completely surrounded by the domain D_2, filled by the same solution completely. In general case there may be a convective transfer in the domain D_2 and filtration flow in the domain D_1. Thus a general mathematical model of heat and mass transfer processes is considered system is following:

$$\frac{\partial T_1}{\partial \tau} + \left(V_f \cdot \nabla\right) T_1 = a_1 \Delta T_1 + q_{T_1}, \tag{1}$$

$$\frac{\partial C_{i1}}{\partial \tau} + \left(V_f \cdot \nabla\right) C_{i1} = d_{i1} \Delta C_{i1} + q_{i1}, \qquad i = \overline{1, N}, \tag{2}$$

$$\frac{\partial T_2}{\partial \tau} + \left(V_C \cdot \nabla\right) T_2 = a_2 \Delta T_2, \tag{3}$$

$$\frac{\partial C_{i2}}{\partial \tau} + \left(V_C \cdot \nabla\right) C_{i2} = d_{i2} \Delta C_{i2}, \qquad i = \overline{1, N}. \tag{4}$$

where T_1 is temperature in the domain D_1 (the one-temperature model, assuming the temperatures of frame and solution in pores are equal, is used here), V_f is filtration

velocity, a_1 is thermal diffusivity of porous media, q_{T_1} is heat source, concerning the metabolism of cells, C_{i1} is concentration of the *i*-th component in porous media, d_{i1} is diffusion coefficient of *i*-th component in the porous media, q_{i1} is sourse (sink) of the *i*-th component in porous media, concerning the metabolism of cells, T_2 is temperature in the domain D_2, V_2 is flow velocity in the domain D_2, a_2 is thermal diffusivity of solution, C_{i2} is concentration of *i*-th component in the domain D_2, d_{i2} is diffusion coefficient of *i*-th component in the domain D_2, N_{i2} number of components, participating of heat and mass transfer process, τ is time, Δ is Laplas operator.

Restrict the following consideration by the case:

$$V_f = 0, \tag{5}$$

$$V_C = 0, \tag{6}$$

what corresponds to conventional multicellular structure, formed by independent cells, that is simple colony of one-cellular organisms in immovable fluid. Then

$$\frac{\partial T_1}{\partial \tau} = a_1 \Delta T_1 + q_{T_1}, \tag{7}$$

$$\frac{\partial C_{i1}}{\partial \tau} = d_{i1} \Delta C_{i1} + q_{i1}, \qquad i = \overline{1, N}, \tag{8}$$

$$\frac{\partial T_2}{\partial \tau} = a_2 \Delta T_2, \tag{9}$$

$$\frac{\partial C_{i2}}{\partial \tau} = d_{i2} \Delta C_{i2}, \qquad i = \overline{1, N}. \tag{10}$$

If the condition (6) is not realised, it could be better to not consider the system (3), (4), but to take into acount a convective transfer using boundary conditions for equations (7), (8). This assumption is quite proved, since the system (7), (8) describes enough slow prosesses.

Let prescribe boundary conditions for the systems (7), (8) and (9), (10). Note the common boundary of the domain D_1 and D_2 as Γ and reminder part as Γ_1 and Γ_2 correspondingly. The first kind boundary conditions can be presribed on the boundaries Γ_1 and Γ_2:

$$T_1\big|_{\Gamma_1} = T_{1e}, \tag{11}$$

$$C_{i1}\big|_{\Gamma_1} = C_{i1e}, \tag{12}$$

$$T_2\big|_{\Gamma_2} = T_{2e}, \tag{13}$$

$$C_{i2}\big|_{\Gamma_2} = C_{i2e}, \tag{14}$$

or the second kind boundary condition

$$\lambda_1 \frac{\partial T_1}{\partial n}\bigg|_{\Gamma_1} = q_{1e}, \tag{15}$$

$$d_{1i} \frac{\partial C_{i1}}{\partial n}\bigg|_{\Gamma_1} = g_{i1e}, \tag{16}$$

$$\lambda_2 \left.\frac{\partial T_2}{\partial n}\right|_{\Gamma_2} = g_{2e}, \tag{17}$$

$$d_{i2} \left.\frac{\partial C_{i2}}{\partial n}\right|_{\Gamma_2} = g_{i2e}, \tag{18}$$

or the third boundary condition

$$\lambda_1 \left.\frac{\partial T_1}{\partial n}\right|_{\Gamma_1} + \alpha_1 \left(T_1 \Big|_{\Gamma_1} - T_{1e} \right) = 0, \tag{19}$$

$$d_{i1} \left.\frac{\partial C_{i1}}{\partial n}\right|_{\Gamma_1} + \alpha_{i1} \left(C_{i1}\big|_{\Gamma_1} - C_{i1e} \right) = 0, \tag{20}$$

