

# Two models of protoplasm microstructure of the living cell in resting state

D.V. Prokhorenko\*, V.V. Matveev †

September 15, 2011

## Abstract

In order to develop the methods of thermodynamic analysis for the living cell, two models of protoplasm microstructure of the living cell in resting state were suggested. Both models are based on the assumption that the Ling's cell as a statistical mechanics system is non-ergodic. In the first, Van der Waals model, the protein-protein interactions, which form the physical basis for the cell functioning, are considered as a interactions of key importance. It is postulated that protein molecules are situated in points of some space lattice (the Ling model of a cell) they assemble to aggregates at equilibrium state, corresponding to the dead protoplasm. In the second model we consider protein conformation at the resting state and conformation changes while the cell is passing from the resting state to the equilibrium state (dead protoplasm). The investigation of the models and comparison of their characteristics showed that the convenient tool to define the energy minimum of the system under consideration is a Hamiltonian describing the superfluid Bose gas on protein configuration space. Our approach allows us to define the thermodynamic features of the living (at resting state) and dead protoplasm in a new way: in the first case the system is characterized by the unfolded state of proteins, in the second case proteins are folded and aggregated. Obtained results prove the applicability of our approaches for thermodynamic characteristics of the Ling model of a cell.

---

\*Institute of Spectroscopy, Russian Academy of Sciences, 142190 Moscow Region, Troitsk, prokhordv@yandex.ru

†Institute of Cytology, 194064 Russian Academy of Sciences, Saint Petersburg, vladimir.matveev@gmail.com

# 1 Introduction

R. Feynman wrote: "All things are made of atoms, and that everything that living things do can be understood in terms of the jiggling and wiggling of atoms." (Feynman, 1963). To move beyond this assertion, it is necessary to adopt common principles of organization of atoms and molecules in living systems. These principles, compatible with the existing analytical apparatus of thermodynamics and statistical physics, have been formulated by Gilbert Ling (Ling, 2006). The living cell model created by him was used as a starting point of his study.

According to Ling, fundamental properties of the living cell are explained by the single physical factor — sorption properties of its proteins. An unfolded (linear) protein molecule binding water (multilayer adsorption) and  $K^+$  (in the presence of  $Na^+$ ) under the control of ATP represents the smallest part (unit) of a living protoplasm which still keeps the main physical characteristics of the living cell. Later Matveev (2005) offered to call the unit as a physiological atom or physioatom.

The main physical state of the physioatom, and accordingly, the cells comprising them, is, according to Ling, a resting state. The physical nature of this state determines, on the Ling's theory, all forms of biological activity of the cell and therefore the analysis of this state is a key issue of the physical theory of the living cell.

Compatibility of the Ling's resting cell organization principles with analytical methods of modern theoretical physics was first shown in our previous work (Prokhorenko and Matveev, 2011). The base of our approach is the fact that the majority of statistical mechanics systems (including the most realistic ones) are non-ergodic that was proved by one of us (Prokhorenko, 2009). The generalized thermodynamic analysis (generalized thermodynamics) of Ling's cell we proposed (Prokhorenko and Matveev, 2011) allowed us to explain (in framework of adopted boundary conditions) a number of physiological phenomena that occur when cell is in activated (excited) state: exothermicity of transition to excited state, change of cell volume, folding of natively unfolded proteins (which determine, by Ling, a main features of the resting state), efflux of cell  $K^+$  and wider — major redistribution of physiologically important ions between the cell and its environment. However, we determined the sign (direction) only of these processes, there were no numerical evaluations. In other words, the results were obtained as inequalities. These are the normal features of

thermodynamics (not of the generalized one only): it allows us to obtain general relations between thermodynamic variables which are independent on a nature of intermolecular interactions. It is needed to construct models with desired properties (including microscopic models) to obtain specific numerical values of thermodynamic variables and then investigate them by methods of statistical mechanics.

Indeed, inequalities we have determined (Prokhorenko and Matveev, 2011) were based on the postulate of relative entropy maximum for the resting cell standing in the state of thermodynamic equilibrium with environment. However, an equilibrium with environment does not mean the equilibrium state (the absolute maximum of entropy) of a system; that's why the relative nature of the entropy maximum is indicated. We consider the resting cell as a system in a steady non-equilibrium state described by the generalized Gibbs distribution (Prokhorenko and Matveev, 2011). In other words, the case is the maximum among of all the states described by generalized Gibbs distributions and constructed using the fixed set of first integrals in the involution. These inequalities give evidences of the negative determinacy of the second entropy derivative matrix with respect to parameters describing a system in a state corresponding to the relative entropy maximum.

Involvement of statistical mechanics methods brings up an issue of certain properties of the investigated system. Ling's model of the living cell gives, in our opinion, an interesting material for such analysis. So, after construction of the generalized thermodynamics of the resting state, set out in (Prokhorenko and Matveev, 2011), it makes sense to turn to some of the structural characteristics of the investigated system (as it often happened in the history of thermodynamics and statistical mechanics). In our case, the problem arises of constructing various models of protoplasm, and their investigation by various (mostly approximate) methods of theoretical physics. In this paper, the authors make the first steps in this direction.

The first model, we call the Van der Waals model, focuses on the nature of interactions between protein molecules only. As Ling, we assume that protein molecules in the resting cell embedded at specific sites in the lattice of a crystal, and the distances between proteins are so long that interaction between them can be neglected. This assumption makes it possible to use the method for calculating thermodynamic potentials of ideal systems in order to determine thermodynamic potentials of the resting protoplasm with a specified

structure. In the case of dead protoplasm (the state opposite to the living resting state), the protein molecules are associated due to secondary (non-covalent) bonds in large equilibrium aggregates. In this case, to calculate thermodynamic potentials we use the formula, we have obtained in this paper, for corrections of free energy values in the case of formation of large aggregates.

As part of the Van der Waals model we have obtained (i) numerical estimation for heat amount released when erythrocyte die, (ii) the estimation for number of protein aggregates appeared in dead protoplasm, and (iii) the estimation for fraction of whole cell volume occupied by these aggregates. All these estimates are in good (qualitative) agreement with available experimental data.

In our second model, we also assume that protein molecules in the resting cell embedded at specific sites in the lattice of a crystal, but at this time the focus is on internal structure of a protein. We consider this model at zero temperature (the energy scale), which makes it possible to use (to calculate the ground state) some effective Hamiltonian describing a superfluid Bose gas in the configuration space of a protein molecule. Based on the representations set forth in (Prokhorenko and Matveev, 2011), we define parameters of effective Hamiltonian corresponding to living and dead states of protoplasm; we show (in accordance with our assumptions) that proteins in the resting state (that determine key properties of the system) are natively unfolded, whereas in dead protoplasm the same protein molecules are folded.

In Appendix 1 the process when the living protoplasm transforms into a dead one is considered as it appears in the physical point of view. In Appendix 2 we discuss the mechanism by which ATP is able to effectively influence sorption properties of proteins of Ling's model for water and physiologically important cations.

## **2 Non-Ergodicity and Crystallization**

Let's consider some non-trivial issues that arise when we consider the cell as a nonergodic system. According to the Ling's model (Ling, 2001), water in the resting cell is in a bound quasi-crystalline state (important, water content is about 44 mole/kg wet weight of the cell). The bound state of water and its massive amount in the cell has fundamental importance for

the understanding of physiological processes (Ling, 1997). Therefore, one of key issues of cell physics is the question: which properties the crystal has in terms of our recently proposed approach, generalized thermodynamics (Prokhorenko and Matveev, 2011) Let's begin the consideration of this issue with finding out the relation between non-ergodicity of a system (for example, the Ling's cell) and its solidifying capability at low temperatures.

Despite this problem definition is non-physiological, its solution will allow us to verify once more that a large number of systems of statistical mechanics, including our model, have a non-ergodicity property. Our argument will be largely heuristic rather than rigorously mathematical character. In the mathematical physics the rigorous theory is often preceded by formal theories handling objects of poorly ascertained mathematical context. However, the heuristics presented here are of interest, in our view, as a basis for more rigorous methods.

At first, let's define the ergodicity for statistical mechanics systems.

**Definition.** Suppose the quantum system is described by Hamiltonian  $H$  and  $K_1, \dots, K_l$  are some commuting (among themselves) self-adjoint integrals of motion. The system is called ergodic with respect to the set of integrals  $K_1, \dots, K_l$  if any dynamical variable commuting with  $H, K_1, \dots, K_l$  is their function.

To give a classical analog of this definition we should just replace the word "commutator" by a Poisson bracket everywhere.

Usually, the operator of system momenta  $\vec{P}$  and operator of particles number  $N$  are used as trivial integrals.

At first let's show how the non-ergodicity of a system arises from its solidifying capability at low temperatures. Let's consider the system at solidifying temperatures, supposing them  $T < T_0$   $T_0 > 0$ . In addition, the system can move through the space as a solid body and its coordinates (as as solid body) are six real numbers

$$x_1, x_2, x_3, \varphi_1, \varphi_2, \varphi_3, \tag{1}$$

where  $x_1, x_2, x_3$  are Cartesian coordinates of the system's center of mass, and  $\varphi_1, \varphi_2, \varphi_3$  are some coordinates characterizing the position of a system (as a solid body) relative to its center of mass, for example, Euler angles. Let  $p_1, \dots, p_3, \pi_1, \dots, \pi_3$  be momenta canonically conjugated to them. The Hamiltonian of the whole system

$$\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3) \tag{2}$$

is a function of variables  $x_1, x_2, x_3, \varphi_1, \varphi_2, \varphi_3$ , conjugated momenta to them and operator "in other variables". Free energy of a system is given by:

$$F(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3 | T) = -T \ln \text{tr} e^{-\frac{\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3)}{T}}, \quad (3)$$

where trace is taken by Hilbert space which is "left" after separation of variables describing the motion of a system as a solid body. We won't refine the meaning of words enclosed in quotation marks considering them as intuitive clear. It's clear that  $F(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3 | T)$  does not depend on variable  $\varphi_3$  (if, for example,  $\varphi_1, \varphi_2, \varphi_3$  are Euler angles).

But

$$\ln \text{tr} e^{-\frac{\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3)}{T}} = \sum_{i=0}^{\infty} d_i(x_1, \dots, \pi_3) e^{-\frac{\lambda_i(x_1, \dots, \pi_3)}{T}}, \quad (4)$$

where  $d_i = \dim L_i$  is a dimension of eigenspace  $L_i$  of operator  $\hat{H}(x_1, \dots, \pi_3)$  corresponding to  $\lambda_i$  eigenvalue of operator  $\hat{H}(x_1, \dots, \pi_3)$ . But since  $\sum_{i=0}^{\infty} d_i(x_1, \dots, \pi_3) e^{-\lambda_i(x_1, \dots, \pi_3)\beta}$  ( $\beta := \frac{1}{T}$ ) does not depend on  $\varphi_3$  (for different  $\beta$ ), then  $d_i(x_1, \dots, \pi_3)$  and  $\lambda_i(x_1, \dots, \pi_3)$  are also independent of  $\varphi_3$ . Indeed  $\sum_{i=0}^{\infty} d_i(x_1, \dots, \pi_3) e^{-\lambda_i(x_1, \dots, \pi_3)\beta}$  is really a Laplace transform of a measure

$$\sum_{i=0}^{\infty} \delta(\lambda - \lambda_i(x_1, \dots, \pi_3)) d_i(x_1, \dots, \pi_3). \quad (5)$$

So, for all values  $\varphi_3$  when others values parameters  $x_1, \dots, \pi_3$  are the same, operators  $\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3)$  are unitary equivalent. And after making the appropriate unitary transformation of  $\mathcal{H}$  depending on  $x_1, \dots, \pi_3$ , we can conclude that  $\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3)$  do not depend on  $\varphi_3$ . We have considered variables  $x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3$  as classical ones since they describe macroscopic degrees of freedom and appear to be very large. Now we again consider  $\varphi_3, \pi_3$  as quantum variables, replacing them by corresponding operators  $\hat{\varphi}_3, \hat{\pi}_3$ , and considering the Hamiltonian  $\hat{H}_1(x_1, \dots, x_3, \varphi_1, \varphi_2, p_1, \dots, p_3, \pi_1, \pi_2)$  obtained by replacing the variables  $\varphi_3, \pi_3$  with the corresponding quantum-mechanical operators  $\hat{\varphi}_3, \hat{\pi}_3$ , in  $\hat{H}$  to describe our system. This operator acts in Hilbert space  $\mathcal{H} \otimes \Gamma$  where  $\Gamma$  is a Hilbert space corresponding to operators  $\hat{\varphi}_3, \hat{\pi}_3$ . The fact of independence of  $\hat{H}(x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3)$  of  $\varphi_3$  is stated now as commutativity of  $\hat{H}_1$  with  $\hat{\pi}_3$ , and the presence of nontrivial first integral of a system

means of course the Hamiltonian degeneracy. The last fact can indicate the non-ergodicity of the system, but this new integral should be commutative with the momenta operator. It can be achieved for example by consideration of the integral  $\Pi := \frac{\hat{\pi}_3}{G}$  instead of  $\hat{\pi}_3$ , where  $G$  behaves like  $\sim V^{\frac{5}{3}}$  if the volume  $V$  of the system approaches infinity. Then  $\Pi$  asymptotically commutes with the momenta operator which means the non-ergodicity of the system. The reason for choosing  $G \sim V^{\frac{5}{3}}$  is shown below.

However, instead of considering  $\Pi$  as a new independent integral we prefer other way. Variables  $x_1, \dots, x_3, \varphi_1, \dots, \varphi_3, p_1, \dots, p_3, \pi_1, \dots, \pi_3$  are canonically conjugated variables satisfying to the Hamilton's evolution at temperatures  $T < T_0$  for the Hamiltonian  $F(x_1, \dots, \pi_3|T)$  (see section 3). Just as we did before, we can show that  $F(x_1, \dots, \pi_3|T)$  does not depend on  $x_1, \dots, x_3, \varphi_1, \dots, \varphi_3$ . But the system in the equilibrium state has the energy (in the thermodynamic limit) proportional to the volume of this system, therefore  $E \leq CV$  for some constant  $C$ . On the other hand, if  $I_1, I_2, I_3$  are the eigenvalues of the inertia operator of our system as a solid body and  $\omega_1, \omega_2, \omega_3$  are components of angular velocity along corresponding principal axes of inertia operator, then  $E \geq \frac{I_1}{2}\omega_1^2 + \frac{I_2}{2}\omega_2^2 + \frac{I_3}{2}\omega_3^2$ . However,  $I_1, I_2, I_3 \sim V^{\frac{5}{3}}$ . Therefore, in the thermodynamic limit  $\omega_1 = \omega_2 = \omega_3 = 0$  and our system can move only parallel to itself in other words,  $\dot{\varphi}_1 = \dot{\varphi}_2 = \dot{\varphi}_3 = 0$ . So, variables  $\varphi_1, \varphi_2, \varphi_3$  are motion integrals of the system commuting with the impulse operator which makes our system non-ergodic one.

Since  $CV \geq E \geq \frac{I_1}{2}\omega_1^2 + \frac{I_2}{2}\omega_2^2 + \frac{I_3}{2}\omega_3^2 = \frac{\pi_1^2}{2I_1} + \dots + \frac{\pi_3^2}{2I_3}$ , and  $I_1, I_2, I_3 \sim V^{\frac{5}{3}}$  then  $\pi_1, \pi_2, \pi_3 \sim V^{\frac{4}{3}}$ .

At low angular velocities  $\omega_1, \dots, \omega_3$  the free energy of the whole system is presented as

$$F(x_1, \dots, \pi_3) = F_0(x_1, \dots, p_3) + \frac{I_1\omega_1^2}{2} + \dots + \frac{I_3\omega_3^2}{2}, \quad (6)$$

for some function  $F_0(x_1, \dots, p_3)$  of variables  $x_1, \dots, p_3$ . Momentum variables  $\pi_1, \dots, \pi_3$  can be chosen so that time rates of change of canonically conjugated coordinates may be equal to  $\omega_1, \dots, \omega_3$ . Then  $\pi_1 = I_1\omega_1, \dots, \pi_3 = I_3\omega_3$  and the effective Hamiltonian of the system equals to

$$F(x_1, \dots, \pi_3) = F_0(x_1, \dots, p_3) + \frac{\pi_1^2}{2I_1} + \dots + \frac{\pi_3^2}{2I_3}. \quad (7)$$

The form of this Hamiltonian together with the fact that in the thermodynamic limit  $\pi_1, \pi_2, \pi_3 \sim V^{\frac{4}{3}}$  imply that  $\varphi_1, \varphi_2, \varphi_3$  are the integrals of motion commuting with an operator of the total system momenta.

Now let us ask the question arising out of the context of our analysis: why the crystalline state of matter is stable at temperatures different from zero. The fact that matter solidifies at zero temperature is almost evident: configuration of the system must achieve the minimum potential energy. The question arises: why do atoms keep on doing just small oscillations around points of the lattice at non-zero temperature and why does the lattice remain faultless, though thermal fluctuations seem to break it. This question is closely related to the question of why Ling's cell is stable at relatively high temperatures. We shall try to answer with help of our generalized thermodynamics (Prokhorenko and Matveev, 2011).

So, let  $\mathcal{H}$  be a Hilbert space of our system,  $\hat{H}$  is a Hamiltonian of our system, and  $E_0$  is the lowest number belonging to spectrum, and  $\hat{E}_0$  is a spectral projection of  $\hat{H}$  onto the eigensubspace  $\hat{H}$  corresponding to the eigenvalue  $E_0$ .

In classical terms, at  $T = 0$  atoms composing the system have an arrangement which meets the condition of minimum potential energy. This means the body solidifies at  $T = 0$ . As we suppose, at that moment atoms are situated in points of a crystal lattice. But according to the accepted approach this lattices are not invariant under infinitesimal rotation, i.e. the system state obtained from the initial one by an infinitesimal rotation does not align with the initial one. This results degeneracy of  $E_0$ , i.e.  $\text{tr}\hat{E}_0 > 1$ .