$$\lambda_2 \left.\frac{\partial T_2}{\partial n}\right|_{\Gamma_2} + \alpha_2 \left(T_2\big|_{\Gamma_2} - T_{2e} \right) = 0, \tag{21}$$

$$d_{i2} \left.\frac{\partial C_{i2}}{\partial n}\right|_{\Gamma_2} + \alpha_{i2} \left(C_{i2}\big|_{\Gamma_2} - C_{i2e} \right) = 0, \tag{22}$$

where $T_{1e}, C_{i1e}, T_{2e}, C_{i2e}, g_{1e}, g_{i1e}, g_{2e}, g_{i2e}$ are known functions, all coefficients in boundary conditions (11) – (22) are understood in conventional sense. Let consider boundary conditions on the boundary Γ. It is evident, that

$$T_1\big|_{\Gamma} = T_0\big|_{\Gamma}, \tag{23}$$

$$C_{i1}\big|_{\Gamma} = C_{i2}\big|_{\Gamma}. \tag{24}$$

It is possible to formulate the second condition as a forth kind boundary condition.

$$\lambda_1 \left.\frac{\partial T_1}{\partial n}\right|_{\Gamma} = \lambda_2 \left.\frac{\partial T_2}{\partial n}\right|_{\Gamma}, \tag{25}$$

$$d_{i1} \left.\frac{\partial C_{i1}}{\partial n}\right|_{\Gamma} = d_{i2} \left.\frac{\partial C_{i2}}{\partial n}\right|_{\Gamma}. \tag{26}$$

Conditions (25), (26) correspond to the case of cell fission in whole domain D_1. However, it is possible the situation, when the fission of cells takes place only on the boundary Γ, then condition (25) is saved, but condition (26) must be replaced by following condition:

$$d_{i1} \left.\frac{\partial C_{i1}}{\partial n}\right|_{\Gamma} - d_{i2} \left.\frac{\partial C_{i2}}{\partial n}\right|_{\Gamma} = \chi_i \frac{\partial n}{\partial \tau}, \tag{27}$$

here $\frac{\partial n}{\partial \tau}$ is velocity of the boundary Γ propagation (velocity of biological structure growth), χ_i is "expenditure" coefficient of the *i*-th component during growth of biological structure. Note that the condition (27) is not conventional Stefan condition (nevertheless its form coincides with Stefan condition), because right hand part of the condition (27) is determined by fission process, that is by parameters determining the fission process such as the temperature, concentrations and possibly the histories, therefore right hand part of the condition (27) is prescribed. It means that the given problem is similar to phase transition problem under prescribed velocity of phase

boundary motion. The moving boundary velocity is determined in the considered problem as a function of metabolism intensity.

The case, when cellular mass growth takes place in whole domain D_1 is more complex then previous one. Consider a function describing metabolism intensity. As it is noted earlier, metabolism intensity is assumed proportional to a cellular mass growth (nevertheless the cell fission is very complex process with possibly enough large delay time that is with sufficient influence of previous history of the process). Let metabolism intensity function $\omega(T_1, C_{i1})$ is defined, then correspondent source terms are following:

$$q_{i1} = \chi_i \omega, \tag{28}$$

$$q_{\Gamma_1} = \chi_\Gamma \omega. \tag{29}$$

The function ω is determined experimentally. The following fig. 1 – 10 show possible dependencies of the function ω on temperature, concentrations of nutrient substances and excrements:

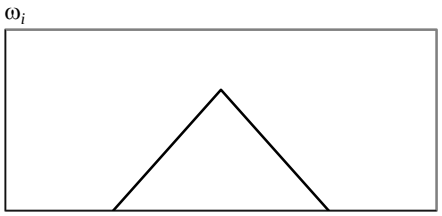

Fig. 1

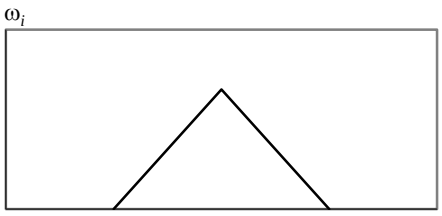

Fig. 2

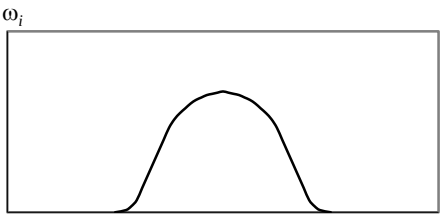

Fig. 3

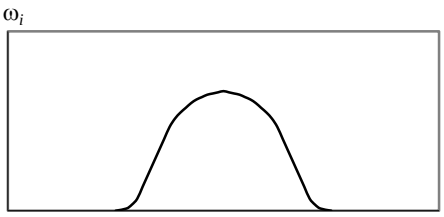

Fig. 4

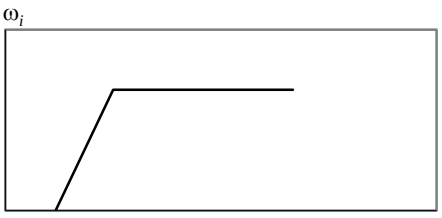

Fig. 5

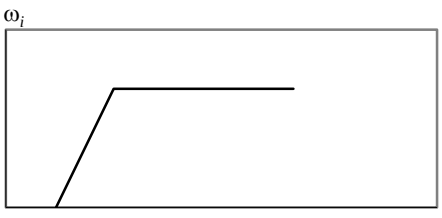

Fig. 6

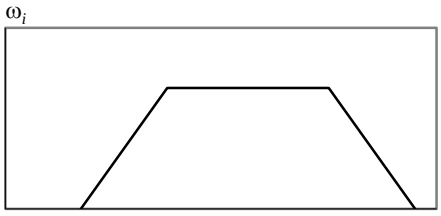

Fig. 7

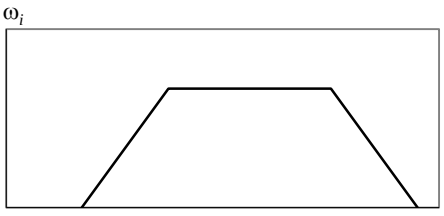

Fig. 8

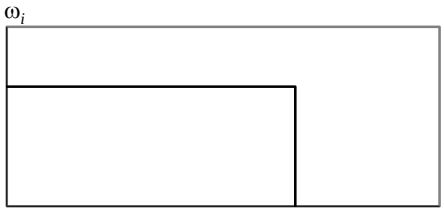

Fig. 9

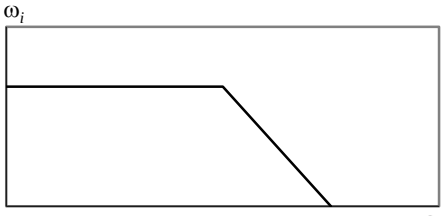

Fig. 10

where ω_i is function of influence of the *i*-th parameter on the metabolism velocity function. It is evident, that

$$\omega = \prod_{i=1}^{N+1} \omega_i . \tag{30}$$

The cases, presented on the fig. 1 – 4, correspond to existence of clear optimum of metabolism intensity. The cases 9 and 10 concern excrement concentration influence. As it is noted earlier the growth of cellular mass is proportional to metabolism intensity

$$q_s = \chi_s \omega - \chi_0 \omega_0 . \tag{31}$$

Terms indicated by «0» in last relationship correspond to regular metabolism, which is specific for tissues of highest animals.

Let consider a problem about motion of the boundary Γ again, in particular, let consider the case, when local volume change is determined by relation (31). The velocity (deformation) field depends on mechanical links between cells. If cells are «free» in intercellular solution the model of distributed sources in incompressible fluid can be applied, according to which the velocity of the boundary Γ is determined as

$$V_n(x_0) = \frac{\partial}{\partial n} \int_{D_1} q_s(x) \varphi_0(x, x_0) dx, \tag{32}$$

where x_i is arbitrary point of the curveline Γ.

If the cells are linked mechanically between themselves, to determine the motion of the boundary Γ it is necessary to solve an elasto-plastic problem, as a rule, under large strains. Consideration of such problems requires especial investigation and will not be made in the present work.

However, the another case is possible in biological structures, a biological structure grows saving its shape in this case. Thus change of the structure volume can be referred to the boundary Γ uniformly:

$$\delta\Omega_{D_1} = \int_{D_1} q_s(x)dx. \tag{33}$$

The replacement of the boundary Γ is determined by the following relation:

$$\delta\Gamma = \frac{\delta\Omega_{D_1}}{S}, \tag{34}$$

here S is square of surface Γ (length of curveline Γ in the plane case).

Dependencies, presented on fig. 1 – 10, and formalism, defined by the relationship (30), have universal nature and can be applied to any biological systems. However, more sophisticated metabolism processes are intrinsic for tissues of highest animals. If for simplest organisms linear dependence of growth velocity on metabolism intensity defined by relationship (31) is intrinsic, a tissue existence during an enough long time without growth, but under non-zero metabolism intensity, restricted by some limits, is possible for more complex multicellular organisms.