Now let's complete  $\{\hat{H}\}$  to obtain the complete set of (commuting) observed values by self-adjoint operators  $\hat{K}_1, \hat{K}_2, \dots$ . Here we use Dirac terminology (Dirac, 1958).

Completeness of the system of observables  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$  means that their joint spectrum is simple (non-degenerated). Let  $P_1, P_2, \dots$  be orthogonal projectors in  $\mathcal{H}$  projecting to the subspaces of subspace  $\text{Im}\hat{E}_0$  (i.e.  $P_i\hat{E}_0 = \hat{E}_0P_i = P_i$ ) and are projections to their own subspaces of operators family  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$ . All  $P_1, P_2, \dots$  are clearly one-dimensional due to completeness of operators family  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$ . The generalized microcanonical distribution (Prokhorenko and Matveev, 2011) describing our system, can be taken, for example, in the following form:

$$\rho = P_f, \tag{8}$$

for any  $f$ .

Observed values of the integrals  $K_i, i = 1, 2, \dots$  in the state  $\rho$  are given by the following formula:

$$K'_i = \text{tr}(\rho K_i). \tag{9}$$

Let  $SO(3)$  be a group of self-rotations in Euclidean three-dimensional space,  $o$  is an arbitrary element of this group,  $\hat{o}$  is a unitary representation of  $o$  in the state space  $\mathcal{H}$  of our system. When subjected to transformation  $o \in SO(3)$  the state  $\rho$  comes to  $\hat{o}\rho\hat{o}^+$ . Let's show that, if necessary, replacing the complete set  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$  of observables by another complete set  $\hat{H}, \hat{L}_1, \hat{L}_2, \dots$  allows us to choose  $f$  from (8) so that for some  $o \in SO(3)$  and for some integer  $i$

$$\text{tr}(\rho K_i) \neq \text{tr}(\hat{o}\rho\hat{o}^+ K_i). \quad (10)$$

If the stated conclusion is false, then  $\forall i, j = 1, 2, \dots, \forall o \in SO(3)$ , we have

$$\text{tr}(\hat{o}P_i\hat{o}^+P_j) = \text{tr}(P_iP_j) = \delta_{ij}. \quad (11)$$

But the latest means that  $\forall i = 1, 2, \dots$

$$\hat{o}P_i\hat{o}^+ = P_i. \quad (12)$$

Let  $f_i$  be a unitary vector stretching the image  $P_i$ . It follows from (12) that  $\forall i = 1, 2, \dots$

$$\hat{o}f_i = \exp(i\varphi_i(o))f_i \quad (13)$$

for some functions  $\varphi_i(o)$  on  $SO(3)$ . The last conclusion is true for any complete set of observables  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$ . In particular it is clear that in (13) we can choose arbitrary the orthonormal basis  $\{f_i\}$  in  $\text{Im}\hat{E}_0$ . Thus  $\forall o \in SO(3)$ , the restriction of  $\hat{o}$  on  $\text{Im}\hat{E}_0$  should be diagonal in any orthonormal basis, therefore, the restriction of  $\hat{o}$  on  $\text{Im}\hat{E}_0$  must be proportional to identical operator. But  $SO(3)$  has no one-dimensional representations except the trivial one. Therefore,  $\forall o \in SO(3)$   $\hat{o} = 1$ . Thus, any ground state of our system under each rotation should come to itself; but it is false as we seen above. The statement is established.

So, the generalized microcanonical distribution  $P_f$  have the property that some rotation of a system causes the change of integral  $K_i$  averaged over this state for some  $f, i = 1, 2, \dots$

Now, if we give a sufficiently small non-zero temperature to our system, then (as it follows from the principle of physical continuity) for this temperature there exists a (generalized) equilibrium state described by a generalized microcanonical distribution  $\rho$ , such that after some system rotation the corresponding observable value of integral  $K_i$  must change for some  $i = 1, 2, \dots$ . But the system entropy does not change under the rotation of the system. This means that for a fixed energy (corresponding to enough small temperatures) the system

entropy has a plateau of  $d > 0$  dimensions that provides the stability of our generalized microcanonical distributions, as it was discussed in our previous work (Prokhorenko and Matveev, 2011).

In addition, let's remark that instead of speaking about the completeness of the system of observables  $\hat{H}, \hat{K}_1, \hat{K}_2, \dots$ , we should speak about the macroscopical completeness of this system. We say that the system of macroscopical observables quantities  $\hat{O}_1, \hat{O}_2, \dots$  is macroscopically complete if any macroscopical quantity (which clearly commutates with  $\hat{O}_1, \hat{O}_2, \dots$  because all macroscopical quantities are simultaneously measurable) is a function of observables quantities  $\hat{O}_1, \hat{O}_2, \dots$ .

Thus, for enough small temperatures the system have stable stationary states which are described by generalized microcanonical distributions which are not reduced to the common microcanonical distribution. We identify the crystal states of the matter exactly with such states, and the stability of the crystal state could be explained by just proven stability of the corresponding microcanonical distribution.

### 3 Van der Waals Model of Protoplasm

The general description of this model is presented in the introduction. Within the framework of this model and basing on our generalized thermodynamics, we give numerical estimates for some changes proceeding in a cell while it excites or becomes damaged: the amount of emitted heat by the cell and amount of released potassium ions from the cell to environment (according to Ling, potassium ions in the resting state are bounded by proteins).

Let's consider two extreme protoplasm states: resting state and "dead" protoplasm. First, let's discuss how does the dead protoplasm appear in the context of our model.

In the dead protoplasm protein molecules are in the folded state (Prokhorenko and Matveev, 2011), and we suppose they are homogeneous balls of radius  $r_0$  and dielectric permittivity  $\varepsilon'$ . The dielectric permittivity of the other matter in the cell is denoted by  $\varepsilon$ . Assume that  $M$  is a mass of a protein molecule. Since a protein molecule contains a lot of atoms,  $M$  is a very large quantity.

Let's write out the equation of motion which describes the motion of protein molecules. We suppose that the cell is described by classical mechanics, however further obtained results

clearly imply that the answer for the quantum case is the same. The motion of protein molecules may be considered as classical motion because of a high value of  $M$ . Let's denote  $x = (p, q)$  are coordinates and momenta of all protein molecules. Put by definition that  $y = (p', q')$  are coordinates and momenta of all other protoplasm components. Let  $H(x, y)$  be the Hamiltonian of the whole protoplasm. Then Hamilton's differential equations on  $x$  take the following form:

$$\begin{aligned}\dot{p} &= -\frac{\partial H(x, y)}{\partial q}, \\ \dot{q} &= \frac{\partial H(x, y)}{\partial p}.\end{aligned}\tag{14}$$

However, since the cell is dead, its distribution function is a Gibbs distribution function. In particular, the conditional probability density that variable  $x$  takes value  $x'$  provided variable  $y$  takes value  $y'$  is given by:

$$w(x'|y') = \frac{1}{Z_1(x')} e^{-\frac{H(x', y')}{T}},\tag{15}$$

where  $T$  is a system temperature and

$$Z_1(y') := \int dx e^{-\frac{H(x, y')}{T}}.\tag{16}$$

Since protein molecules move slowly and their mass  $M$  is very large (thousands of  $D$ ), in (14) we can replace right parts by their averages over distribution  $w(y|x)$ . Omitting rather trivial calculations, we find that the averaged system (14) is a Hamiltonian one too and the corresponding Hamiltonian is a free energy of the system. More specifically, the averaged system (14) is given by:

$$\begin{aligned}\dot{p} &= -\frac{\partial F(x|T)}{\partial q}, \\ \dot{q} &= \frac{\partial F(x|T)}{\partial p},\end{aligned}\tag{17}$$

where

$$F(x|T) := -T \ln \int dy e^{-\frac{H(x, y)}{T}}.\tag{18}$$

This is a standard adiabatic limit.

Note two more properties.

1. If our whole system (protoplasm) is described by a Gibbs distribution:

$$w(x, y) = \frac{1}{Z} e^{-\frac{H(x, y)}{T}}, \quad (19)$$

then, the distribution of probability that protein molecules are situated in the given point of phase space can be achieved by integrating (19) by  $dy$ . The distribution of probability  $w(x)$  to find protein molecules in the given point of the configuration space is:

$$w(x) = \text{const} e^{-\frac{F(x|T)}{T}}. \quad (20)$$

That is, again we received the Gibbs distribution in which the Hamiltonian is the effective Hamiltonian for protein molecules we received above.

2. By using a standard formula we can calculate the free energy of protein system  $F'(T)$  for Hamiltonian  $F(x|T)$ . Elementary calculations give:

$$F'(T) = F(T) := -T \ln \int dx dy e^{-\frac{H(x, y)}{T}}, \quad (21)$$

i.e.  $F'(T)$  equals to the free energy of the whole system  $F(T)$ .

Now let's define the form of our effective Hamiltonian  $F(x|T)$  as a function of coordinates and momentas of protein molecules. We suppose the contribution to  $F(x|T)$  nontrivially dependent on  $x$  is caused by Van der Waals interaction between protein molecules and therefore  $F(x|T)$  is given by:

$$F(x|T) = E_{kin}(p) + F_0(T) + \sum_{i>j} V(q_i - q_j|T), \quad (22)$$

where  $E_{kin}(p)$  is a kinetic energy of protein molecules as material points,  $F_0(T)$  is a function of temperature and  $q_i$   $p_i$ ,  $i = 1, 2, 3, \dots$  are Cartesian coordinates of protein molecules and canonically conjugated momenta.  $V(x|T)$ — is a pair interaction potential of the following form:

$$\begin{aligned} V(q|T) &= +\infty \text{ if } |q| < 2r_0, \\ V(q|T) &= -\frac{C}{r^6}, \text{ if } |q| \geq 2r_0, \end{aligned} \quad (23)$$

where  $C$  is some positive constant. The explicit formula expressing  $C$  in terms of  $\varepsilon$ ,  $\varepsilon'$ ,  $r_0$  can be retrieved, for example, from (Lifshitz and Pitaevsky, 1978). Now, we find thermodynamic variables for the case just described. The solution of this problem providing that

$$\frac{\min_{2r_0 < r} |V(r|T)|}{T} \ll 1 \quad (24)$$

is stated in many textbooks, for example (Landau, Lifshitz, 1995). However, in real cells (for example, erythrocyte) this condition is not fulfilled; this is a subject of a special analysis in the next section. For simplicity here we suppose that condition (24) is fulfilled.

In the case of the living cell, as we shall see later, the free energy of a cell is given by expression:

$$F(V, T)_l = F_0(V, T) + F_{id}(V, T), \quad (25)$$

where  $F_0(V, T)$  is a free water energy where all the proteins are eliminated and  $F_{id}$  is free protein energy calculated as if it was an ideal gas. For the dead protoplasm

$$F(V, T)_l = F_0(V, T) + F_{id}(V, T) + \Delta F(V, T), \quad (26)$$

where

$$\Delta F(V, T) = -T \ln \left[ \int_V \dots \int_V \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} e^{-\frac{1}{T} \sum_{1 \leq i < j \leq N} V(q_i - q_j | T)} \right]. \quad (27)$$

Note that when we use formulas (25), (26), (27), we neglect the conformational part of the free energy. There is one more omitted contribution to the free energy, which is caused by possibility of protein molecules rotation as a unit. However, these contributions for fully unfolded and folded protein conformation differ only by the value of const  $T$  and therefore, as it will be clear from the following, omitting of those contributions does not influence the final results.

For the case when (24) is fulfilled and a gas is so much rarefied that we can take into account only pair collisions, the calculations of integral (27) are made in many textbooks (for example, see (Landau and Lifshitz, 1995)). But to find  $\Delta F(V, T)$  in the real case we should derive an expression for  $\Delta F(V, T)$  when condition (24) is fulfilled and only pair collisions are taken into account. Therefore, we give here derivation for  $\Delta F(V, T)$  (condition (24) is fulfilled). Put by definition ( $U(q|T) := \sum_{1 \leq i < j \leq N} V(q_i - q_j | T)$ ). Then

$$\Delta F(V, T) = -T \ln \left[ \int_V \dots \int_V \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} \{ e^{-\frac{U(q|T)}{T}} - 1 \} + 1 \right] \quad (28)$$

If we take into account only pair collisions and suppose them rare, then the whole configuration space of the system  $\mathcal{C} = \mathbb{R}^3 \times \dots \times \mathbb{R}^3$  should be divided into subareas with equal

volume  $\mathcal{C}_{i,j}$ ,  $1 \leq i < j \leq N$  such that in each of them collisions of  $i$ -th and  $j$ -th particles happens. But in  $\mathcal{C}_{i,j}$   $U(q|T) = V(q_i - q_j|T)$  So:

$$\Delta F(V, T) = -T \ln \left[ \sum_{1 \leq i < j \leq N} \int_{\mathcal{C}_{i,j}} \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} \{ e^{-\frac{V(q_i - q_j|T)}{T}} - 1 \} + 1 \right]. \quad (29)$$

But pairs  $(i, j)$  such, that  $1 \leq i < j \leq N$  could be chosen by  $\frac{N(N-1)}{2} \approx \frac{N^2}{2}$  ways. So, we have

$$\begin{aligned} \Delta F(V, T) = -T \ln \left[ \frac{N^2}{2V^2} \int_V \int_V d^3 q_1 d^3 q_2 \{ e^{-\frac{V(q_1 - q_2|T)}{T}} - 1 \} + 1 \right] = \\ -T \ln \left[ \frac{N^2}{2V} \int_V d^3 q \{ e^{-\frac{V(q|T)}{T}} - 1 \} + 1 \right] \end{aligned} \quad (30)$$

Expanding the logarithm in a Taylor series near 1, the final result is

$$\Delta F(V, T) = -T \frac{N^2}{2V} \int_V d^3 q \{ e^{-\frac{V(q|T)}{T}} - 1 \}. \quad (31)$$

In the area  $r := |q| < 2r_0$   $\{ e^{-\frac{V(q|T)}{T}} - 1 \} = -1$  and in the area  $r > 2r_0$   $\{ e^{-\frac{V(q|T)}{T}} - 1 \} = -\frac{V(q|T)}{T}$  due to weakness of interaction. Put by definition:

$$\begin{aligned} b &= \frac{16\pi r_0^3}{3}, \\ a &= 2\pi \int_{2r_0}^{+\infty} |V(r|q)| r^2 dr. \end{aligned} \quad (32)$$

Notice by the way that using our choice of potential

$$a = \frac{\pi C}{12r_0^3}. \quad (33)$$

With these notations we can rewrite  $F(V, T)$  in the following way:

$$\Delta F(V, T) = T \frac{N^2}{V} \left( b - \frac{a}{T} \right). \quad (34)$$

So

$$\begin{aligned} S_d &= S_0 + S_{id} - b \frac{N^2}{V}, \\ E_d &= E_0 + E_{id} - \frac{N^2 a}{V}, \end{aligned} \quad (35)$$

where  $S_d$  and  $E_d$  are entropy and energy of the dead protoplasm respectively,  $S_0$  and  $E_0$  are entropy and energy of the protoplasm where all the protein molecules are eliminated and  $S_{id}$  and  $E_{id}$  are entropy and energy of the ideal gas of protein molecules.

That is a definition of the thermodynamic features of the dead protoplasm in our model. Now, let's consider the living protoplasm. Let's divide the effective Hamiltonian of the protein system obtained by the method of adiabatic limit into two summands:

$$H = H_{v-d-W} + H', \quad (36)$$

Here  $H_{v-d-W}$  contains the kinetic energy of proteins as material points and energy of the Van der Waals interaction between them. The Hamiltonian  $H'$  depends on variables describing internal degrees of freedom of proteins. We suppose that in a certain sense  $H' \ll H_k$ , where  $H_k$  is the kinetic energy of all protein molecules. Next, according to our common view (Prokhorenko and Matveev, 2011), in the living protoplasm some first integrals in the involution  $K_1, \dots, K_n$  are active and a statistical weight of protein molecules is given by:

$$W(E) = \int \prod_{i=1}^N dp_i dq_i \prod_{j=1}^n \delta(K_j - K'_j) \delta(H_{v-d-V} + H' - E), \quad (37)$$

where  $p_i, q_i$  are momenta and coordinates of  $i$ -th protein.

Let's try to define the form of integrals  $K_i$ . According to Ling, intracellular water in the resting living protoplasm is in the bound state and protein molecules form a paracrystals. Since we suppose the living state differs from non-living by activity of integrals  $K_i$ , then it's reasonable to assume that fixation of protein molecules in points of lattice is performed by means of multiplier  $\prod_{j=1}^n \delta(K_j - K'_j)$  in the integral of the statistical weight definition. Therefore, we just suppose that

$$\prod_{j=1}^n \delta(K_j - K'_j) = \prod_{i=1}^N \delta(q_i - q'_i), \quad (38)$$

where  $q_i$  are coordinates of  $i$ -th point of protein molecules lattice. But on the support of  $\prod_{i=1}^N \delta(q_i - q'_i)$  the potential energy of protein interaction  $\sum_{i>j} V(x_i - x_j|T)$  is a constant.

Furthermore, we can suppose that on the support  $\prod_{i=1}^N \delta(q_i - q'_i)$  the potential energy of proteins  $\sum_{i>j} V(q_i - q_j|T) = 0$ . Indeed, if proteins are situated in points of the lattice we mentioned above, then

$$\sum_{i>j} V(q_i - q_j|T) \sim \frac{N}{r^6}, \quad (39)$$

where  $r$  is a minimal distance between proteins. But  $r \sim (\frac{V}{N})^{1/3}$ . Therefore:

$$\sum_{i>j} V(q_i - q_j|T) \sim N(\frac{N}{V})^2. \quad (40)$$

Further we show that if the potential energy of protein molecules interaction is neglected, then, when the cell is dying, the quantity of emitted heat and the number of potassium ions released from the cell, calculated for one protein molecule, is a linear polynomial in  $\frac{N}{V}$  with an accuracy up to logarithmic factors. So, as follows from (40), in (37) in the limit of low density the potential energy of protein interaction in  $H_{v-d-W}$  can be neglected just kinetic energy  $H_k$ . Eventually, for the statistical weight:

$$W(E) = \int \prod_{i=1}^N dp_i dq_i \prod_{j=1}^N \delta(q_j - q'_j) \delta(H_k + H' - E). \quad (41)$$

Since  $H' \ll H_k$  we can write over this expression in the following way:

$$W(E) = \int \prod_{i=1}^N dp_i dq_i \prod_{j=1}^N \delta(q_j - q'_j) \delta(\sum_{i=1}^N \frac{p_i^2}{2M} - E). \quad (42)$$

Consequently with an accuracy of inessential multiplier, the statistical weight  $W$  equals to the statistical weight for the ideal gas. Therefore, in our model thermodynamic variables for the living protoplasm take the form of:

$$\begin{aligned} E_l &= E_0 + E_{id}, \\ S_l &= S_0 + S_{id}. \end{aligned} \quad (43)$$

Here  $E_l$  and  $S_l$  are entropy and energy of the living protoplasm. Obviously  $E_d < E_l$ , i.e. our model predicts that activation and death of the protoplasm is an exothermal reactions. Numerical evaluations are given in the next section. So, we have the following amount for the quantity of released heat:

$$Q = \frac{N^2 a}{V}. \quad (44)$$

The ability of variables  $q_i$  or closed to them play the role of motion integrals in our model is appeared from the following additional conclusions. Let's denote by  $E_{kin}$  a kinetic energy of one protein molecule. Obviously

$$|\dot{q}_i| \leq \sqrt{\frac{2E_{kin}}{M}} \sim \sqrt{\frac{T}{M}}. \quad (45)$$

Therefore, in the limit  $M \rightarrow \infty$  (very large mass of protein)  $\dot{q}_i = 0$  and  $q_i$  are motion integrals.

Now we define the number of potassium ions releasing from the dying cell. In our previous work (Prokhorenko and Matveev, 2011) the following formula was obtained. Let's suggest that the number of first integrals in the involution is so large that the number of active integrals can be characterized by continuous parameter  $s \in [0, 1]$ . In addition, the number of active first integrals is increasing function of  $s$  and a case of  $s = 0$  corresponds to the case when none of integrals is active, and case of  $s = 1$  corresponds to the case when all the first integrals are active. Supposes  $s$  infinitesimally varies  $s \mapsto s' = s - \delta s$ ,  $\delta s > 0$ , where  $s$  is infinitely small. Now, let's define the function of entropy  $(\delta f)(S)$  by the condition  $(\delta f)(S) = (\delta S)_E$ , ( $s \mapsto s' = s - \delta s$ ). This definition is correct due to a proven assertion (Prokhorenko and Matveev, 2011) that  $(\delta S)_E$  ( $s \mapsto s' = s - \delta s$ ,  $\delta s > 0$ ) is a constant along any adiabatic process. So, let  $s \mapsto s' = s - \delta s$ ,  $\delta s > 0$ ,  $\delta s$ , is infinitely small. As it was shown in (Prokhorenko and Matveev, 2011), the increasing of number of potassium ions in the cell  $\delta N$  can be found using the following formula:

$$\delta N = T(\delta f)'(S)\left(\frac{\partial S}{\partial \mu}\right)_T, \quad (46)$$

where  $\mu$  is a chemical potential of potassium ions in the cell.

First, let's define  $\left(\frac{\partial S}{\partial \mu}\right)_T$ . Suppose by definition  $\tilde{F}_0(V, T)$  is the free energy of the protoplasm where potassium ions absent.

Suppose by definition  $\tilde{F}_0(V, T)$  is the free energy of the ideal gas at temperature  $T$  while its mass equals to the mass of potassium ion  $M$  and the gas contains only one molecule. It is known (Landau and Lifshitz, 1995) that

$$\phi(V, T) = -T \ln\left[V\left(\frac{MT}{2\pi\hbar^2}\right)^{\frac{3}{2}}\right]. \quad (47)$$

Suppose by definition  $\psi(V, T)$  is potassium solvability in the protoplasm, i.e. change of the free protoplasm energy during transition of one potassium ion from the infinity to the given point. Then the change of the free protoplasm energy after adding one potassium ion to this protoplasm is just a sum of  $\varphi(T, V)$  and  $\psi(V, T)$ . So, the free energy of all the protoplasm is

$$\tilde{F}_0(V, T) \mapsto \tilde{F}(V, T) = \tilde{F}_0(V, T) + \varphi(T, V) + \psi(V, T). \quad (48)$$

If there are  $N$  potassium ions inserted to the protoplasm, but  $N$  is still very small, then an

interaction between different potassium ions can be neglected and we have:

$$\tilde{F}_0(V, T) \mapsto \tilde{F}(V, T) = \tilde{F}_0(V, T) + N\varphi(T, V) + N\psi(V, T) + NT \ln\left(\frac{N}{e}\right). \quad (49)$$

The last summand arises because of a common combinatorial multiplier  $\frac{1}{N!}$  included to definition of the partition function of potassium ions.

We neglect the solvability of potassium ions in our calculations, in other words we accept  $\psi(V, T) = 0$ .

Put by definition

$$\mathcal{A}(V, T) := V\left(\frac{MT}{2\pi\hbar^2}\right)^{\frac{3}{2}}. \quad (50)$$

Eventually, after introduction of  $N$  potassium ions into the protoplasm, the free protoplasm energy changes as follows:

$$\tilde{F}_0(V, T) \mapsto \tilde{F}(V, T) = \tilde{F}_0(V, T) + N\psi(T, V) + NT \ln\left(\frac{N}{e\mathcal{A}(V, T)}\right). \quad (51)$$

Notice that the quantity  $\frac{N}{\mathcal{A}(V, T)} \ll 1$  since by order of magnitude this value is a density of particles in phase-space cells of constant-energy surface and thus it is very small, because the gas of potassium ions, as we admitted, is strongly rarefied (particularly, this allows us to use formulas of the classic statistical mechanics).

Potassium adsorption is taken into account in the solvability  $\psi(V, T)$ . We supposed that this solvability equals to zero but this assumption is not quite right. After cell death the chemical potential of potassium ions, obtained by differentiating the free energy over with number of potassium ions, remains constant. Since while the cell is dying, it issues  $\approx 0.98$  of the total amount of potassium ions, solvability  $\psi(V, T)$  increases by  $T \ln 50$ . Though this section contains exact equalities, actually this equalities are approximate because we neglect a unity compared to  $\ln\left(\frac{N}{e\mathcal{A}(V, T)}\right)$  and change of  $\psi(V, T)$  by value of  $T \ln 50$ . However, the following analysis establishes that contribution of those omitted summands is inessential.

When  $N$  potassium ions are inserted into the protoplasm, the entropy changes as follows:

$$\tilde{S}_0(V, T) \mapsto \tilde{S}(V, T) = \tilde{S}_0(V, T) - N \ln\left(\frac{N}{e\mathcal{A}(V, T)}\right). \quad (52)$$

We have

$$\left(\frac{\partial \tilde{S}}{\partial \mu}\right)_T = \frac{\left(\frac{\partial \tilde{S}}{\partial N}\right)_T}{\left(\frac{\partial \mu}{\partial N}\right)_T}. \quad (53)$$

Further:

$$\left(\frac{\partial \tilde{S}}{\partial N}\right)_T = -\ln\left(\frac{N}{e\mathcal{A}(V, T)}\right). \quad (54)$$

And:

$$\mu = \left(\frac{\partial \tilde{F}(V, T, N)}{\partial N}\right)_T = T \ln\left(\frac{N}{e\mathcal{A}(V, T)}\right). \quad (55)$$

Therefore:

$$\left(\frac{\partial \mu}{\partial N}\right)_T = \frac{T}{N}. \quad (56)$$

Eventually:

$$\left(\frac{\partial \tilde{S}}{\partial \mu}\right)_T = \frac{N}{T} \ln\left[\frac{e\mathcal{A}(V, T)}{N}\right], \quad (57)$$

and

$$\delta N = N(\delta f)'(S) \ln\left[\frac{e\mathcal{A}(V, T)}{N}\right]. \quad (58)$$

## 4 Van der Waals Model of Protoplasm. Numerical Evaluations 1. Potassium Ions Efflux from the Cell and Heat Release

This section is concerned with getting numerical evaluations basing on the Van der Waals model (see above) and comparing them with experimental data. To specify model parameters (cell size, quantity of proteins and ions in the cell) we chose a human erythrocyte, the well-studied cell having a relatively simple structure-function organization.

It's known that potassium ions density in the living erythrocyte is estimated as  $n = 6.02 \times 10^{19} \text{ cm}^{-3}$ . Let's assume that when an erythrocyte is dying the potassium concentration in this erythrocyte becomes equal to the potassium concentration in the blood plasma, 2 – 4 mmol/l, i.e. about 0.96 – 0.98 of potassium ions, which the living cell contained, release from the erythrocyte.

We consider the cell at a temperature of  $300K$ . A potassium nucleus contains 19 protons and 20 neutrons, therefore, the mass of potassium ions can be estimated as  $39m_n$  where  $m_n$  is the mass of neutron.

In the previous section the formula was derived describing the change of a number of potassium ions in the cell when the infinitesimal change of a number of active integrals  $s \mapsto s' = s - \delta s$ ,  $\delta s$  is infinitely small. Let's write it one more time:

$$\delta N = N(\delta f)'(S) \ln\left[\frac{e\mathcal{A}(V, T)}{N}\right]. \quad (59)$$

The last formula (58) can be interpreted as a differential equation on  $N$ . Being integrated this equation expresses of potassium efflux from the dying cell through other cell parameters.

First, let's find  $(\delta f)'(S)$ . We have:

$$\delta f(S) = (\delta S)_E = (\delta S)_T - (\delta E)_T \left(\frac{\partial S}{\partial E}\right)_T. \quad (60)$$

But

$$\left(\frac{\partial S}{\partial E}\right)_N = \frac{1}{T} \quad (61)$$

Therefore

$$\delta f(S) = (\delta S)_E - \frac{1}{T}(\delta E)_T. \quad (62)$$

Using the fact that (see Prokhorenko and Matveev, 2011)

$$\frac{\partial(\delta S)_T}{\partial(\delta E)_T} = \frac{1}{T}, \quad (63)$$

we find

$$\frac{d\delta f(S(T))}{dT} = \frac{1}{T^2}(\delta E)_T. \quad (64)$$

And finally

$$(\delta f)'(S) = \frac{1}{T^2}(\delta E)_T \frac{\partial T}{\partial S} = \frac{1}{C_V T}(\delta E)_T, \quad (65)$$

where  $C_V$  is the heat capacity of the cell at the constant volume. Now, we assume the heat capacities of living and dead cells are almost the same, and in all following formulas the heat capacity of a cell can be replaced by an average value  $C_V$  which does not depend on the number of active first integrals in the involution. Eventually, we have

$$\frac{\delta N}{N} = -\frac{1}{TC_V}(\delta E)_T \ln\left[\frac{N}{e\mathcal{A}(V, T)}\right]. \quad (66)$$

For convenience of further calculations let's introduce a new variable

$$\Lambda := \frac{N}{e\mathcal{A}(V, T)}. \quad (67)$$

Then we have:

$$\delta \ln \Lambda = -\frac{1}{TC_V}(\ln \Lambda)(\delta E)_T. \quad (68)$$

As before, we use lower indexes  $l$  and  $d$  to denote variables relating to the living and dead cell respectively. Equation (68) is easy to integrate resulting:

$$\frac{\ln \Lambda_d}{\ln \Lambda_l} = \exp\left(\frac{Q}{C_V T}\right), \quad (69)$$

where  $Q$  is a heat amount released from the cell while it is dying.

The last formula gives an implicit expression for heat generation  $Q$  and its derivation was based just on common thermodynamic considerations without regard to properties of any certain model. Therefore, it can be used for verification of our generalized thermodynamics.

However, note that (69) is inconvenient for calculations, so, let's simplify it using smallness of  $\Lambda_l$ . For this purpose let's consider the expression  $\ln x$ , where  $x$  is a very small positive number. Then  $\ln x$  value is very large in modulus and has a sign minus. Let's increase  $x$  by factor of  $k$  where  $k$  is not too large natural number  $\ln x \mapsto \ln x + \ln k$  i.e. practically unalters. We have:

$$\frac{\ln \Lambda_d}{\ln \Lambda_l} = \left| \frac{\ln \Lambda_d}{\ln \Lambda_l} \right| = \exp\left\{ \int_{|\ln \Lambda_l|}^{|\ln \Lambda_d|} \frac{dx}{x} \right\}. \quad (70)$$

According to the newly stated remark, on the whole integrating interval we can replace  $x$  by  $|\ln \Lambda_l|$  and eventually we obtain:

$$\frac{\ln \Lambda_d}{\ln \Lambda_l} = \left\{ \frac{\Lambda_l}{\Lambda_d} \right\}^{\frac{1}{|\ln \Lambda_l|}}. \quad (71)$$

Eventually, we receive the following implicit expression for heat generation:

$$\frac{N_l}{N_d} = \exp\left\{ |\ln \Lambda_l| \frac{Q}{C_V T} \right\}. \quad (72)$$

Data listed in this section are enough to calculate  $|\ln \Lambda_l|$ . Omitting corresponding numerical calculations, we present the result:  $|\ln \Lambda_l| \approx 16.1$ . The resulting formula for heat generation is:

$$\frac{N_l}{N_d} = \exp\left\{ \frac{16.1Q}{C_V T} \right\}. \quad (73)$$

From here it is easy to find  $\frac{Q}{C_V T} \cdot \frac{N_i}{N_d} \approx 50$ .  $\ln 50 = 3.93$ . By taking a logarithm of both parts we find:

$$\frac{Q}{C_V T} \approx 0.24. \quad (74)$$

To check this heat generation value we can carry the following qualitative reasoning. Let's consider a human cell at temperature  $T_h = 37C = 310K$  or  $37^0C$ . The room temperature (normal for a man's functioning)  $T_r = 20C = 293K$ . According to Ling's theory, the cell life activity is expressed as the cycle motion "resting $\leftrightarrow$ exciting". If the cell was always in thermodynamic equilibrium with the thermostat, then, at transition "resting $\leftrightarrow$ exciting", the  $Q$  heat would released. Let's accept that in the resting state a cell has a room temperature. Let  $a$  be a digit making  $Q = \alpha C_V T$ . If the cell is heat sealed, then in transition from the resting state to the excited state the temperature of the cell rises from  $T_r$  to  $T_e$  and it is likely to be correct that there is an approximate correlation  $(T_e - T_r)/T_h = \alpha$ . Now, as the cell moves through time cyclically, we have a mean temperature for time  $T_h$ . It is reasonable to suggest that  $T_h = (T_e + T_r)/2$ , or in other words  $T_e - T_r = 2(T_h - T_r)$ . But  $T_h - T_r = 17K$ . Therefore  $T_e - T_r = 34K$  and  $\alpha = (T_e - T_r)/T_h = 34/310 = 0.11$ , which coincides with our result in the order of magnitude. The fact that the calculation for heat emission of the dying erythrocyte using data on potassium efflux from the cell appears approximately 2.5 times higher than just stated value is reasonable because the exciting can be considered as a stage towards death (Matveev, 2005).

The assumption we stated that the erythrocyte temperature at rest equals to the room one  $T_{room}$  can be explained in the following way. Since the erythrocyte moves through time cyclically: resting $\leftrightarrow$ exciting, then the erythrocyte can be considered as a heat engine, and room temperature is a temperature of a cooler of this engine. As the room temperature is the most comfortable for a man, we may consider that the erythrocyte at the room temperature, as at the cooler temperature, operates in the most optimum mode. The resting temperature  $T_r$  is the lowest temperature achieved by the erythrocyte during all the resting  $\leftrightarrow$  exciting cycle. If  $T_r > T_{room}$  is correct, then heat transfer from the erythrocyte to the cooler will beat tended by heat transfer from a warmer body to a colder one, i.e. entropy increase. This means the erythrocyte as a heat engine would operate not optimally. Conversely suppose that  $T_r < T_{room}$ . If the erythrocyte is functioning in the optimum mode (without entropy increase), then the erythrocyte have to pass the part of the cycle when the erythrocyte

temperature  $T < T_r$  being surrounded by an adiabatic "cover". It becomes incomprehensible why does the erythrocyte need this part of the cycle and also, according to Carnot's theorem on the efficiency of heat engines, erythrocyte efficiency could be raised by means of the cooler temperature (room temperature) decreasing.