Other specific feature of metabolism processes in multicellular organisms is possibility of death of part of cells, without metabolism stopping. A death of cells of the simplest organisms is possible too, however there is possible practically stopping of metabolism without death of cells in the simplest organisms, what is completely impossible for multicellular one. Cell death in the case of multicellular organisms can be determined by several criteria:

1) metabolism intensity is less than the first critical level (but more than the second one) during enough long time (a cell doesn't perish due to starvation, but stops fission and dies as a result of old age);

2) metabolism intensity is less than the second critical level (a cell dies due to starvation);

3) concentration of some nutrient substance is less than the first critical level (but more than the second one) during enough long time (see fig. 5);

4) concentration of some nutrient substance is less than the second critical level;

5) excrement concentration is more than the first critical level (but is less than the second one) during enough long time (see fig. 10);

6) excrement concentration is more than the second critical level (see fig. 9);

7) presence of some poison, concentration of which is more than the first critical level (but is less than the second one) during enough long time;

8) pressure of some poison, concentration of which is more than the second critical level (mortal concentration) (see fig. 9);

9) external attack (mechanical, electrical, and radioactive);

10) death of cells due to action of immune system of the organism.

One-dimensional case. Consider a one-dimensional case. The governing equations in this case are

$$\frac{\partial T_1}{\partial \tau} = a_1 \frac{\partial^2 T_1}{\partial x^2} + q_{T_1}, \tag{35}$$

$$\frac{\partial C_{i1}}{\partial \tau} = d_{i1}\frac{\partial^2 C_{i1}}{\partial x^2} + q_{i1}, \quad i = \overline{1,N}, \tag{36}$$

$$\frac{\partial T_2}{\partial \tau} = a_2\frac{\partial^2 T_2}{\partial x^2}, \tag{37}$$

$$\frac{\partial C_{i2}}{\partial \tau} = d_{i2}\frac{\partial C_{i2}}{\partial x^2}, \quad i = \overline{1,N}. \tag{38}$$

Let prescribe boundary conditions. As earlier, one from three main boundary conditions can be prescribe, for example, the first kind boundary condition:

$$T_1\big|_{x=x_1} = T_{1e}, \tag{39}$$

$$C_{i1}\big|_{x=x_1} = C_{i1e},$$

$$T_2\big|_{x=x_2} = T_{2e}, \tag{40}$$

$$C_{i2}\big|_{x=x_2} = C_{i2e},$$

or the second kind boundary condition:

$$\lambda_1\frac{\partial T_1}{\partial x}\bigg|_{x=x_1} = q_{1e}, \tag{41}$$

$$d_{i1}\frac{\partial C_{i1}}{\partial x}\bigg|_{x=x_1} = q_{i1e},$$

$$\lambda_2\frac{\partial T_2}{\partial x}\bigg|_{x=x_2} = q_{2e}, \tag{42}$$

$$d_{i2}\frac{\partial C_{i2}}{\partial x}\bigg|_{x=x_2} = q_{i2e},$$

or the third kind boundary condition:

$$\lambda_1\frac{\partial T_1}{\partial x}\bigg|_{x=x_1} + \alpha_1\left(T_1\big|_{x=x_1} - T_{1e}\right) = 0, \tag{43}$$

$$d_{i1}\frac{\partial C_{i1}}{\partial x}\bigg|_{x=x_1} + \alpha_{i1}\left(C_{i1}\big|_{x=x_1} - C_{i1e}\right) = 0,$$

$$\lambda_2\frac{\partial T_2}{\partial x}\bigg|_{x=x_2} + \alpha_2\left(T_2\big|_{x=x_2} - T_{2e}\right) = 0, \tag{44}$$

$$d_{i2}\frac{\partial C_{i2}}{\partial x}\bigg|_{x=x_2} + \alpha_{i2}\left(C_{i2}\big|_{x=x_2} - C_{i2e}\right) = 0.$$

Let consider boundary conditions on the growth boundary $x = y$:

$$T_1\big|_{x=y} = T_0\big|_{x=y}, \tag{45}$$

$$C_{i1}\big|_{x=y} = C_{i2}\big|_{x=y}.$$

The following conditions correspond to case cell fission in whole domain D_1:

$$\lambda_1 \frac{\partial T_1}{\partial x}\bigg|_{x=y} = \lambda_2 \frac{\partial T_2}{\partial x}\bigg|_{x=y}, \tag{46}$$

$$d_{i1} \frac{\partial C_{i1}}{\partial x}\bigg|_{x=y} = d_{i2} \frac{\partial C_{i2}}{\partial x}\bigg|_{x=y}. \tag{47}$$

The last condition must be replaced by following condition for the case, when cell fission takes place only on the tissue boundary:

$$d_{i1} \frac{\partial C_{i1}}{\partial x}\bigg|_{\Gamma} - d_{i2} \frac{\partial C_{i2}}{\partial x}\bigg|_{\Gamma} = \chi_i \frac{\partial x}{\partial \tau}. \tag{48}$$

Let consider as the simplest example one-dimensional (in space) one phase Stefan problem, which is described by the following equation:

$$\frac{\partial C}{\partial \tau} = d \frac{\partial^2 C}{\partial x^2} + q, \tag{49}$$

with the boundary conditions:

$$C\big|_{\Gamma} = C_e, \tag{50}$$

$$C\big|_{\Gamma_{p.t.}} = C_{p.t.}, \tag{51}$$

$$\frac{\partial C}{\partial x}\bigg|_{\Gamma} = q_e, \tag{52}$$

$$d \frac{\partial C}{\partial x}\bigg|_{\Gamma} = \chi \frac{\partial y}{\partial \tau}, \tag{53}$$

where $\Gamma_{p.t.}$ is the boundary of phase transformation, y is its coordinate.