Now let's try to calculate  $Q$  basing on our investigated (Van der Waals) model. For this purpose we should find an interaction constant  $C$  in the law  $V(r) = \frac{C}{r^6}$ . To do this, we proceed from the formula taken from (Lifshitz and Pitaevsky, 1978). Suppose there are two parallel non-overlapping semi-spaces and a distance between them is  $l$ . Let  $\varepsilon$  be a dielectric permittivity of the semi-spaces and  $\varepsilon'$  is a dielectric permittivity of the cavity between them. Suppose  $l$  is such a large that if  $\omega$  is a frequency of the electromagnetic wave distributed in the cavity between semi-spaces and having wavelength  $l$ , then  $\hbar\omega \ll T$ . That is obviously our case. Then, the force of attraction between two semi-spaces as per unit area of the border space of each semi-space is equal to:

$$P = \frac{T}{16\pi^2 l^3} \int_0^{+\infty} x^2 \left[ \left\{ \frac{\varepsilon + \varepsilon'}{\varepsilon - \varepsilon'} \right\}^2 e^x - 1 \right]^{-1} dx. \quad (75)$$

Now, suppose that the semi-spaces consist of folded hemoglobin molecules and the cavity between them is filled with water. The dielectric permittivity of the water  $\varepsilon = 81$  and the dielectric permittivity of the hemoglobin  $\varepsilon' \approx 2$ . Therefore, the factor  $\left\{ \frac{\varepsilon + \varepsilon'}{\varepsilon - \varepsilon'} \right\}^2 \approx 1$  and the force of attraction between two semi-spaces as per unit area of the border space of each of them is equal to

$$P = \frac{T}{16\pi l^3} \int_0^{+\infty} x^2 [e^x - 1]^{-1} dx. \quad (76)$$

The involved integral can be easily calculated with any desired degree of precision, for example:

$$\begin{aligned} \int_0^{+\infty} x^2 [e^x - 1]^{-1} dx &= \int_0^{+\infty} x^2 e^{-x} [1 - e^{-x}]^{-1} dx = \\ &= \int_0^{+\infty} x^2 [e^{-x} + e^{-2x} + e^{-3x} + \dots] dx = \\ &= 2 \left[ 1 + \frac{1}{2^3} + \frac{1}{3^3} + \dots \right] = 2 \left[ 1 + 1/8 + 1/27 + 1/64 + \dots \right] \approx 2.35. \end{aligned} \quad (77)$$

Therefore, we come to the following formula for the force of attraction between the semi-spaces:

$$P = \frac{2.35T}{16\pi l^3}. \quad (78)$$

Let  $V_{1H}$  be a volume of one hemoglobin molecule. Now, we can calculate a potential energy  $\mathcal{U}(l)$  per unit of the surface plane using a formula for attraction potential of two hemoglobin molecules (23) in the following way:

$$\mathcal{U}(l) = -\frac{C}{V_{1H}^2} 2\pi \int_0^{+\infty} r dr \int_0^{+\infty} dx \int_0^{+\infty} dy \frac{1}{(x+y+l)^2 + r^2)^3}. \quad (79)$$

Omitting rather trivial integrating we find

$$\mathcal{U}(l) = -\frac{\pi C}{12V_{1H}^2} \times \frac{1}{l^2}. \quad (80)$$

Differentiating the last expression with respect to  $l$  we find:

$$P = \frac{\pi C}{6V_{1H}^2} \times \frac{1}{l^3} \quad (81)$$

Comparing the last formula with (78) gives the following result:

$$C = V_{1H}^2 \frac{7.05T}{8\pi^2}. \quad (82)$$

It follows

$$a = V_{1H}T \times \frac{7.05}{72} = 9.79 \times 10^{-2} V_{1H}T \quad (83)$$

Note that everywhere above we measured the temperature  $T$  in energy units. Let  $T'$  be an absolute temperature expressed in Kelvin degrees. There is a relation  $T = k_B T'$  where  $k_B = 1.38 \times 10^{-16} \text{ergK}^{-1}$ . Hereafter  $Q_v$  means the heat released from a cell within the framework of the Van der Waals model. We want to estimate  $\frac{Q_v}{CT}$ . Then, for heat generation:

$$O_v = 1.35 \times 10^{-17} N^2 \left(\frac{V_H}{V}\right) \left(\frac{V_{1H}}{V_H}\right) \text{erg} \times K^{-1} T' \quad (84)$$

where  $V_H$  is the volume of all hemoglobin contained in the dead erythrocyte.

We need to know the cell volume  $V$ , volume of all hemoglobin  $V_H$  contained in the dead cell, mass of all the hemoglobin  $M_H$ , specific heat capacity of hemoglobin per unit

mass  $C_M$ . Calculating this data we find  $V = 10^{-10} \text{cm}^3$  (Levine et al., 2001).  $C_M = 3.2 \times 10^7 \text{erg g}^{-1} \text{K}^{-1}$  (Kholodny et al., 1987). Further it's known that hemoglobin concentration  $C_H = 5 \text{mmol} \times \text{L}^{-1}$ ,  $C_H = 5 \times 10^{-6} \text{mol} \times \text{cm}^{-3}$  (Van Beekvelt et al., 2001). The volume of "dead" hemoglobin is  $V_H = 32.6 \times 10^3 \text{cm}^3 / \text{mol}$  (Arosio et al., 2002).  $N = 3.02 \times 10^8$  (Van Beekvelt et al., 2001). Therefore,

$$\frac{V_H}{V} = 0.163 \quad (85)$$

But hemoglobin concentration in the human erythrocyte is  $0.33 \text{g/cm}^3$  (Van Beekvelt et al., 2001) and its density in the dead cell (in the supercluster) is approximately two times greater than the water density (Van Beekvelt et al., 2001; Arosio et al., 2002). It follows the mass of the erythrocyte  $M_C = 1.16 \times 10^{-10} \text{g}$ . The heat capacity  $C_V$  is  $C_V = M_C C_M = 3.71 \times 10^{-3} \text{erg K}^{-1}$ .

Let's calculate  $N^2 \frac{V_H}{V}$ . Taking into account that  $N^2 = 9.12 \times 10^{16}$ , we find

$$\frac{N^2 V_H}{V} = 1.49 \times 10^{16}. \quad (86)$$

Eventually

$$\frac{Q_v}{C_V T} = 54 \frac{V_{1H}}{V_H} \quad (87)$$

Here we see that if we take a true value  $\approx 3.3 \times 10^{-9}$  for  $\frac{V_{1H}}{V_H}$ , then the resulting value for  $\frac{Q_v}{C_V T}$  is many times smaller than  $\frac{Q_v}{C_V T} = 0.24$  we found before.

This fact has the following explanation. Our derivation of corrections to the free energy was correct only upon the following condition:

$$\frac{\min_{2r_0 < r} |V(r|T)|}{T} \ll 1 \quad (88)$$

Let's calculate the value in the right part of this inequality. Suppose two protein molecules are situated so that a distance between their centers is slightly more than  $2r_0$ . Then, the potential energy between them is  $U = -C \frac{1}{(2r_0)^6}$ . We have shown above that  $C = V_{1H}^2 T \frac{7.05}{8\pi^2}$ . Here, after elementary calculations, we find

$$\frac{U}{T} = \frac{7.05}{288} \approx 2.5 \times 10^{-2}, \quad (89)$$

i.e. our criterion is really fulfilled. However, when two protein molecules come to each other such close that  $2\pi\hbar \frac{c}{l} \approx 1$ , the forces whose contribution we did not take into consideration

before begin to play a significant role. We mean Casimir forces caused by the energy of zero-point oscillations of the electromagnetic field in the space between proteins, and which significantly exceed forces we took into consideration before. These forces can be interpreted as chemical ones. As a result, considering these new forces, it is reasonable to expect that in the real dead protoplasm the protein molecules stick together to balls or superclusters, and we should consider this effect in derivation of  $\Delta\tilde{F}(V, T)$ . The following section generalizes the derivation of corrections to the free energy in case of possible clustering, and it becomes clear that if  $V_{KH}$  denotes the volume of such a cluster and  $Q_v$  is a heat generation of the Van der Waals model, and  $Q_{kv}$  is a heat generation for the same model (considering the possible clustering), then

$$Q_{kv} = Q_v \frac{V_{KH}}{V_{1H}}. \quad (90)$$

As a result, we have

$$\frac{Q_{kv}}{C_V T} = 54 \frac{V_{KH}}{V_H} \quad (91)$$

If this new formula considering collective phenomena is correct, then we shall find that the dead protoplasm should contain  $\approx 225$  superclusters or aggregates, the properties of which we cannot characterize yet because the conclusion about the number of clusters is a result of a rather common theoretical analysis. On the other hand, the protein aggregation in case of the cell death is a well-known phenomenon.

## 5 Van der Waals Model of Protoplasm. Numerical Evaluations 2. Clustering of Protein Molecules

In this section we estimate a correction to the free protein energy  $\Delta F$  with respect to their clustering. The correction  $\Delta F(V, T, N)$  is

$$\Delta F = -T \ln \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} e^{-\frac{U(q)}{T}}. \quad (92)$$

Here  $q_1, \dots, q_N$  are Cartesian coordinates of all molecules having numbers  $1, \dots, N$  and symbol  $q$  means coordinates of all molecules:  $q := (q_1, \dots, q_N)$ .  $U(q)$  is given by

$$U(q) = U_u(q) + U_s(q). \quad (93)$$

Here  $U_u$  is a potential energy of the Van der Waals attraction between particles:

$$U_u(q) = \sum_{1 \leq i < j \leq N} V_u(q_i - q_j), \quad (94)$$

where

$$V_u(q) = -C \frac{1}{|q|^6}. \quad (95)$$

Hereafter  $C$  value is considered as a small parameter used to make any asymptotical expansions.

$$U_s(q) = U_s^1(q) + U_s^2(q), \quad (96)$$

where  $U_s^1(q)$  is a potential energy of repulsion between protein molecules, arising due to their volume is low bounded. For example:

$$\begin{aligned} U_s^1(q) &= \sum_{1 \leq i < j \leq N} V_s^1(q_i - q_j), \\ V_s^1(q) &= 0, \text{ if } |q| > 2r_0, \\ V_s^1(q) &= +\infty \text{ if } |q| \leq 2r_0, \end{aligned} \quad (97)$$

$r_0$  is a radius of the protein molecule.  $U_s^2$  is a potential energy of Casimir forces, arising in very closed distances between protein molecules due to zero-point oscillations of the electromagnetic field in the gap between separate proteins. These forces are short-ranged but they have a high degree of cooperativity which contributes to clusters formation.

Potentials  $U_s$ ,  $U_s^1$ ,  $U_s^2$  we sometimes call superpotential, and forces corresponding to them, superforces, as  $U_s^1$ ,  $U_s^2$  are much greater than  $U_u(q)$  and the effective consideration of  $U_s$  in the Gibbs exponent comes down to the fact that the whole configuration space of molecules is replaced by its part.

Let's represent  $\Delta F$  in the following form

$$\Delta F = \Delta F_0 + \Delta F_1 + \dots, \quad (98)$$

where  $\Delta F_0$  is a zero-order value of vanishing on  $C$ ,  $\Delta F_1$  is a value of the first order of vanishing on  $C$  and so on.

Let's begin from the definition of  $\Delta F_0$ , in other words, put  $C = 0$  and  $U(q) = U_s(q)$ .

Due to presence in  $U_s$  all the molecules stick together to clusters (balls  $B$ ) of  $N_B$  molecules in each. Let  $N_k$  be a number of such balls (clusters). Obviously  $N = N_B N_k$ .

By definition all the clusters identical and there are

$$\frac{1}{N_k!} \frac{N!}{(N_B!)^{N_k}} \quad (99)$$

of equivalent ways to distribute molecules by clusters. Let's fix one of these ways which we will follow hereafter, where molecules having coordinates  $q_1, \dots, q_{N_B}$  belong to the first cluster  $B_1$ , molecules having coordinates  $q_{N_B+1}, \dots, q_{2N_B}$  belong to the second cluster  $B_2$  and so on.

During  $F_0$  calculation we naturally neglected interaction between clusters, so:

$$\Delta F_0 = -T \ln \frac{N!}{N_k!} \left[ \frac{1}{N_B!} \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_{N_B}}{V} e^{-\frac{U_B(q_1, \dots, q_{N_B})}{T}} \right]^{N_k}, \quad (100)$$

where by definition we set:

$$U_B(q_1, \dots, q_{N_B}) = \sum_{1 \leq i < j \leq N_B} V_s^1(q_i - q_j) + U_s^2(q_1, \dots, q_{N_B}). \quad (101)$$

We proceed from the assumption that the cluster is a ball and bonding forces between molecules in the cluster are so strong that the cluster volume equals to a sum of volumes of molecules it consists of (that why cluster density can exceed the water density).

Further, one of variables  $q_1, \dots, q_{N_B}$  is a center of inertia of cluster  $B$ . The choice of such a variable can be performed in  $N_B$  ways. Supposing the center of the cluster inertia is  $q_1$  we find by integrating it:

$$\Delta F_0 = -T \ln \frac{N!}{N_k!} \left[ \frac{1}{(N_B - 1)!} \int \frac{d^3 q_2}{V} \dots \frac{d^3 q_{N_B}}{V} e^{-\frac{U_B(0, \dots, q_{N_B})}{T}} \right]^{N_k}, \quad (102)$$

And the center of cluster  $B$  is 0.

Then, we assume every molecule in the cluster moves in an effective field  $W$  and  $U_s^2(0, \dots, q_{N_B}) = W(N_B - 1)$ . Instead of integral  $\int_{B \times \dots \times B} d^3 q_2 \dots d^3 q_{N_B}$  the presence of multiplier  $e^{-\frac{U_s^1(q_1, \dots, q_{N_B})}{T}}$  imposes the use of integral

$$\int'_{B \times \dots \times B} d^3 q_2 \dots d^3 q_{N_B}, \quad (103)$$

where prime points at the incompressibility of molecules. Using  $N! \approx \left(\frac{N}{e}\right)^N$  we receive:

$$\Delta F_0 = -T \ln \frac{1}{N_k!} \left[ \frac{1}{(N_B - 1)!} \left(\frac{N}{e}\right)^{N_B} \int'_{B \times \dots \times B} \frac{d^3 q_2}{V} \dots \frac{d^3 q_{N_B}}{V} e^{-\frac{W(N_B - 1)}{T}} \right]^{N_k}. \quad (104)$$

But integral  $\int_{B \times \dots \times B} d^3 q_2 \dots d^3 q_{N_B}$  is easy and equals to

$$\int_{B \times \dots \times B} d^3 q_2 \dots d^3 q_{N_B} = (N_B - 1)! \left(\frac{V_B}{N_B}\right)^{N_B-1}, \quad (105)$$

where  $V_B$  is the cluster volume and  $V_b := \frac{V_B}{N_B}$  is the volume of one protein molecule. As a result, we obtain:

$$\Delta F_0 = -T N_k \ln N_B \left[ \left(\frac{V_B}{V_k}\right)^{N_B-1} \frac{1}{e^{N_B-1}} e^{\frac{-W(N_B-1)}{T}} \right], \quad (106)$$

where  $V_k := \frac{V}{N_k}$  is the volume which falls on one cluster.

Now, let's derive the equilibrium condition for the cluster  $B$  from which we essentially can define the volume of this cluster. Let's consider one equilibrium cluster in the volume  $V_k$ . Now we are generally interesting in configuration part of the free energy since it splits from the kinetic one.

Let's add one more protein molecule to the volume  $V_k$ . Its free energy is

$$f_1 = -T \ln \int_{V_k} \frac{1}{V_k} d^3 q = 0. \quad (107)$$

If this protein falls to the cluster, then  $N_B$  is increased by a unit, but since the cluster is equilibrium  $\Delta F_0$  should not change. In other words, the following equality should take place:

$$\frac{d\Delta F_0}{dN_B} = 0. \quad (108)$$

The equilibrium condition (108) is actually a common thermodynamic condition of equilibrium if we suppose a number of protein molecules in a cell  $N$  to be a parameter which has an influence on the system condition. But we can use this condition only if  $N$  is not preserved, put it otherwise, is not a motion integral. But the fact that  $N$  is not a motion integrals follows from the fact that in the living cell the quantity of protein molecules does not remain invariant because of permanently proceeding processes of proteins synthesis and degradation.

The equation (108) leads to the equality:

$$\frac{1}{N_B} + \ln\left(\frac{V_B}{V_k}\right) + (N_B - 1) \frac{V_b}{V_B} - 1 - \frac{W}{T} = 0. \quad (109)$$

In other words:

$$\frac{V_B}{V_k} = e^{\frac{w}{T}}. \quad (110)$$

Finally:

$$\Delta F_0 = -TN_k \ln N_B + T[N - N_k]. \quad (111)$$

As the number of clusters is small ( $N_k \ll N$ ), then in square bracket of the second summand  $N_k$  can be neglected as compared with  $N$ . Since  $N_B$  conversely is very large, we can neglect a logarithmic term as compared with  $TN$ . As a result, we find:

$$\Delta F_0 = TN. \quad (112)$$

This term just comes down to the additive renormalization of the entropy and therefore in can be omitted.

Now, let's calculate  $\Delta F_1(V, T, N)$ . We have:

$$\Delta F_1 = \Delta F - \Delta F_0 + O(C^2). \quad (113)$$

Let's recall, that  $C$  is considered as as mall parameter. It won't be a great mistake if instead of  $\Delta F_0$  we take  $\Delta F_0$  calculated by  $N - 2$  molecules in the same volume  $V$  at the same temperature  $T$ . We have:

$$\begin{aligned} \Delta F_1 &= -T \ln \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} e^{\frac{-U(q) + \Delta F_0}{T}} + O(C^2) \\ &= -T \ln \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} \prod_{1 \leq i < j \leq N} [e^{-\frac{V_u(q_i - q_j)}{T}} - 1 + 1] e^{\frac{-U_s(q) + \Delta F_0}{T}} + O(C^2) \\ &= -T \ln \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} \left\{ 1 + \sum_{1 \leq i < j \leq N} [e^{-\frac{V_u(q_i - q_j)}{T}} - 1] \right\} e^{\frac{-U_s(q) + \Delta F_0}{T}} + O(C^2) \\ &= -T \ln \left\{ 1 + \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} \left\{ \sum_{1 \leq i < j \leq N} [e^{-\frac{V_u(q_i - q_j)}{T}} - 1] e^{\frac{-U_s(q) + \Delta F_0}{T}} \right\} \right\} + O(C^2). \end{aligned} \quad (114)$$

Eventually, we obtain:

$$\Delta F_1 = -T \ln \left\{ 1 + \frac{N^2}{2} \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} [e^{-\frac{V_u(q_1 - q_2)}{T}} - 1] e^{\frac{-U_s(q) + \Delta F_0}{T}} \right\} + O(C^2). \quad (115)$$

Since the number of clusters  $N_k$  is still sufficiently large, we neglect cases when  $q_1$  and  $q_2$  are in the same cluster and suppose them lying in different clusters  $B_1$  and  $B_2$ . Values  $q_1$  and

$q_2$  are simultaneous centers of the corresponding clusters with probability  $\frac{1}{N_B^2}$ . Taking this into account:

$$\Delta F_1 = -T \ln \left\{ 1 + \frac{N^2}{2} N_B^2 \int \frac{d^3 q_1}{V} \dots \frac{d^3 q_N}{V} [\langle e^{-\frac{V_u(q'_1 - q'_2)}{T}} \rangle - 1] e^{\frac{-U_s(q) + \Delta F_0}{T}} \right\} + O(C^2). \quad (116)$$

Here variables  $q_1$  and  $q_2$  are already centers of inertia of clusters  $B_1$  and  $B_2$ . Variables  $q'_1$ ,  $q'_2$  are equiprobably and independently distributed along clusters  $B_1$  and  $B_2$  and angle brackets mean the averaging over positions  $q'_1$  and  $q'_2$ .