Let transform the problem into dimensionless form. Let $\overline{C} = \dfrac{C - C_k}{C_n - C_k}$ is the dimensionless concentration, $X^* = \dfrac{x}{l}$ is dimensionless coordinate, $F = \dfrac{\tau d}{l^2}$ is the some dimensionless number similar to number of Fourier in the theory of a thermal conduction.

Then the dimensionless form of the initial equation is

$$\frac{\partial \overline{C}}{\partial F} = \frac{\partial^2 \overline{C}}{\partial X^*} + q, \tag{54}$$

and dimensionless form of boundary conditions

$$\overline{C}\big|_{\Gamma} = \overline{C_e}, \tag{55}$$

$$\overline{C}\big|_{\Gamma_{p.t.}} = \overline{C}_{p.t.}, \tag{56}$$

$$\frac{d}{l}(C_n - C_k) \frac{\partial \overline{C}}{\partial X^*}\bigg|_{\Gamma} = q_e, \tag{57}$$

$$\frac{\partial \overline{C}}{\partial X^*}\bigg|_{\Gamma} = \frac{\partial Y^*}{\partial \tau_{st}}, \tag{58}$$

where $\tau_{st} = \dfrac{d(C_n - C_k)\tau}{\chi l^2}$ is dimensionless time, concerning motion of the boundary, $St = \dfrac{\tau_{st}}{F}$ is Stefan number.

Then the initial equation can be written as

$$\frac{\partial \overline{C}}{\partial \tau_{st}} St = \frac{\partial^2 \overline{C}}{\partial X^{*2}} + q. \tag{59}$$

As a rule, growth of biological tissue is rather slowly, therefore it is expedient to try to apply solution method, developed for slow phase transition calculation, to the considered problem. The mentioned approach is based on small parameter method, according to which the problem solution will be searched in form of series:

$$\overline{C}(x,\tau) = \overline{C}^0(x,\tau) + \sum_{k=1}^{\infty} St^k \overline{C}^k(x,\tau). \tag{60}$$

Let's substitute representations (60) in initial formulation of the problem (49) – (53), we shall receive:

$$St\frac{\partial \overline{C^0}}{\partial \tau} + St\frac{\partial}{\partial \tau}\sum_{k=1}^{\infty} St^k \overline{C^k} = \frac{\partial^2 \overline{C^0}}{\partial X^{*2}} + \frac{\partial^2\left(\sum_{k=1}^{\infty} St^k \overline{C}\right)}{\partial X^{*2}} + q, \tag{61}$$

$$St\frac{\partial \overline{C^0}}{\partial \tau} + \sum_{k=1}^{\infty} St^{k+1}\overline{\frac{\partial C^k}{\partial \tau}} = \frac{\partial^2 \overline{C^0}}{\partial X^{*2}} + \sum_{k=1}^{\infty} St^k \frac{\partial^2 \overline{C^k}}{\partial X^{*2}} + q, \tag{62}$$

$$\frac{\partial^2 \overline{C^0}}{\partial X^{*2}} + q = 0, \tag{63}$$

$$\frac{\partial^2 \overline{C^1}}{\partial X^{*2}} = \frac{\partial \overline{C^0}}{\partial \tau},\ \frac{\partial^2 \overline{C^i}}{\partial X^{*2}} = \overline{\frac{\partial C^{i-1}}{\partial \tau}}. \tag{64}$$

The general solution of the equation (63) is

$$C = a_1 x + b_1, \tag{65}$$

$$C = \iint q\,dx + a_2 x + b_2,\ (\text{if } q(x) \neq 0). \tag{67}$$

Let x_1 is the coordinate of the left-hand edge, x_2 is the coordinate of the right edge, and y is the coordinate of moving phase transition boundary. Let boundary-values of the functions are known:

$$C(x_1) = f_1,$$

$$C(x_2) = f_2,$$

$$C(x_2) = f_2,$$

$$d_1 \frac{dC_1}{dx} - d_2 \frac{dC_2}{dx} = V, \tag{68}$$

where $V = V(C)$ is velocity of phase transition boundary propagation, which one depends on function of a metabolism. The function of a metabolism is determined through concentrations of nutrient substances.