Considering the meaning of  $\Delta F_0$ , the last equation can be rewritten in the following way:

$$\begin{aligned} \Delta F_1 &= -T \ln \left\{ 1 + \frac{N^2}{2V} N_B^2 \int_{|q| > 2r_B} d^3 q [\langle e^{-\frac{V_u(q'_1 - q'_2)}{T}} \rangle - 1] \right. \\ &\times \left. \left[ \frac{N^{N_B - 1}}{(N_B - 1)!} \int_{B \times \dots \times B} \frac{d^3 q_2}{V} \dots \frac{d^3 q_{N_B}}{V} e^{\frac{-U_s(0, \dots, q_2)}{T}} \right]^2 \right\} + O(C^2) = \\ \Delta F_1 &= -T \ln \left\{ 1 + \frac{N^2}{2V} N_B^2 \int_{|q| > 2r_B} d^3 q [\langle e^{-\frac{V_u(q'_1 - q'_2)}{T}} \rangle - 1] \right. \\ &\times \left. \left[ \left( \frac{V_B}{V_k} \right)^{N_B - 1} e^{\frac{-W(N_B - 1)}{T}} \right]^2 \right\} + O(C^2), \end{aligned} \quad (117)$$

where  $r_B$  is a radius of a cluster  $V_B = \frac{4\pi}{3} r_B^3$ . But taking into account the clusters equilibrium conditions we derived, the expression inside the last square bracket equals to 1. Eventually:

$$\begin{aligned} \Delta F_1 &= -T \ln \left\{ 1 + \frac{N^2}{2V} N_B^2 \int_{|q| > 2r_B} d^3 q [\langle e^{-\frac{V_u(q'_1 - q'_2)}{T}} \rangle - 1] \right\} + O(C^2) \\ &= -T \frac{N^2}{2V} N_B^2 \int_{|q| > 2r_B} d^3 q [\langle e^{-\frac{V_u(q'_1 - q'_2)}{T}} \rangle - 1] + O(C^2). \end{aligned} \quad (118)$$

This formula assumes that cluster  $B_1$  has a center of inertia in zero,  $q$  is a coordinate of center of inertia of cluster  $B_2$ ,  $q'_1$  and  $q'_2$  are variables which are uniformly and independently distributed over cluster  $B_1$  and  $B_2$  respectively.

This formula particularly proves the rule (90) quoted in the end of the previous section.

Now, let's define a part which "dead" protein in the protoplasm occupies in the whole cell volume. Suppose the cluster of dead protoplasm proteins is situated in the volume and has an  $V' := \frac{V}{N_k}$  equilibrium volume. If the cluster has the equilibrium size, then inserting one protein molecule to it needs a zero work  $A$ , in other words, an average potential energy of the protein molecule in the cluster equals to zero. But all the protein molecules are

situated in the neutral external field outside the cluster and in the field  $W$  inside the cluster. Let's consider the chosen protein  $\mathfrak{B}$ , it has three degrees of freedom described by Cartesian coordinates  $q^1, q^2, q^3$  and radius  $q^4$  (the protein can be compressed). The only thing we can do is to take a positively defined quadratic form of coordinates  $q^1, \dots, q^4$  as a raw estimation for the potential energy of protein inside the cluster  $V(q^1, \dots, q^4)$ :

$$V(q^1, \dots, q^4) = W + \sum_{i,j=1,\dots,4} (q^i - q_0^i) B_{i,j} (q^j - q_0^j), \quad (119)$$

where  $q_0^1, \dots, q_0^4$  are equilibrium coordinates of the protein molecule. For kinetic energy of the chosen protein  $\mathfrak{B}$  as a raw estimation too we take a positively defined form of velocities  $\dot{q}^1, \dots, \dot{q}^4$ :

$$E_{kin} = \sum_{i,j=1,\dots,4} \dot{q}^i A_{i,j} \dot{q}^j \quad (120)$$

Note, that protein molecule in the water does not behave as an oscillator along  $q_4$  because a water is incompressible.

But in the case of classical mechanics the average potential energy of one-dimensional oscillator equals to  $\frac{1}{2}T$ . Therefore, the condition  $A = 0$  leads to  $W = -2T$ . This equilibrium condition cluster lets us find:

$$\frac{V_B}{V'} = e^{\frac{W}{T}} = e^{-2} \approx 0.136, \quad (121)$$

which is in a good agreement with true value  $\frac{V_B}{V'} = 0.163$  (see section 4).

## 6 Superfluid Bose Gas on Protein Configuration Space as Model of Living Cell Protoplasm

In this section we discuss the second model of the living cell protoplasm, the superfluid Bose gas on the protein configuration space. The common description of this model is given in the introduction section. While investigating this model we'll show that when the Ling's protoplasm dies, the folding of protein molecules occurs, how the Ling's theory postulates on the qualitative level (Ling, 2001).

The protoplasm is considered at zero temperature. This allows us to apply essential tools of theoretical physics but conclusions made for such extreme conditions are useful for understanding the properties of the real cell.

Let's proceed to conclude our "superfluid" model. Suppose there are  $N$  protein molecules in the protoplasm,  $x_i$ ,  $i = 1, \dots, N$  are coordinates of their centers of inertia and  $\sigma_i$  are parameters, passing some space  $X$  with measured  $d\mu$  describing inner freedom degrees of the protein molecule (its configuration). Then, the state of  $N$  protein molecules is described by the wave function  $\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N)$  depending on coordinates  $x_i, \sigma_i$  of protein molecules. This wave function fulfills the normalizing condition:

$$\int |\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N)|^2 dx_1, \dots, dx_n d\mu(\sigma_1) \dots d\mu(\sigma_N) = 1 \quad (122)$$

and symmetry condition  $\forall P \in S_N$  permutation of the set of  $N$  elements

$$(\hat{P}\Psi)(x_1, \sigma_1, \dots, x_N, \sigma_N) := \Psi(x_{P(1)}, \sigma_{P(1)}, \dots, x_{P(N)}, \sigma_{P(N)}) = \chi(P)\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N), \quad (123)$$

where  $\chi(P) \equiv 1$  if protein molecules satisfy to the Bose — Einstein statistics, and  $\chi(P) = \text{sgn}(P)$  (signum of permutation) if protein molecules satisfy to the the Fermi — Dirac statistics.

To describe this system, by using common considerations we'll try to find its Hamiltonian as per the adiabatic limit method (see the previous section). Suppose  $V(x_1, \sigma_1, \dots, x_N, \sigma_N)$  is a change of the smallest eigenvalue of the protoplasm Hamiltonian while adding there  $N$  protein molecules having coordinates  $x_1, \sigma_1, \dots, x_N, \sigma_N$ , and  $\hat{V}$  is an operator of multiplication of wave function of our system on  $V(x_1, \sigma_1, \dots, x_N, \sigma_N)$ . Then, obviously, the effective Hamiltonian of our system is

$$\hat{H}_{eff} = \sum_{i=1}^N \hat{T}_i + \hat{V}, \quad (124)$$

where  $\hat{T}_i$  is a kinetic energy operator of  $i$ -th protein as a material point:

$$\hat{T}_i = -\frac{1}{2M} \nabla_i^2. \quad (125)$$

To simplify our model let's suppose  $\hat{V}$  describes only a pair interaction of protein molecules.

$$\hat{V} = \sum_{i=1}^N \hat{V}_i + \sum_{N \geq i > j \geq 0} \hat{V}_{i,j}, \quad (126)$$

where in Dirac notation

$$\langle \sigma_1, x_1, \dots, x_n, \sigma_n | \hat{V}_i | x_1, \sigma'_1, \dots, x_n, \sigma'_n \rangle = U_1(x_i, \sigma_i | x'_i, \sigma'_i) \quad (127)$$

for some function  $U_1(x'_i, \sigma'_i | x'_i, \sigma'_i)$  fulfilling obvious conditions arising from the Hermitian nature of  $\hat{V}_i$ . Similarly

$$\langle \sigma_1, x_1, \dots, x_n, \sigma_n | \hat{V}_{i,j} | x_1, \sigma'_1, \dots, x_n, \sigma'_n \rangle = U_2(x_i, \sigma_i, x_j, \sigma_j | x'_i, \sigma'_i, x'_j, \sigma'_j) \quad (128)$$

for some function  $U_2(x_i, \sigma_i, x_j, \sigma_j | x'_i, \sigma'_i, x'_j, \sigma'_j)$  fulfilling evident conditions arising from the Hermitian nature of  $\hat{V}_{i,j}$ .

We consider the protoplasm at the zero temperature (measured in the energy scale). The following objection may arise against this acceptance: at zero temperature all the metabolic process in cell are stopped and the cell dies (it is the way how the non-equilibrium thermodynamics understands the life and the death). However, it is well-known that cells (even embryos including human ones) come back to life after freezing in the liquid nitrogen when there are no flows of matter or energy at all. Our approach differs: we consider the living state as stationary and thermodynamically sustainable, but not the equilibrium one. Precisely this state is "freezing" and can keep its properties even at the absolute zero. That's why the frozen cell comes back to life when temperature conditions became normal again. The thermodynamic identity of the resting state of the living and cells allows us to apply the same analytical apparatus.

As the average kinetic energy of a heat motion of the protein molecule  $T_i$  at temperature  $T$  is equal to  $kT$ , so at the zero temperature kinetic energy equals to zero. Therefore, we can omit the term corresponding to kinetic energy from the Hamiltonian  $H_{eff}$ . In other words, when  $T = 0$  we have the following expression for  $H_{eff}$ :

$$\hat{H}_{eff} = \sum_{i=1}^N \hat{V}_i + \sum_{N \geq i > j \geq 0} \hat{V}_{i,j}. \quad (129)$$

With regard to the protein molecules themselves, according to Ling's model of the cell (Ling, 2001), they are situated in points of a lattice and emerged into the volume of water associated with these proteins (the water is as well structured and ordered), while  $i$ -th point has coordinates  $x_i$ .  $\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N)$  has the following form:

$$\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N) = C \sum_{P \in S_N} \prod_{i=1}^N \delta(x'_i - x_{P(i)}) A^P(\sigma_1, \dots, \sigma_N) \chi(P), \quad (130)$$

where  $A^P$  fulfills the following property arising from the property of  $\Psi(x_1, \sigma_1, \dots, x_N, \sigma_N)$  to fulfill the Bose-Einstein or Fermi-Dirac statistics:

$$A^{PQ^{-1}}(\sigma_{Q(1)}, \dots, \sigma_{Q(N)}) = A^P(\sigma_1, \dots, \sigma_N), \quad (131)$$

and a divergent constant  $C$  is chosen from the condition

$$C \int dx_1, \dots, dx_N \left( \prod_{i=1}^N \delta(x_i - x'_i) \right)^2 = 1. \quad (132)$$

At  $T = 0$  the whole protein system is in the ground state  $\Psi_0(x_1, \sigma_1, \dots, x_N, \sigma_N)$  which can be defined based upon the requirement of minimality of the averaged Hamiltonian  $H_{eff}$  over all normalized states. In other words, in the state  $\Psi_0$  the averaged value  $\langle \Psi | \hat{H}_{eff} | \Psi \rangle$  of the effective Hamiltonian reaches its minimum value

$$E_0 = \min_{\|\Psi\|=1} \langle \Psi | \hat{H}_{eff} | \Psi \rangle. \quad (133)$$

Taking into account the aforesaid, in searching the minimum value of  $\langle \Psi | \hat{H}_{eff} | \Psi \rangle$  we can restrict ourselves to states of the form (130). Since for states of the form (130) the coordinates of inertia centers of proteins are localized, we may say that  $\hat{V}_i$  acts only in  $L^2(X, d\mu)$  and  $\hat{V}_{i,j}$  acts in  $L^2(X^2, d\mu \times d\mu)$ . Then, our variational problem comes down to finding the functional minimum

$$\int d\mu(\sigma_1) \dots d\mu(\sigma_N) A^*(\sigma_1, \dots, \sigma_N) \left\{ \left( \sum_{i=1}^N \hat{V}_i + \sum_{N \geq i > j \geq 0} \hat{V}_{i,j} \right) A \right\}(\sigma_1, \dots, \sigma_N) \quad (134)$$

upon the additional condition

$$\int |A(\sigma_1, \dots, \sigma_N)|^2 d\mu(\sigma_1) \dots d\mu(\sigma_N) = 1. \quad (135)$$

Let's introduce a function  $V_2(\sigma_1, \sigma_2 | \sigma'_1, \sigma'_2 | x'_i, x'_j)$  with a formula

$$V_2(\sigma_1, \sigma_2 | \sigma'_1, \sigma'_2 | x'_i, x'_j) = U_2(x'_i, \sigma_1, x'_j, \sigma_2 | x'_i, \sigma'_1, x'_j, \sigma'_2). \quad (136)$$

Then, in obvious notations

$$\langle \sigma_1, \dots, \sigma_N | \hat{V}_{i,j} | \sigma'_1, \dots, \sigma'_N \rangle = V_2(\sigma_i, \sigma_j | \sigma'_i, \sigma'_j | x_i, x_j). \quad (137)$$

Let  $P$  be any permutation from  $S_N$ . Let's define the operator  $\hat{V}_{i,j}^P$  with the following formula

$$\langle \sigma_1, \dots, \sigma_N | \hat{V}_{i,j}^P | \sigma'_1, \dots, \sigma'_N \rangle = V_2(\sigma_i, \sigma_j | \sigma'_i, \sigma'_j | x_{P(i)}, x_{P(j)}). \quad (138)$$

Let by definition

$$\hat{V}_{ij}^e := \frac{1}{|S_N|} \sum_{P \in S_N} \hat{V}_{i,j}^P. \quad (139)$$

Let's renumber protein molecules in such a way that the protein which starts the numeration is situated sufficiently far from the cell surface. Then

$$\langle \sigma_1, \dots, \sigma_n | \hat{V}_{ij}^e | \sigma'_1, \dots, \sigma'_n \rangle = \frac{1}{N} \sum_{k=1}^N V_2(\sigma_i, \sigma_j | \sigma'_i, \sigma'_j | x_0, x_k); \quad (140)$$

Let by definition

$$U_2(\sigma_1, \sigma_2 | \sigma'_1, \sigma'_2) := \frac{1}{N} \sum_{k=1}^N V_2(\sigma_1, \sigma_2 | \sigma'_1, \sigma'_2 | x_0, x_k). \quad (141)$$

Now, we'll show that within the framework of some approximation the class of functions, where solution of variational problem we just set up is searched, can be narrowed down to symmetrical functions, i.e. such functions that  $\forall P \in S_N$

$$A^P(\sigma_1, \dots, \sigma_N) = A^{id}(\sigma_1, \dots, \sigma_N) =: A(\sigma_1, \dots, \sigma_N). \quad (142)$$

We suppose that  $\hat{V}_{i,j}$  is proportional to real constant  $\lambda$  which is a small parameter. Therefore, if parameter  $\lambda$  is enough small, the different protein molecules can be considered as non-correlated ones, in other words, behaving independently. This means that the wave function  $A(\sigma_1, \dots, \sigma_N)$  can be represented in the following form:

$$A(\sigma_1, \dots, \sigma_N) = \prod_{i=1}^N \xi(\sigma_i) \quad (143)$$

for a function  $\xi(\sigma) \in L_2(X, d\mu)$  fulfilling the following normalizing condition:

$$\int |\xi(\sigma)|^2 d\mu(\sigma) = 1. \quad (144)$$

Let  $\hat{U}^1$  be an operator in  $L_2(X, d\mu)$  which have matrix elements in  $\sigma$ -representation defined by function  $U_1$ , and  $\hat{U}^2$  be an operator in  $L_2(X \times X, d\mu \times d\mu)$  which have matrix elements in  $\sigma$ -representation defined by function  $U_2$ . Let's denote  $U_2(\xi)$  as an operator in  $L_2(X, d\mu)$  defined from the following relation:

$$\langle f | U_2(\xi) | g \rangle = \langle f \otimes \xi | U_2 | g \otimes \xi \rangle. \quad (145)$$

The approximation we've just described is called a mean field approximation and time evolution of function  $\xi$  in it is defined by the following equation:

$$i \frac{\partial}{\partial t} \xi = \hat{V}^1 \xi + N \hat{V}^2(\xi) \xi. \quad (146)$$

Any how, in our approximation

$$A(\sigma_1, \dots, \sigma_N) \sim \prod_{i=1}^N \xi(\sigma_i). \quad (147)$$

As the class of test functions is narrowed down to the symmetrical ones in our variational problem, then, instead of  $\hat{H}_{eff}$  minimum eigenvalue calculation, we can seek the minimum eigenvalue of the Hamiltonian:

$$\hat{H}'_{eff} = \sum_{i=1}^N \hat{V}_i + \sum_{N \geq i > j \geq 0} \hat{V}_{i,j}^e. \quad (148)$$

Within the framework of our approximation the energy of the ground state of  $\hat{H}'_{eff}$  is equal to the energy of the ground state of  $\hat{H}_{eff}$ .

**Proposition.** There exist functions  $U'_1(\sigma_1|\sigma'_1)$ ,  $U'_2(\sigma_1, \sigma_2|\sigma'_1, \sigma'_2)$  such as if  $\hat{V}'_i$ ,  $\hat{V}'_{i,j}$  operators defined by the following relations

$$\begin{aligned} \langle \sigma_1, \dots, \sigma_N | \hat{V}'_i | \sigma'_1, \dots, \sigma'_N \rangle &= U'_1(\sigma_i | \sigma'_i), \\ \langle \sigma_1, \dots, \sigma_N | \hat{V}'_{ij} | \sigma'_1, \dots, \sigma'_N \rangle &= U'_2(\sigma_i, \sigma_j | \sigma'_i, \sigma'_j), \end{aligned} \quad (149)$$

the operators  $V'_i$  and  $V'_{ij}$  are Hermitian ones,

$$\hat{H}'_{eff} = \sum_{i=1}^N \hat{V}'_i + \sum_{N \geq i > j \geq 0} \hat{V}'_{i,j}. \quad (150)$$

and operators  $V'_i$  and  $V'_{ij}$  fulfill one more condition being as follows. Let  $\{\varphi'_n | n = 0, 1, \dots\}$  be an orthonormal basis of eigenfunctions of operator  $\hat{U}'_1$  in  $L_2(X, d\mu)$  defined by the following equation:

$$(\hat{U}'_1 \varphi)(\sigma) = \int U'_1(\sigma, \sigma') \varphi(\sigma') d\mu(\sigma'). \quad (151)$$

Let  $U'_2$  is the operator in  $L_2(X \times X, d\mu \times d\mu)$  specified by the relation

$$(\hat{U}'_2 \varphi)(\sigma_1, \sigma_2) = \int U'_2(\sigma_1, \sigma_2 | \sigma'_1, \sigma'_2) \varphi(\sigma'_1, \sigma'_2) d\mu(\sigma) d\mu(\sigma'). \quad (152)$$

Let  $(\hat{U}'_2)_{mn, m'n'}$  be a matrix element of operator  $\hat{U}'_2$  with respect to the basis  $\{\varphi_i \otimes \varphi_j | i, j = 0, 1, \dots\}$ .

$$(\hat{U}'_2)_{mn, m'n'} = \langle \varphi_m \otimes \varphi_n | \hat{U}'_2 | \varphi_{m'} \otimes \varphi_{n'} \rangle. \quad (153)$$

Then, for any  $n = 1, 2, 3, \dots$

$$(U'_2)_{00,0n} = 0 \quad (154)$$

and similar equalities take place where index  $n$  stands on remaining three places and other have zeros.

**Proof.** Let  $\hat{U}_1$  be an operator in specified by the following relation:

$$(\hat{U}'_1\varphi)(\sigma) = \int U'_1(\sigma, \sigma')\varphi(\sigma')d\mu(\sigma'), \quad (155)$$

and let  $\{\varphi_n|n = 0, 1, \dots\}$  be an orthonormal basis of eigenfunctions of operator  $\hat{U}_1$ .

We represent the operator  $\hat{V}_{i,j}^e$  as a sum of three summands:

$$\hat{V}_{i,j}^e = \hat{V}_{i,j}^{e,1} + \hat{V}_{i,j}^{e,2} + \hat{V}_{i,j}^{e,3}, \quad (156)$$

where operators  $\hat{V}_{i,j}^{e,1}$ ,  $\hat{V}_{i,j}^{e,2}$ ,  $\hat{V}_{i,j}^{e,3}$  are based on functions  $(U_2^1)(\sigma_1, \sigma_2)$ ,  $(U_2^2)(\sigma_1, \sigma_2)$ ,  $(U_2^3)(\sigma_1, \sigma_2)$  defined below by the principle which the  $\hat{V}_{ij}^e$  is based on  $U_2(\sigma_1, \sigma_2|\sigma'_1, \sigma'_2)$ . The functions  $U_2^1$ ,  $U_2^2$ ,  $U_2^3$  are defined by the following condition. Let  $\hat{U}_2^1$ ,  $\hat{U}_2^2$ ,  $\hat{U}_2^3$  be operators based on functions  $U_2^1$ ,  $U_2^2$ ,  $U_2^3$  using the same scheme as used by the operator  $\hat{U}_2$  based on the function  $U_2$ . Among all matrix elements of operators  $\hat{U}_2^1$ ,  $\hat{U}_2^2$  only the following elements are non-zero:  $(U_2^1)_{00,0m}$ ,  $(U_2^1)_{00,m0}$ ,  $(U_2^2)_{m0,00}$ ,  $(U_2^2)_{0m,00}$ ,  $m = 1, 2, \dots$  and among all matrix elements of the operator  $\hat{U}_2^3$  only remained elements are non-zero. It is easily seen that if we redefine  $\hat{V}_{i,j}^{e,3}$  in a proper manner, then we can include summands corresponding to  $\hat{V}_{i,j}^{e,1}$ ,  $\hat{V}_{i,j}^{e,2}$  into  $\hat{V}_i$ .

But  $\hat{V}_{ij}^e$  and, consequently,  $\hat{V}_{ij}^{e,1}$  are first-order values by the constant of protein interaction  $\lambda$ . Therefore, in just described substitution, the basis of eigenfunctions of operator  $\hat{U}_1$   $\{\varphi_n|n = 0, 1, 2, \dots\}$  passes to the basis of eigenfunctions of redefined operator  $\hat{U}'_1$   $\{\psi_n|n = 0, 1, 2, \dots\}$  such that  $\varphi_n - \psi_n$  are the first-order of vanishing values by a coupling constant  $\lambda$   $\forall n = 0, 1, 2, \dots$

The matrix elements of just redefined  $\hat{V}_{ij}^e$  of the form  $(\hat{U}_2)_{00,0m}$   $m = 1, 2, \dots$  ( $\hat{U}_2$  is coupled with  $\hat{V}_{ij}^e$  by the relation we've mentioned above) relating to the basis  $\{\varphi_n\}$  are equal to zero. But since  $\hat{V}_{ij}^e$  are of first-order of vanishing by the interaction constant, then matrix elements of the form  $(\hat{U}_2)_{00,0m}$  of redefined ( $\hat{U}_2$ ) related to the basis  $\{\psi_n\}$  are of the second order of vanishing by the coupling constant.

The procedure described above can be continued endlessly by sequentially lowering the order of vanishing of those terms we want to omit in the Hamiltonian.

The proposition may be considered as a proven one even without discussing a problem of convergence of the above described iteration procedure, as all formulas which may be derived hereafter will be just asymptotic expansions in a small parameter  $\lambda$ .

So, the effective Hamiltonian for considered system of protein molecules, which we want to use for defining the ground state of our system, has the following form:

$$H'_{eff} = \sum_{i=1}^N \hat{V}_i + \sum_{1 \leq i \leq j \leq N} \hat{V}_{ij}^e. \quad (157)$$

Here operators  $\hat{V}_i$  have "act" only on coordinate  $\sigma_i$  of the wave function and differ from each other only by a number of the coordinate on which they "act". Operators  $\hat{V}_{ij}$  "acts" only on coordinates of numbers  $i$  and  $j$  of the wave function and differ from each other only by numbers of coordinates on which they "acts".

Operator  $\hat{V}_{ij}$  "acts" only on coordinates of numbers  $i$  and  $j$  of the wave function and differ from each other only by numbers of coordinates on which they "acts".

If in (157) we evidently extract the dependence from the interaction constant and number of particles, then we shall find

$$H_{eff} = \sum_{i=1}^N \hat{V}_i + \frac{\lambda}{N} \sum_{1 \leq i \leq j \leq N} \tilde{V}_{ij}^e, \quad (158)$$

where prime of  $H_{eff}$  is omitted and  $\tilde{V}_{ij}^e$  does not depend on  $N$  (asymptotically at  $N \rightarrow \infty$ ).

We intend to investigate the Hamiltonian  $H_{eff}$  using the apparatus of secondary quantization.

Let  $\{\varphi_n | n = 0, 1, 2, \dots\}$  be still an orthonormal basis of eigenfunctions of operator  $\hat{U}_1$ . Let  $\mathcal{F} = \Gamma(L_2(X, d\mu))$  be a boson Fock space over  $L_2(X, d\mu)$ . Let  $a_i^+$ ,  $a_i$  be operators of particles creation and annihilation in the state  $\varphi_i$  acting in  $\mathcal{F}$ .  $\forall i = 0, 1, \dots$  operators  $a_i^+$  and  $a_i$  are conjugated to each other and fulfill the following canonical commutating relations:

$$\begin{aligned} [a_i, a_j] &= [a_i^+, a_j^+] = 0, \quad i, j = 0, 1, 2, \dots, \\ [a_i, a_j^+] &= \delta_{ij}, \end{aligned} \quad (159)$$

where  $\delta_{ij}$  is a common Kronecker delta. We suppose that eigenfunctions  $\varphi_n$  are numerated in such a way that  $E_n$  increases with increasing of number  $n$ . In representation of the secondary

quantization the Hamiltonian  $H_{eff}$  is given by:

$$H_{eff} = \sum_{n=0}^{\infty} E_n a_n^+ a_n + \frac{\lambda}{2N} \sum_{m,n,m',n'} a_m^+ a_n^+ (U_2)_{mn,m'n'} a_{m'} a_{n'}. \quad (160)$$

But it is a common Hamiltonian studied in the superfluid theory, and we can use the same methods for its investigation.

At  $T = 0$  a portion of proteins is in the ground state  $\varphi_0$ . Let  $N_0$  be a number of protein molecules in the ground state. As  $\frac{\lambda}{N} \ll 1$ , then  $\frac{N-N_0}{N_0} \ll 1$ . Because of this reason in the right part of relation  $a_0 a_0^+ - a_0^+ a_0 = 1$  we can neglect a unity and suppose  $a_0$  and  $a_0^+$  are usual  $c$ -numbers.

So, we can simply suppose that  $a_0 = \sqrt{N} e^{-i\varphi}$  and  $a_0^+ = \sqrt{N} e^{i\varphi}$  and for some real number  $\varphi$ .

Now let's consider the second summand in the right part of (160). According to the assumption proven above we can suppose that this summand has no terms linear by  $a_i^+$ ,  $a_i$ ,  $i = 1, 2, \dots$ . Quadratic terms have an order of  $\lambda$ , cubic  $\frac{\lambda}{\sqrt{N}}$ , and quartic  $\frac{\lambda}{N}$ . Therefore, supposing the number of proteins in the cell is finite but a sufficiently large and interaction constant  $\lambda$  is small, in the Hamiltonian (160) we can keep only quadratic terms on operators  $a_i^+$ ,  $a_i$ ,  $i = 1, 2, \dots$

Consequently, the effective Hamiltonian  $H_{eff}$  is given by:

$$H_{eff} = \pi c N_0 + \sum_{n=1}^{\infty} E_n a_n^+ a_n + \lambda \left\{ \sum_{m,n=1}^{\infty} A_{mn} e^{-2i\varphi} a_m^+ a_n^+ + \sum_{m,n=1}^{\infty} A_{mn}^* e^{2i\varphi} a_m a_n + \sum_{m,n=1}^{\infty} B_{mn} a_m^+ a_n \right\}. \quad (161)$$

Here  $c$  is a material constant (does not depend on  $N_0$ ),  $A_{mn}$ ,  $B_{mn}$  are some matrixes  $A_{mn} = A_{nm}$ ,  $B_{mn}^* = B_{nm}$ ,  $\star$  is a sign of complex conjugation.

There is a classical variable  $\varphi$  which is canonically conjugated to variable  $J = \pi N_0$ . Variable  $\varphi$  satisfies the equation  $\dot{\varphi} = c$  and, therefore, value  $\psi = \varphi - ct$  ( $t$  is time) is a motion integral. Whole our system (denoted by  $M$ ) has a structure of a direct product of two systems  $M = M_1 \times M_2$  where, roughly speaking, the system  $M_1$  is described by variables  $\varphi$  and  $J$ , and the  $M_2$  system is described by (noncommutative) variables  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$

Now, let's consider two cases: when the cell is a live and when it is dead. In the case of the living cell, the expression under the integral for statistical weight contains a multiplier

$\delta(\varphi - \varphi')$ ,  $\varphi'$  is a fixed real number, and now the free energy  $F(\varphi')$  is a function of  $\varphi'$ . However, one can readily see that the free energy  $F(\varphi')$  does not depend on  $\varphi'$ . Indeed, the change of  $\varphi'$  to the value  $\delta\varphi$  can really be compensated by proper canonical transformation of operators  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$ :

$$\begin{aligned} a_n^+ &\mapsto a_n^+ e^{i\delta\varphi}, \\ a_n &\mapsto a_n e^{-i\delta\varphi}. \end{aligned} \tag{162}$$

Now, integral  $\varphi$  fulfills the equivalence principle we have considered above (Prokhorenko and Matveev, 2011). As the formula of the generalized microcanonical distribution includes a multiplier factor  $\delta(\varphi - \varphi')$ , the  $M_2$  system may be described by using the Hamiltonian (161) where  $\varphi$  is given as a some value and  $N_0$  is given taking into account that the total system particles number is equal to  $N$ .

Now, let's consider a dead cell. In this case the cell is described by means of the equilibrium Gibbs distribution. Let's write out Hamilton's equations for  $\varphi$  and  $J$ . So, we have:

$$\begin{aligned} \dot{\varphi} &= c, \\ \dot{J} &= 0 + \lambda L(a^+, a), \end{aligned} \tag{163}$$

where  $L(a^+, a)$  is a quadratic function of operators  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$ . But if  $N \rightarrow \infty$ , then  $J \sim N$ , and  $L(a^+, a) \sim 1$ . Therefore, when  $N$  values are high enough,  $L(a^+, a)$  value may be neglected in the Hamiltonian equations for  $\varphi$  and  $J$  and the following equations are obtained:

$$\begin{aligned} \dot{\varphi} &= c, \\ \dot{J} &= 0. \end{aligned} \tag{164}$$

Thus, when  $N$  values are high enough, dynamics of the  $M_1$  system separates from the dynamics of  $M_2$ . This means that dynamical variables for  $M_1$  and  $M_2$  systems are independent and the probability distribution for the  $M_1$  system, corresponding to Gibbs distribution for the whole system, is defined by the formula:

$$\rho(\varphi, J) = \text{const} \delta(J - J'). \tag{165}$$

Now, let's define the distribution function for the system  $M_2$ . For this we use a classical analogy. Suppose the Hamiltonian system  $K$  has a structure of direct product of systems

$K_1$  and  $K_2$ ,  $K = K_1 \times K_2$  and  $H(x, y)$  is the Hamiltonian of the whole system,  $x \in K_1$ ,  $y \in K_2$ . If the  $K$  system is described by the Gibbs canonical distribution corresponding to  $T$  temperature, then the probability distribution for the  $K_2$  system is the following:

$$\rho(y) = \frac{1}{Z} e^{-\frac{F(y|T)}{T}}, \quad (166)$$

where

$$F(y|T) = -T \ln \int d\Gamma_x e^{-\frac{H(x,y)}{T}}, \quad (167)$$

and  $Z$  is a normalized factor. Alternately, as can be seen above, the effective Hamiltonian for the  $K_2$  system can be obtained in the following way. Let's write out the Hamiltonian equations for the system  $K_2$ . Assume  $p$  and  $q$  are canonical coordinates and momenta for the system  $K_2$  system. Then:

$$\begin{aligned} \dot{p} &= -\frac{\partial H(x, y)}{\partial q}, \\ \dot{q} &= \frac{\partial H(x, y)}{\partial p}. \end{aligned} \quad (168)$$

Now, if we average right parts of the two last equations by the conditional Gibbs distribution for  $K_1$   $w(x|y)$  having a specified value  $y \in K_2$ , then we obtain closed with respect to  $y$  Hamiltonian equations where  $F(y|T)$  is the Hamiltonian.

Therefore, in order to define the effective dynamics for the  $M_2$  system for a dead cell, the following method, reasoning by analogy, can be used. Heisenberg equations for  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$  can be written out and averaged over  $\varphi$  and  $J$ . However, as shown above, if  $N \rightarrow \infty$ , then  $\varphi$  is independent of  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$  and distribution for  $\varphi$  is uniform. Direct calculation shows that if the right parts of Heisenberg equations for  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$  are averaged by the uniformly distributed  $\varphi$ , we obtain Heisenberg equations where the Hamiltonian is:

$$\begin{aligned} H_{eff} &= cN_0 + \sum_{n=1}^{\infty} E_n a_n^+ a_n \\ &+ \lambda \sum_{m,n=1}^{\infty} B_{mn} a_m^+ a_n. \end{aligned} \quad (169)$$

It's evident, when  $T = 0$   $N = N_0$ , i.e. all protein molecules are folded.