Let's consider the elementary case, if the velocity of promoting of boundary of linear growth of a cell is by a stationary value:

$$V = V(C). \tag{69}$$

Then we shall write a set of equations:

$$\begin{aligned} a_1 x_1 + b_1 &= f_1, \\ a_2 x_2 + b_2 + Q(x_2) &= f_2, \\ a_1 y + b_1 &= a_2 y + b_2 + Q(y), \\ d_1 a_1 - d_2 a_2 - d_2 \frac{dQ}{dx}\bigg|_{x=y} &= V. \end{aligned} \tag{70}$$

Let $d_2 \frac{dQ}{dx}\Big|_{x=y} = h$, then having decided (solved) a system (70), we can find coefficients a_1, a_2, b_1, b_2:

$$a_2 = \frac{f_1 - f_2 - Q(y) + Q(x_2) + (V + d_2 h)(y - x_1)\frac{1}{d_1}}{y + \frac{d_2}{d_1}(x_1 - y) - x_2}, \tag{71}$$

$$a_1 = \frac{1}{d_1}\left(V + d_2 \left(h + \frac{f_1 - f_2 - Q(y) + Q(x_2) + (V + d_2 h)(y - x_1)\frac{1}{d_1}}{y + \frac{d_2}{d_1}(x_1 - y) - x_2} \right) \right), \tag{72}$$

$$b_1 = f_1 - \frac{x_1}{d_1}\left(V + d_2 \left(h + \frac{f_1 - f_2 - Q(y) + Q(x_2) + (V + d_2 h)(y - x_1)\frac{1}{d_1}}{y + \frac{d_2}{d_1}(x_1 - y) - x_2} \right) \right), \tag{73}$$

$$b_2 = f_2 - Q(x_2) - x_2 \frac{f_1 - f_2 - Q(y) + Q(x_2) + (V + d_2 h)(y - x_1)\frac{1}{d_1}}{y + \frac{d_2}{d_1}(x_1 - y) - x_2}. \tag{74}$$

Let's consider a case, if the velocity of promoting of boundary of linear growth (increase) linearly depends on concentration:

$$V = kC. \tag{75}$$

Then we shall note a set of equations:

$$\begin{aligned} a_1 x_1 + b_1 &= f_1, \\ a_2 x_2 + b_2 + Q(x_2) &= f_2, \\ a_1 y + b_1 &= a_2 y + b_2 + Q(y), \\ d_1 a_1 - d_2 a_2 - d_2 \frac{dQ}{dx}\bigg|_{x=y} &= k(a_1 y + b_1). \end{aligned} \tag{76}$$

Having decided (solved) this system, we shall discover coefficients a_1, b_1, a_2, b_2:

$$a_1 = d_2 \frac{\frac{dQ}{dX} + \frac{f_1 + f_2 - Q(x_2) + Q(y)}{y - x_2}}{d_1 - k(y - x_1) + \frac{(x_1 + y)d_2}{y - x_2}}, \tag{77}$$

$$a_2 = (d_1 - ky + kx_1)\frac{\frac{dQ}{dX} + f_1 + f_2 - Q(x_2) + Q(y)}{d_1 - k(y - x_1) + \frac{(x_1 + y)d_2}{y - x_2}} - \frac{kf_1}{d_2} - \frac{dQ}{dX}, \tag{78}$$

$$b_1 = f_1 - x_1 d_2 \frac{\frac{dQ}{dX} + f_1 + f_2 - Q(x_2) + Q(y)}{d_1 - k(y - x_1) + \frac{(x_1 + y)d_2}{y - x_2}}, \tag{79}$$

$$b_2 = f_2 - x_2 \left[z(d_1 - ky + kx_1)\frac{\frac{dQ}{dX} + f_1 + f_2 - Q(x_2) + Q(y)}{d_1 - k(y - x_1) + \frac{(x_1 + y)d_2}{y - x_2}} - \frac{kf_1}{d_2} z - \frac{dQ}{dX} \right]. \tag{80}$$

Boundary element method application. The above-developed algorithm cannot be directly applied to the two-dimensional and three-dimensional problems because boundary-value problems for partial differential equations arise in the mentioned cases instead boundary-value problems for ordinary differential equations as above. Thus two- and three-dimensional cases require some numerical method for solution of elliptic boundary-value problems in moving boundary domain. The most powerful tool for such problems is boundary element method [6; 8], which requires a reformulation of the considered problems as boundary integral equations.