Now, let's pass to analysis of  $H_{eff}$  using a well-known theory of normal forms of quadratic Hamiltonians. For Hamiltonians of a general type this theory was developed by H. Poincare

and G.D. Birkhoff (see Arnold, 2003) and for quantum mechanics it was adapted by N.N. Bogoliubov (Bogoliubov and Bogoliubov (jr), 1984). This theory was established only for dynamical systems with a finite number of degrees of freedom, but we use it for systems with an infinite number of degrees of freedom, as it is a standard practice in physics. For this purpose we replace the Hamiltonian  $H_{eff}$  by cuted Hamiltonian  $H_{eff}^c$  describing the system having  $L$  degrees of freedom:

$$H_{eff}^c = \pi c N_0 + \sum_{n=1}^L E_n a_n^+ a_n + \lambda \left\{ \sum_{m,n=1}^L A_{mn} e^{-2i\varphi} a_m^+ a_n^+ + \sum_{m,n=1}^L A_{mn}^* e^{2i\varphi} a_m a_n + \sum_{m,n=1}^L B_{mn} a_m^+ a_n \right\}. \quad (170)$$

In this case, the theory of quadratic Hamiltonians confirms that for general matrixes  $A_{mn}$ ,  $B_{mn}$  there is such a linear transformation of creation and annihilation operators  $a_n^+$ ,  $a_n$ ,  $n = 1, 2, \dots$  to operators  $\xi_n^+$ ,  $\xi_n$ ,

$$\begin{aligned} \xi_n^+ &= \sum_{m=1}^L U_{nm} a_m^+ + \sum_{m=1}^L V_{nm} a_m, \\ \xi_n &= \sum_{m=1}^L U_{nm}^* a_m + \sum_{m=1}^L V_{nm}^* a_m^+ \end{aligned} \quad (171)$$

that  $\forall n = 1, 2, \dots$   $\xi_n$  is conjugated to  $\xi_n^+$ ; this transformation is canonical:

$$\begin{aligned} [\xi_n, \xi_m] &= [\xi_n^+, \xi_m^+] = 0, \\ [\xi_n, \xi_m^+] &= \delta_{nm}, \quad m, n = 1, 2, 3, \dots \end{aligned} \quad (172)$$

and using new variables, Hamiltonian  $H_{eff}^c$  is:

$$H_{eff}^c = \sum_{i=1}^K \omega_n \xi_n^+ \xi_n + \sum_{i=K+1}^L \chi_n (\xi_n^+ \xi_n^+ + \xi_n \xi_n). \quad (173)$$

$\omega_n$ ,  $\chi_n$  are some real numbers. However, the physical considerations make clear that  $H_{eff}^c$  should be low bounded. Let's denote  $\mathcal{H}^c$  as Hilbertian space where Hamiltonian  $H_{eff}^c$  acts. This Hilbertian space is represented by the tensor product of Hilbertian spaces  $\mathcal{H}_i^c$

$$\mathcal{H}^c = \bigotimes_{i=1}^L \mathcal{H}_i^c, \quad (174)$$

where every  $\mathcal{H}_i^c$  is isomorphic to  $L_2(R)$  and this isomorphism can be chosen in such a way that the following condition is fulfilled. In  $L_2(R)$  the operators of coordinate  $\hat{q}$  and momenta  $\hat{p}$  operate in the standard way:

$$\hat{p}\hat{q} - \hat{q}\hat{p} = \frac{1}{i}. \quad (175)$$

$\xi_n^+$  and  $\xi_n$  operate only on the  $n$ -th multiplier in (174). The isomorphism between  $\mathcal{H}_i^c$  and  $L_2(R)$  mentioned above can be chosen in such a way that due to this isomorphism the following is correct:

$$\begin{aligned} \xi_n &= \frac{1}{\sqrt{2}}(\hat{p} - i\hat{q}), \\ \xi_n^+ &= \frac{1}{\sqrt{2}}(\hat{p} + i\hat{q}). \end{aligned} \quad (176)$$

But due to the isomorphism between  $\mathcal{H}_n^c$  and  $L_n(R)$  mentioned above the operator  $\xi_n^+\xi_n^+ + \xi_n\xi_n$  equals to the operator  $\hat{p}^2 - \hat{q}^2$ . Evidently, the last operator is not neither low nor upper bounded. Therefore, the physical requirement of positiveness of  $H_{eff}^c$  results in the fact that in the right part of (173) only the first summand in the right part is non-zero. As a result:

$$H_{eff}^c = \sum_{i=1}^L \omega_n \xi_n^+ \xi_n, \quad (177)$$

and for any  $n = 1, 2, 3, \dots$   $\omega_n$  is a real positive number.

Operators  $\xi_n^+$ ,  $\xi_n$  are creation and annihilation operators of some quasi-particles. As the formula (177) indicates, at zero temperature all occupation numbers of these quasi-particles are equal to zero:  $n_l^\xi = 0$ ,  $l = 1, 2, \dots$

Now, we are interested in the average:

$$\langle a_n^+ a_n \rangle, \quad n = 1, 2, \dots \quad (178)$$

for the ground state of our effective Hamiltonian. Evidently, the condition  $n_l^\xi = 0$ ,  $l = 1, 2, \dots$  implies  $\forall n = 1, 2, \dots$

$$\langle a_n^+ a_n \rangle = \sum_{m=1}^{\infty} |V'_{nm}|^2, \quad (179)$$

where matrix  $V'_{nm}$  is defined according to following equation:

$$a_n^+ = \sum_{m=1}^L U'_{nm} \xi_m^+ + \sum_{m=1}^L V'_{nm} \xi_m. \quad (180)$$

Clearly for the interaction of general form  $\hat{U}_2$  between protein molecules  $\sum_{m,n=1}^L |V'_{nm}|^2 > 0$ . This means that  $\langle a_n^\dagger a_n \rangle > 0$  at least for one  $n = 1, 2, \dots$

So, if the cell is live, then the number of protein molecules in the unfolded state is non-zero.

As a conclusion of this section we note that according to above reasoning, the number of protein molecules in the unfolded state approaches the finite value, if the cell volume tends to infinity. The last should mean that the number of the unfolded protein molecules in the real cell is negligible. The possible solution of this difficulty is the fact that the protoplasm has a quasi-crystalline structure only locally within the range of a small volume we call a domain consisting of several physioatoms. Therefore, we can supply the stated analysis only within the range of one domain. Since the domain number in the cell is proportional to its volume, then the number of protein molecules in the unfolded state is also proportional to its volume and has a non-zero value (per unit volume) in the thermodynamic limit.

## 7 Discussion of Relation between Mean Field Model and Superfluid Bose Gas Model on Protein Configuration Space

In the previous section we quoted the nonlinear Schrodinger equation describing our system in a mean field approximation:

$$i \frac{\partial}{\partial t} \xi = \hat{V}^1 \xi + N \hat{V}^2(\xi) \xi, \quad \xi \in L_2(X, d\mu), \quad (181)$$

where  $\xi \in L_2(X, d\mu)$ , and  $\hat{V}^1, \hat{V}^2(\xi)$  are operators in  $L_2(X, d\mu)$ .

The question arises, to which degree the results obtained within the framework of the mean field method (superfluid model) correlate with results obtained within the model of the superfluid Bose gas on the protein configuration space. Now, we'll show that these two models give the same result for spectrum of single-particle excitations.

Suppose  $\hat{U}_2$  used to construct  $\hat{V}^2(\xi)$  fulfills the condition which defines, as was said, that all the matrix elements of  $\hat{U}_2$  such that for them three of four indexes equal to zero and

fourth is non-zero equal to zero. Here we discussed matrix elements regarding the basis of eigenfunctions of operator  $\hat{V}^1$ .

Since the interaction constant  $\lambda$  is small and almost all protein molecules are in the normal unfolded state, then  $\xi$  is given by:

$$\xi = \varphi_0 + \eta, \quad (182)$$

where  $\eta$  is orthogonal to  $\varphi_0$ ,  $\varphi_0, \varphi_1, \varphi_2, \dots$  are an orthonormal basis of eigenfunctions of operator  $\hat{V}^1$ , and  $\varphi_0$  corresponds to the minimum eigenvalue of  $\hat{V}^1$ . The value  $\eta$  is a first-order value by the coupling constant  $\lambda$ . Let  $\eta_n$  be Fourier coefficients of vector  $\eta$  with regard to basis  $\varphi_n$

$$\eta = \sum_{n=1}^{\infty} \eta_n \varphi_n. \quad (183)$$

If in (182) we keep only terms linear on  $\eta$ , then complex conjugate to (182) has the following form:

$$-i \frac{\partial}{\partial t} \eta_n^* = E_n \eta_n^* + \sum_{m=1}^{\infty} B_{mn} \eta_m^* + 2 \sum_{m=1}^{\infty} A_{mn}^* \eta_m, \quad n = 1, 2, \dots \quad (184)$$

A similar derivation can be made for the equation for  $\frac{\partial}{\partial t} \eta_n$ . On the other hand in superfluid model, after suitable canonical transformation,  $a_n^+, a_n$ , satisfy the Heisenberg equation:

$$\dot{a}_n^+ = i[H_{eff}, a_n^+], \quad \dot{a}_n = i[H_{eff}, a_n]. \quad (185)$$

If we write down these equations in close detail, then we receive:

$$-i \frac{\partial}{\partial t} a_n^+ = E_n a_n^+ + \sum_{m=1}^{\infty} B_{mn} a_m^+ + 2 \sum_{m=1}^{\infty} A_{mn}^* a_m, \quad n = 1, 2, \dots \quad (186)$$

and an equation obtained from the previous one by the Hermitean conjugation.

But equations (184) and (186) have the same form, therefore, if variables  $\{a_n^+, a_n\}$  and  $\{\eta_n^+, \eta_n\}$  are subjected to linear transformation of the same form, then equations (184) and (186) for transformed variables coincide. Particularly, if the linear transformation transfers  $\{a_n^+, a_n\}$  into  $\{\xi_n^+, \xi_n\}$ , then  $\eta_n$  transformed under the same transformation are changed according to the following law:

$$\eta_n = \text{conste}^{-i\omega_n t}. \quad (187)$$

So  $\eta$  is given by

$$\eta = \sum_{n=1}^{\infty} f_n e^{-i\omega_n t}. \quad (188)$$

This formula shows that Bogolyubov's frequencies also describe a spectrum of single-particle excitations in the mean field model.

## 8 Comparison of Van der Waals Protoplasm Model and Superfluid Bose Gas Model on Configuration Space of Protein Molecule

The present work considers two models of Ling's cell protoplasm microstructure.

In the first model called Van der Waals model, we supposed that nontrivial first integrals of the system are so that their fixing by predefined values characterizing the resting state of a cell leads to the fact that protein molecules are situated in points of a lattice in the unfolded conformation. In addition, if the rapid descending of Van der Waals interaction between protein molecules with distance increasing is taken into account, the thermodynamic features of the living protoplasm can be calculated just as for the ideal gas of proteins. The thermodynamic features of the dead protoplasm can be calculated using a well-known Van der Waals interpolation formula for the free energy of a system. With this model we've obtained an expression for the quantity of heat the cell released while dying, and for a number of potassium ions releasing from the cell during this process.

In the second model we emphasize the analysis of internal protein molecules structure. As we have already mentioned, the protein molecules are supposed to be situated in points of a lattice, but have nontrivial internal degrees of freedom; and we study the structure of the ground state of this molecular system. The present work shows that within the range of weak interaction between protein molecules, the ground state of the interacting proteins system should be outlined as a ground state of the Hamiltonian of the Bose gas with a weak interaction on the protein molecule configuration space. To analyze this Hamiltonian we used standard methods of the superfluid theory. Taking into account that the interaction between protein molecules is weak and the bulk of protein molecules of the system is in the ground folded state, our Hamiltonian can be replaced with an effective quadratic one, but

it has different forms depending on if the cell is live or dead. In addition, it clears up which nontrivial motion integrals in the involution should be included to the generalized Gibbs distribution describing the living cell. The use of these effective quadratic Hamiltonians reveals that in the dead cell all the protein molecules significant for model properties are folded, while in the resting living cell the number of unfolded protein molecules is non-zero.

The question arises: what is the relation between considered protoplasm models? Particularly, how do conservation laws postulated for them link? We think, the considered models complement each other and connection of the named conservation laws comes down to the following. If we fix the motion integrals for the second model by some predefined values, then protein molecules are in the unfolded state, and we can suppose that the nature of interaction between different protein molecules provides the formation of a lattice being an energetically favorable structure. In other words, the conservation laws for the first model appear to be consequences of the conservation laws for the second model. If we conversely consider the Van der Waals protoplasm model as the main one and assign conservation laws to it, according to which the protein molecules in the living state are situated in points of a lattice, then it is reasonable to suggest that such a space configuration of protein molecules would be favorable for the unfolded (not folded) state of protein molecules for a number of reasons. In other words, the conservation laws for the second model are consequences of the conservation laws for the first model. This situation is certainly very inexact and hypothetical.

The questions, on which principles should new models be constructed (except ones considered here) and how to develop the kinetic theory of the living cell, are the subject of further investigations.

## 9 Conclusion

In the present work we have constructed and investigated properties of two complementary models of protoplasm — physical basis of life. The work was realized basing on generalized thermodynamics we proposed (Prokhorenko and Matveev, 2011). Within the framework of stated assumptions we explained a number of properties and phenomena observed in living cells, formalized (in the extended sense) by the physical theory of the living cell by Ling

(2001). However, the results we had formerly obtained, were inequalities and denoted only processes direction (in excitation and death of a cell heat releases, volume reduces and so on), there were no certain numerical evaluations obtained. To obtain them we need to specify the properties of intermolecular interactions which escape from the point of view of available analyze methods. That's why, we should construct different protoplasm models emphasizing one system parameter after another.

In the present work we constructed and investigated two models of protoplasm: one of them is naturally called Van der Waals model, and other is the model of superfluid Bose gas on the protein molecule configuration space. Our aim in this work was not to construct a model giving the most exact agreement with experimental data but to show that the constructing of such models is reasonable and possible. Qualitative agreement of the obtained results with experimental data gives an evidence of vitality of the thermodynamic theory of the living cell we proposed (Prokhorenko and Matveev, 2011).

Our theory can face the misapprehension from devotees of the non-equilibrium thermodynamics, as it is based on the equilibrium statistical physics and thermodynamics. Their main argument is evident: in the equilibrium state the maximum entropy is reached, therefore, the cell cannot perform the biological work. However, the other fact is also evident: the non-equilibrium thermodynamics still haven't given the quantitative description even for elementary phenomena, for example, electric resting potential. In addition, if we accept that the cell is living under the laws of non-equilibrium thermodynamics, we must also recognize that 200 years experience in successful modeling properties of the cell by non-living systems is untenable in principle. It would ruin all our knowledge about the living cell without giving anything in return. As for our generalized thermodynamics, the essential clarification is required: though the states which it operates are static by time, they are not equilibrium in the sense that their entropy is not the maximum one of all the states having the same energy (this is an essential feature of the state of the living material). The existence of such states even for the most realistic statistical mechanics systems is proven by one of us (Prokhorenko, 2009).

We are very grateful to P. Agutter, A.V. Koshelkin, Yu. E. Lozovik, A.V. Zayakin, E.N. Telshevskiy and N.V. Puzyrnikova for valuable critical comments on this article and very useful discussions.

# 10 Appendix 1. Transition of Cell from Living to Dead State in Weak External Alternating Field

Here and in our previous work (Prokhorenko and Matveev, 2011) we considered two extreme states of a cell: non-equilibrium state of rest and equilibrium state corresponding to death. Now, let's ask a question, can we describe death of the protoplasm within the framework of our generalized thermodynamics, i.e. to construct an example of a process transferring a cell from the living state of rest to the state corresponding to death. If we could not construct an example of such a process, all our theory would appear to be doubtful. In addition, up till now we considered only equilibrium statistical mechanics of the living cell, and the constructing of an example of the transformation process is the first step toward the construction of the non-equilibrium statistical mechanics of the living cell.

Let's start the analysis of the cell death mechanism from a certain problem of the non-equilibrium statistical mechanics. Let's consider the Hamilton system having  $n$  degrees of freedom which is described by the Hamiltonian  $H(p, q)$  in the field of external forces  $\varepsilon f(t)$ ,  $\varepsilon \in \mathbb{R}$  such that the complete Hamiltonian of the system is as follows:

$$\Gamma = H + \varepsilon f(t)P, \tag{189}$$

where  $P(p, q)$  is a function of canonically conjugated momenta and coordinates of a system. We suppose that applied force  $f(t)$  is a real function of time of the following form:

$$f(t) = \sum_{\nu} a_{\nu} \cos(\nu t + \varphi_{\nu}), \tag{190}$$

where phases  $\varphi_{\nu}$  are independent random values uniformly distributed by a circle. We suppose the frequency spectrum of the applied force is essentially continuous, so that sums of the following form

$$\sum_{\nu} F(\nu) a_{\nu}^2 \tag{191}$$

with continuous  $F(\nu)$  in the limit can be replaced by integrals

$$\int_0^{+\infty} F(\nu) I(\nu) d\nu. \tag{192}$$

This problem was considered by N.N. Bogoliubov (1945) and here we briefly quote the results obtained by them (relevant only to classical mechanics).