Let consider the initial boundary value problem (7) – (27). Small parameter method application to this problem is, generally speaking, similar to above one-dimensional case application (see, for example, [2; 3]). Restrict the following consideration by plane case

and by zero approximation of small parameter method, what corresponds to very small value of the Stefan number analog. Thus

$$\Delta T_1^0 = -\frac{q_{T_1}}{a_1}, \tag{81}$$

$$\Delta C_{i1}^0 = -\frac{q_{i1}}{d_{i1}}, \qquad i = \overline{1,N}, \tag{82}$$

$$\Delta T_2^0 = 0, \tag{83}$$

$$\Delta C_{i2}^0 = 0, \qquad i = \overline{1,N}. \tag{84}$$

Boundary conditions for the system (81) – (84) coincide with boundary conditions for the initial system. Let apply methods of potential theory to the system (81) – (84).

$$\chi(x_0)T_1^0(x_0) = \int_{\Gamma_1} \varphi_0(x,x_0)\frac{\partial T_1^0}{\partial n}\,ds - \int_{\Gamma_1} T_1^0\,\frac{\partial \varphi_0(x,x_0)}{\partial n}\,ds + \int_D \varphi_0(x,x_0)\frac{q_{T_1}}{a_1}\,dx\,dy, \tag{85}$$

$$\chi(x_0)C_{i1}^0(x_0) = \int_{\Gamma_1} \varphi_0(x,x_0)\frac{\partial C_{i1}^0}{\partial n}\,ds - \int_{\Gamma_1} C_{i1}^0\,\frac{\partial \varphi_0(x,x_0)}{\partial n}\,ds + \int_D \varphi_0(x,x_0)\frac{q_{i1}}{d_{i1}}\,dx\,dy, \tag{86}$$

$$\chi(x_0)T_2^0(x_0) = \int_{\Gamma_2} \varphi_0(x,x_0)\frac{\partial T_2^0}{\partial n}\,ds - \int_{\Gamma_2} T_2^0\,\frac{\partial \varphi_0(x,x_0)}{\partial n}\,ds, \tag{87}$$

$$\chi(x_0)C_{i2}^0(x_0) = \int_{\Gamma_2} \varphi_0(x,x_0)\frac{\partial C_{i2}^0}{\partial n}\,ds - \int_{\Gamma_2} C_{i2}^0\,\frac{\partial \varphi_0(x,x_0)}{\partial n}\,ds. \tag{88}$$

Here the function $\varphi_0(x,x_0)$ is well-known fundamental solution of Laplace equation, which is in plane case

$$\varphi_0(x,x_0) = \frac{1}{2\pi}\ln\left(\frac{1}{\sqrt{(x-x_0)^2+(y-y_0)^2}}\right),$$

and function χ is determined by the observation point position:

$$\chi(x_0) = \begin{cases} 0, (x_0) \notin D, (x_0) \notin \Gamma \\ 1/2, (x_0) \in \Gamma \\ 1, (x_0) \in D. \end{cases}$$

The system (85) – (88) can be easy solved by conventional boundary element method. A specific feature of the problem is boundary condition on the boundary $\Gamma = \Gamma_1 \cap \Gamma_2$, that is boundary of growth. If the forth kind boundary conditions are prescribe on the Γ (volume growth), then correspondent integral equations are simply coupled on the curve-line Γ. If correspondent fluxes on the curve-line Γ are discontinuous, then the gap value on previous time step is used.

A quite natural problem of calculation of last domain integrals in equations (85), (86) arise during the numerical solution. As a rule, it leads to serious computational difficulties, however since the time scale of growth process is enough large and the source terms in the initial equations (81), (82) are understood as averaged in time, the considered source terms are often constant with respect to space variables. The case of constant source is considered in the present work. The domain integrals can be easy transformed in this case

$$\int_{D_1} \varphi_0(x, x_0) q\, dxdy = q \int_{D_1} \operatorname{div} \operatorname{grad} \varphi_1 dxdy = q \int_{\Gamma_1} \frac{\partial \varphi_1}{\partial n} ds, \qquad (89)$$

where $\Delta\varphi_1 = \varphi_0$, that is $\varphi_1 = -\frac{r^2}{8\pi}(\ln r - 1)$.

The results of numerical calculations of model problems of growth of one-cell organism colony are shown in fig. 11, 12 and in tab. 1, 2.

Table 1

Mass of growing biological structure shown in fig. 11

Time (h)	Mass of biological structure
0	0,28378030
1	0,28792960
2	0,29541710
3	0,30700770
4	0,32328381
5	0,34431560
6	0,37013320
7	0,40161840

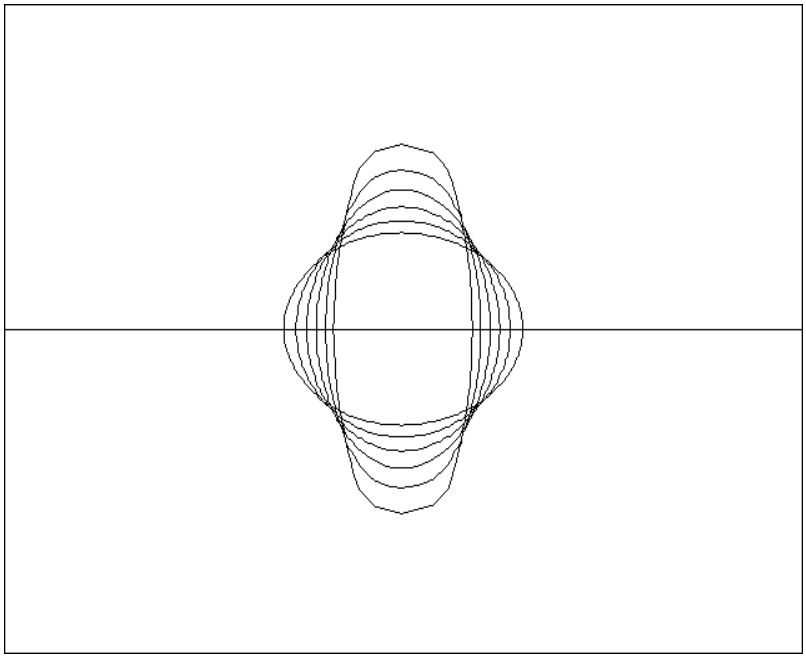

Fig. 11. Growth of biological structure, nitritions are going into the domain from above and from below

Table 2

Mass of growing biological structure shown in fig. 12

Time (h)	Mass of biological structure
0	0,28751980
1	0,30294060
2	0,32969960
3	0,36981910
4	0,42709790
5	0,50863440
6	0,63095590

Growth in direction of maximum concentration of nutrition is evident in both cases. Note only that the structure shown in fig. 11 and 12 initially were the same structure and only nutrition concentrations were different.

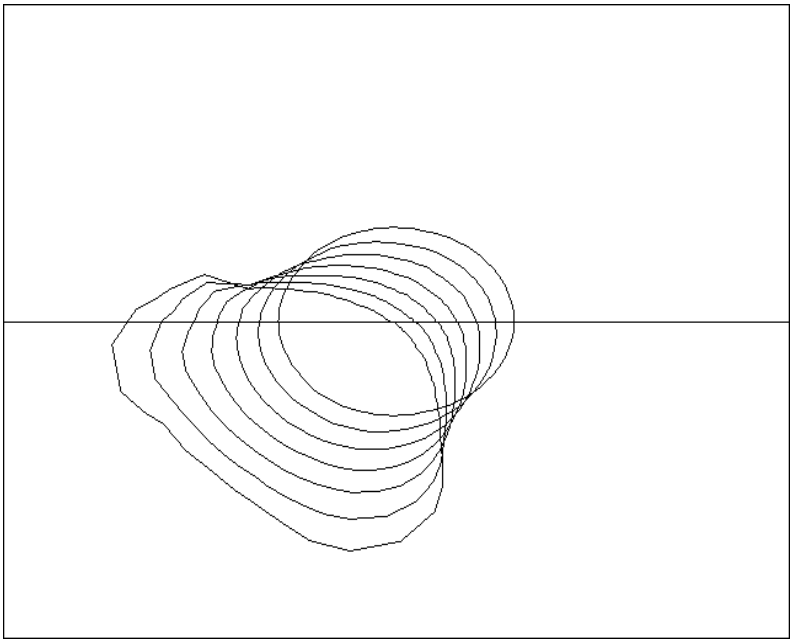

Fig. 12. Growth of biological structure, nitritions are going into the domain from left and from below

Conclusions. The main idea of the present paper is to develop a computational method for the problem of biological structure growth, based on the fact that biological growth is relatively very slow process. Considered circumstance leads to asymptotic analysis based on smallness of relation of correspondent time scales. Nevertheless the problem was formulated in quite general form, as a result of asymptotic analysis by small parameter method it is managed to build an analytical solution in one-dimensional case and to propose effective boundary element algorithm for numerical solution.

Calculations of specific biological structures did not concern the aim of the present work. However the examples of calculations of special model problems show workability and effectiveness of the proposed method.

The next stage of investigation concerning applications of the developed approach to the specific biological problems will be object of following papers, however it will

require an improvement of dependencies, presented in fig. 1 – 10. The following development of the model which can lead to taking into account of filtration flow inside the biological structure, convective effects in surrounding fluids, complex source fields, will require only some computational changes, but will not change the algorithm in general.

There is a quite natural question about applicability of the algorithm to the very important problem of tumor growth. The answer remains unclear at the moment, because it is unclear can the used metabolism model describe a tumor growth process or not. However there is not any mathematical insuperable hindrance, but only biological.

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