Let's denote  $D_t$  is a probability density of coordinates and momenta in a time  $t$  provided that phases  $\varphi_\nu$  have some defined values. The probability density for distribution  $p$  and  $q$  in the common sense, i.e. when phase values  $\varphi_\nu$  are inessential, can be found from  $D_t$  by averaging over all phases:

$$\rho_t = \overline{D_t}. \quad (193)$$

In the initial moment  $t = 0$  we suppose that distribution of coordinates and momenta does not depend on phases, in other terms

$$D_0 = \rho_0. \quad (194)$$

Temporal evolution of  $D_t$  should be passed in accordance with a well-known Liouville's equation:

$$\frac{\partial D_t}{\partial t} = (\Gamma, D_t) + \varepsilon f(t)(P, D_t), \quad (195)$$

where  $(A, B)$  is a Poisson bracket defined by the following formula:

$$(A, B) = \sum_{i=1}^n \left( \frac{\partial A}{\partial q_i} \frac{\partial B}{\partial p_i} - \frac{\partial B}{\partial p_i} \frac{\partial A}{\partial q_i} \right). \quad (196)$$

Let's introduce more one-parameter group of operators  $T_t$   $t \in \mathbb{R}$  acting on dynamical variables according to the formula:

$$T_t F(p, q) = F(p_t, q_t), \quad (197)$$

where  $p_t, q_t$  is a solution of canonical Hamilton equations

$$\begin{aligned} \frac{dp_t}{dt} &= -\frac{\partial H(p, q)}{\partial q}, \\ \frac{dq}{dt} &= \frac{\partial H(p, q)}{\partial p}, \end{aligned} \quad (198)$$

having initial data

$$p_0 = p, \quad q_0 = q. \quad (199)$$

Using these assumptions and designations (Bogoliubov, 1945), in the limit of small  $\varepsilon$  the following equation for  $\rho_t$  was derived:

$$\frac{\partial \rho_t}{\partial t} = [H, \rho_t] + \varepsilon^2 \int_0^t \Delta(t - \tau)(P, (T_{\tau-t}(P, \rho_\tau))) d\tau, \quad (200)$$

where

$$\Delta(\tau) = \frac{1}{2} \int_0^{+\infty} I(\nu) \cos(\nu\tau) d\nu. \quad (201)$$

Further Bogoliubov (1945) considered the case when the system exposed to external force is a harmonic oscillator of  $n$ -dimensions having incommensurate frequencies  $\vec{\omega} = (\omega_1, \dots, \omega_n)$ . Let's denote through a  $\sigma_t = \overline{\rho}_t$  function of action variables obtained from  $\rho_t$  by averaging by angular variables  $\theta_1, \dots, \theta_n$ . Function  $P(p, q)$  becomes a function of action-angle variables and can be expanded to the Fourier series:

$$P = \sum_{\vec{n}} P_{\vec{n}} e^{i\vec{\theta} \cdot \vec{n}}. \quad (202)$$

In this case, at the same initial conditions on  $D_t$ , in the limit of small  $\varepsilon$  the evolution of  $\sigma_t$  is described by the Fokker-Planck equation:

$$\frac{\partial \sigma_t}{\partial t} = \varepsilon^2 \sum_{k=1}^n \sum_{s=1}^n \frac{\partial}{\partial I_s} A_{sk}(I) \frac{\partial \sigma_t}{\partial I_k}, \quad (203)$$

where

$$A_{sk}(I) = \frac{\pi}{4} \sum_{\vec{n}} n_k n_s I(\vec{n} \cdot \vec{\omega}) |P_{\vec{n}}(I)|^2. \quad (204)$$

This equation, particularly, describes diffusion of distributions which at the initial moment can be distributions concentrated in one point, i.e.

$$\sigma_0(t) = \frac{1}{(2\pi)^n} \prod_{k=1}^n \delta(I_k - I_k^0). \quad (205)$$

But the last distribution is a generalized microcanonical distribution which we used to describe the states of rest of the Ling's cell. Therefore, it seems to be natural if the method proposed by Bogoliubov (1945) can be used to construct an example of a cell transformation process from the living to dead (equilibrium) state. Now, we shall show how it can be done using the results of Appendix 1 of the work by (Prokhorenko and Matveev, 2011).

So, assume there is a Hamilton system  $M$  with  $n + k$  degrees of freedom where  $k \ll n$ , which is described by the Hamiltonian  $H$  and where  $k$  independent first integrals in the involution are defined. There was shown in the Appendix 1 of the above-mentioned work that some covering Hamiltonian system  $M'$  of system  $M$  can be represented as a direct

product of  $M' = M'_1 \times M'_2$ , so that the canonically conjugated coordinates on  $M'_2$  are first integrals  $K'_1, \dots, K'_k$  (more properly, their lifting to  $M'$ ) playing a role of momenta and "angle" variables  $\varphi_1, \dots, \varphi_k$ , passing all the real axis and playing a role of coordinates.

Let  $\pi$  be a canonical projection of  $M'$  on  $M$ . The function  $f$  on  $M'$  we (Prokhorenko and Matveev, 2011) called a periodic one if  $f(x) = h(\pi(x))$  for some function  $h$  defined on  $M$ . It has been suggested (Prokhorenko and Matveev, 2011) to represent the mixed state of the  $M'$  system using some positive periodic function  $\rho$  on  $M'$ . Put by definition  $R_L := \{x \in M' \mid |\varphi_1| < L, \dots, |\varphi_k| < L\}$ . If  $A$  is a periodic function on  $M'$ , then its average over the state corresponding to distribution  $\rho$  was suggested (Prokhorenko and Matveev, 2011) to calculate using the following formula:

$$\langle A \rangle = \lim_{L \rightarrow \infty} \frac{\int_{R_L} \rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) A(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) dK_1 \dots d\varphi_k}{\int_{R_L} \rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) dK_1 \dots d\varphi_k}. \quad (206)$$

In this work we have shown that the limit (206) always exists. We shall call the distribution function  $\rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k)$  as a normalized one if

$$\lim_{L \rightarrow \infty} \frac{1}{L^k} \int_{R_L} \rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) dK_1 \dots d\varphi_k = 1. \quad (207)$$

The entropy of a state corresponding to the normalized distribution  $\rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k)$  is defined by the following formula

$$S = - \lim_{L \rightarrow \infty} \frac{1}{L^k} \int_{R_L} \rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) \ln \rho(K_1, \dots, K_k, \varphi_1, \dots, \varphi_k) dK_1 \dots d\varphi_k. \quad (208)$$

The last limit exists while the proof of its existence is the same as for the limit (206).

The Hamiltonian of the covering system  $M'$  we also (without a risk to make an error) denote as  $H$ . If our Hamilton system is a Ling's cell, then  $n \gg k$ . In this case, as shown (Prokhorenko and Matveev, 2011), the dynamics of the system  $M'_2$  can be considered separately. This dynamics is a Hamiltonian one and is defined by Hamiltonian  $F(x|T)$  where  $F(x|T)$  is the free energy of the system  $M'_1$  at temperature  $T$  provided that the  $M'_2$  system is situated in point  $x$ :

$$F(x|T) = -T \ln \int d\Gamma_y^1 e^{-\frac{H(y,x)}{T}}, \quad (209)$$

$y \in M'_1$ ,  $x \in M'_2$ ,  $d\Gamma_y^1$  is an element of phase volume on  $M'_1$ .

But  $K_1, \dots, K_k$  are the motion integrals, therefore  $F(x|T)$ , does not depend on angular variables  $\varphi_1, \dots, \varphi_k$ , but depends only on  $K_1, \dots, K_k$ . Put by definition

$$F'(K_1, \dots, K_k|T) := F(x|T). \quad (210)$$

Further, we are interested in the case when  $F'(K_1, \dots, K_k)$  reaches its minimum in the whole area (of non-zero volume)  $\mathcal{O}$ . In the work by Prokhorenko and Matveev (2011) the corresponding thesis is called the equivalence principle and there was shown that only under condition of  $F'(K_1, \dots, K_k)$  constancy in the whole area  $\mathcal{O}$  of the non-zero volume our generalized thermodynamics gives new results in comparison with the common one and can provide the thermodynamic descriptions of resting state of the Ling's cell.

So,  $F(x|T)$  is a constant on the direct product  $\mathcal{O} \times \mathbb{R}^k$  and, therefore, it defines a trivial dynamics in this area, i.e. if  $(p_0, q_0) \in \mathcal{O} \times \mathbb{R}^k$ , then  $\forall t \in \mathbb{R} (p_t, q_t) = (p_0, q_0)$ .

Using the last circumstance the equation (200) can be simplified as follows

$$\frac{\partial \rho_t}{\partial t} = \varepsilon^2 \int_0^t \Delta(t - \tau)(P, (P, \rho_\tau)) d\tau. \quad (211)$$

However, in the limit of small  $\varepsilon$   $\rho_\tau(z)$  varies with time slowly and is almost constant wherever  $\Delta(t - \tau)$  noticeably differs from zero. Therefore, in the integral from the right part of the last equation we can replace  $\rho_\tau$  by its value at  $\tau = t$ . As

$$\int_0^{+\infty} \Delta(t) dt = \frac{\pi I(0)}{2} \quad (212)$$

we can find

$$\frac{\partial \rho_t}{\partial t} = \frac{\varepsilon^2 \pi I(0)}{2} (P, (P, \rho_t)). \quad (213)$$

This equation of Fokker-Planck type is correct in the area  $\mathcal{O} \times \mathbb{R}^k$ .

As for behavior of function  $\rho_t$  outside the area  $\mathcal{O} \times \mathbb{R}^k$ , the physical considerations make clear that the probability to find the system  $M'$  outside the domain  $\mathcal{O} \times \mathbb{R}^k$  is negligible. Therefore, it is sufficient to investigate the behavior of  $\rho_t$  inside the domain  $\mathcal{O} \times \mathbb{R}^k$  by applying the appropriate boundary conditions for  $\rho_t$  on the boundary of  $\mathcal{O} \times \mathbb{R}^k$  which provide the self-adjointness of equation (213) and keeping the probability:

$$\int_{\mathcal{O} \times \mathbb{R}^k} \rho_t(x) d\Gamma_x^2 = 1, \quad (214)$$

where  $d\Gamma_x^2$  is an element of phase volume on  $M'_2$ . However, we won't make an ascertaining of the form of these boundary conditions but just make an assumption that the domain  $\mathcal{O}$  is a compact manifold (without boundary).

The self-adjointness condition of operator from the right part of the Fokker-Plank equation is a consequence of equality of forward and backward probabilities of arbitrary transition. This equality of forward and backward probabilities of transitions is a consequence of complete Hamiltonian invariance with respect to the time sign conversion operation (See the principle of kinetic coefficients symmetry by L. Onsager).

Now, following Bogolyubov (1945), we can show that the entropy of a state defined by relation (208) is increased monotonically in course of time due to equation (213). The entropy (208) reaches its maximum at the constant distribution function, i.e. at  $t = +\infty$

$$\rho_{+\infty}(K_1, \dots, \varphi_k) = \text{const.} \quad (215)$$

But if the distribution function  $\rho_{+\infty}(K_1, \dots, \varphi_k)$  is constant, then it corresponds to the Gibbs equilibrium microcanonical distribution.

So, an example of the Ling's cell transformation from the living (resting) to the dead state is its evolution in the weak external field which is a sum of harmonic oscillations with continuous frequency spectrum and random independent phases uniformly distributed along the circle; at that, for spectral density of intensity of this field  $I(\nu)$ ,  $I(0) \neq 0$  is required to be fulfilled.

The fact that the Fokker-Planck equation includes the spectral density of intensity only through  $I(0)$  is very significant and can be verified experimentally. This conclusion is in a good agreement with observed destructive influence of infrasound, magnetic storms and any white noises to living organisms.

## 11 Appendix 2. On ATP Structuring Role as Part of (ATP)m-(Protein)n-(H2O)p-(K<sup>+</sup>)q Complex

In this Appendix we discuss the theoretical relation between the capability of an ATP molecule to define the structure of a physioatom in the resting state and non-ergodicity of the Ling's cell. The purpose of this Appendix is to represent a demonstrative physical

view of the structuring ATP influence on the physioatom. We do not give a mathematically consistent characteristic of ATP-protein-water-K<sup>+</sup> interaction here.

We are interested in the following issues. How much is a number of protein molecules in the water-protein complex managed by one ATP molecule? Why the physical disturbance generated by the ATP propagates without dissipation to the large number of proteins and how does this disturbance influence on their conformation?

The fact that, according to our main assumption, the Ling's cell represents a Hamiltonian system having a vast number of first integrals in the involution makes us think, can we use the theory of completely integrable (in the sense of Liouville) systems to describe such a cell? The Korteweg—de Vries equation (Arnold, 2003) which can be an example of a completely integrable system

$$u_t = 6uu_x - u_{xxx} \quad (216)$$

was originated in the shallow water theory (in narrow ship channels). This equation is remarkable by allowing the solutions in a form of solitary waves (solitons) propagating without dissipation. The only parameter characterizing the soliton is its velocity. The Korteweg—de Vries equation also allows for multi-solitonic solutions which break into separate solitons propagating with different velocities at  $t \rightarrow \pm\infty$ . A significant property of multi-solitonic solutions is the fact that in case of solitons collision their velocities do not change.

We consider that the distribution of the ATP molecule physical influence on surrounding protein molecules has something similar to the propagating of solitons because there are many commutative first integrals for the Ling's cell, therefore, this case should be somewhat similar to the case arising in the theory of completely integrable systems.

So that one ATP molecule could effectively manage the surrounding complex of water and proteins, the disturbance transferred by solitons should not dissipate. For analysis simplicity let's suppose that the distribution of the physical impulse from the ATP is described by a one-dimensional Korteweg—de Vries equation. Then every soliton is unambiguously defined by the only parameter, its velocity. Therefore, to prevent loss of information from the ATP molecule, solitons' velocities shall not change after their collision. But the last property is fulfilled for multi-solitonic solutions of the Korteweg—de Vries equation, as we've mentioned above.

The theory of completely integrable systems is a rather developed one (Bullaf and Caudry,



angle variables conjugated to them. We can take  $I_2, \dots, I_N$  as independent first integrals in the involution, which are included in the generalized microcanonical distribution. We have:

$$S(E, I_2, \dots, I_N) = \ln \int dI_1 d\varphi_1 \prod_{i=2}^N d\varphi_i \delta(H(I_1, \dots, I_N) - E). \quad (220)$$

Integrating this formula by  $dI_1$  results in:

$$S(E, I_2, \dots, I_N) = \ln \frac{1}{\left| \frac{\partial H(I_1, \dots, I_N)}{\partial I_1} \right|} + N \ln 2\pi. \quad (221)$$

But  $\omega_1(I_1, \dots, I_N)$  is a frequency corresponding to  $\varphi_1$ ; and it is reasonable to restrict our choice to systems for which  $\omega_1$  is an asymptotically constant at  $N \rightarrow \infty$ . So:

$$S(E, I_2, \dots, I_N) = -\ln \omega_1(I_1, \dots, I_N) + N \ln 2\pi \quad (222)$$

But since  $\omega_1(I_1, \dots, I_N)$  is an asymptotically constant, in the limit of  $N \rightarrow \infty$  can be neglected, and the equivalence principle is fulfilled for integrals  $I_2, \dots, I_N$  in the limit of  $N \rightarrow \infty$ .

## References

Arnold, V.I. (2003). Mathematical methods in classical mechanics, URSS, Moscow.

Arosio, D., Kwansa, H.E., Gering, H., Piszczek, G., Bucci, E. (2002). Static and dynamic light scattering approach to the hydration of hemoglobin and its supertetramers in the presence of osmolites, *Biopolymers*, 63, 1-11.

Bogolyubov, N.N. (1945). Statistical disturbance theory, *Uchenye Zapiski MGU, Fizika, Vypusk 77, Kniga 3*, 74-100.

Bogolyubov, N.N., Bogolyubov N.N. (jr.). (1984). Introduction to quantum statistical mechanics, Nauka, Moscow.

Bullaf, R., Caudry, F. (1999). Solitons, in *Collected works*, Novokuznetskii Institute of Physics and Mathematics, Novokuznetsk.

Dirac, P.A.M. (1958). *The Principles of Quantum Mechanics*, fourth ed, The Clarendon Press, Oxford.

Feynman, R.P., Leighton, R.B., Sands, M. (1963). *The Feynman Lectures on Physics*, Vol. 1, Addison Wesley, Reading MA.

Kholodny, G.A., Ivanova, R.P., Borisova, R.G., Levochkin, Yu.V. (1987). Measurement of some thermal and physical characteristics of erythrocytes. *Kriobiologia*, 4, 46-47.

Landau, L.D., Lifshitz, E.M. (1995). *Theoretical physics*, vol. 5, *Statistical physics*, Nauka, Moscow.

Levine, A.M., Berhane, K., Masri-Lavine, L., Sanchez, M., Young, M., Augenbraun, M., Cohen, M., Anastos, K., Newman, M., Gange, S.J., Watts H. (2001). Prevalence and correlates of anemia in a large cohort of HIV-infected women: Women's Interagency HIV Study, *J Acquir Immune Defic Syndr*, 26(1), 28-35.

Ling, G.N. (1997). Debunking the alleged resurrection of the sodium pump hypothesis, *Physiol Chem Phys Med NMR*, 29, 123-198.

Ling, G.N. (2001). *Life at the Cell and Below-Cell Level. The Hidden History of a Fundamental Revolution in Biology*, Pacific Press, New York.

Ling, G.N. (2006). A convergence of experimental and theoretical breakthroughs affirms the PM theory of dynamically structured cell water at the theory's 40th birthday, in: Edited by Pollack, G.H., Cameron, I.L., Wheatley, D.N. (Eds.), *Water and the Cell*, Springer Verlag, Berlin, New York, 1-52.

Lifshitz, E.M., Pitaevsky, L.D. (1978). *Theoretical physics*, vol. 9, *Statistical physics*, part 2, Nauka, Moscow.

Matveev, V.V. (2005). Protoreaction of protoplasm, *Cell Mol Biol (Noisy-le-grand)*, 51(8), 715-723.

Mozer, J. (1975). Finitely many mass points on the line under influence of an exponential potential - an integrable system, *Proc. Battelle Recontres Lectures Notes in Physics*, 38, 467-497.

Prokhorenko, D.V. (2009). On non-ergodic property of Bose gas with weak pair interaction, *Journal of Physical Mathematics*, Vol. 1, Article ID S090701, 31 pages.

Prokhorenko, D.V., Matveev, V.V. (2011). The significance of non-ergodic property of statistical mechanics systems for understanding resting state of a living cell, *British Journal of Mathematics and Computer Science*, 1, 26-86.

Van Beekvelt, M.C., Colier, W.N., Wevers, R.A., Van Engelen, B.G. (2001). Performance of near-infrared spectroscopy in measuring local O<sub>2</sub> consumption and blood flow in skeletal muscle, *J. Appl. Physiol.*, 90, 511-519.