

<https://doi.org/10.15407/ujpe68.8.525>

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## INFLUENCE OF IRRADIATION ON THE PARAMETERS OF FACILITATED DIFFUSION IN A MODEL MEDICAL-BIOLOGICAL SYSTEMS

*A theoretical model of the diffusion in confined multicomponent systems under irradiation has been developed in the framework of the non-equilibrium thermodynamics formalism. The model allows the stationary diffusion flows to be determined taking the irradiation-induced changes in the equilibrium part of the diffusion coefficient into account. Entropy contributions to the equilibrium part of the diffusion coefficient due to the changes in the thermodynamic properties of liquid systems under irradiation are evaluated for a number of model solutions. It is shown that the permanent irradiation of medical-biological systems can increase the oxygen concentrations in the tissues by reducing the stabilizing effects that are observed in the facilitated diffusion regime without irradiation.*

*Keywords:* facilitated diffusion, diffusion coefficient, irradiation, biological system, ideal solution.

### 1. Introduction. Role of Diffusion Processes in Medical-Biological Liquid Systems under Irradiation

Diffusion is one of the basic processes that provide the functioning of medical-biological systems. Nowadays, the determination of the parameters of diffusion processes is an integral part of researches in such domains as medicine, genetics, and others. Therefore, the presence of a large number of experimental and theoretical works in this area is not unexpected. Another important direction in the research of medical-biological objects is the determination of how radiation affects their functioning. The combination of those directions seems to be interesting, because the understanding of the influence of radiation on transport processes in liquid systems is necessary for the solution of a number of problems. Medicine has to

be distinguished in the first place, because radiation therapy has already been used for a long time, and, today, there exists a wide range of technologies in radiation medicine: from the classical X-ray irradiation to modern methods that involve the treatment of patients with proton or ion beams [1, 2]. Unfortunately, such a treatment can still cause negative effects on healthy tissues as well. The understanding of the physical mechanisms modifying the thermodynamic properties of biological fluids subjected to the irradiation and corresponding changes in the parameters of transport processes can provide an opportunity to improve the existing methods in order to minimize negative consequences.

Very recently, there appeared a new direction of research in radiation medicine, namely, the study of the possibilities of radiation therapy (X-rays, electron and proton beams) in the pulse mode with higher, as compared with the classical approach, energy, which allows the negative effect on healthy tissues to be substantially reduced (the FLASH effect) [3–5]. For example, in work [6], a reduction in the neurotoxicity of irradiation for mice was registered when using FLASH radiotherapy. Currently, there is no complete understanding of the reasons that would explain the higher safety of FLASH irradiation for

Citation: Vlasenko T.S., Gavryushenko D.A., Cherevko K.V., Bulavin L.A. Influence of irradiation on the parameters of facilitated diffusion in a model medical-biological systems. *Ukr. J. Phys.* **68**, No. 8, 525 (2023). <https://doi.org/10.15407/ujpe68.8.525>.

Цитування: Власенко Т.С., Гаврюшенко Д.А., Черевко К.В., Булавін Л.А. Вплив радіаційного опромінення на параметри полегшеної дифузії модельної медико-біологічної системи. *Укр. фіз. журн.* **68**, №8, 527 (2023).

ISSN 2071-0194. *Ukr. J. Phys.* 2023. Vol. 68, No. 8

healthy tissues in comparison with standard radiotherapy techniques.

One of the possible key explanations is a probable reduction of oxygen concentration and hypoxia of healthy tissues [7] owing to the FLASH effect. This mechanism is a promising candidate, because some of the research works presented in the literature show a reduction of the radiation-induced therapeutic effect, if the oxygen concentration in tissues decreases [8]. This relation has a physical explanation as well. According to the available experimental data, a reduction of the oxygen concentration in liquid systems leads to a decrease in the formation of radicals (for example,  $H_2O_2$ ) under irradiation [6].

In the framework of this hypothesis, it is important to consider possible mechanisms of the oxygen concentration reduction in healthy tissues. It should be noted that, today, there are a sufficient number of examples demonstrating the successful application of physical models for the explanation of the processes occurring in medical-biological systems (see, for example, works [9, 10]). Therefore, besides biological effects, an important role in a change in the oxygen concentration in tissues owing to the application of FLASH radiotherapy can be played by physical mechanisms, namely, changes in the magnitude of diffusion flows under the influence of radiation. It is obvious that, in this case, the correct evaluation of the effectiveness of the indicated technology will substantially depend on the correctness of the evaluation of the radiation effect on oxygen transfer processes.

Another area worth be mentioned is genetics. One of the modern breeding methods includes the irradiation of seeds: either seeds in a liquid medium or dry seeds with various water contents [11, 12]. The existing studies make it possible to suppose that the changes in the parameters of transport processes in liquid systems at their irradiation can partially explain the observed mutation and survival parameters. Similar processes can be important for the investigation of the influence of irradiation on complicated biological objects, for example, DNA [13, 14]. If the DNA double helix was broken by the main beam, it can be repaired either correctly or not. Since the mentioned processes in living organisms take place in a liquid medium, the influence of diffusion processes can be important for the evaluation of the probability of that exactly the required components of molecules

get into damaged places, which is, in turn, important for predicting the results of the recovery process.

In many cases, medical-biological objects include spatially confined subsystems. As is known (see, for example, works [15–17]), this can lead to changes in the characteristics of physical processes running in such subsystems. One of the extremely important processes observed in confined subsystems is the process of so-called facilitated diffusion, which occurs in the presence of reverse chemical reactions in the system between the diffusing substance (substrate) and the carrier (macromolecules contained inside the system). As a result, the total diffusion flow consists of two components, namely, the flow of the substrate itself and the flow of the substrate-carrier complex. In particular, the process of oxygen transport by hemoglobin (the evaluation of its parameters under radiation may be important for radiotherapy) is an example of the facilitated diffusion [18]. Furthermore, it was experimentally found that myoglobin (Mb) facilitates the diffusion of  $O_2$  in the cell [19, 20], and, today, there are a number of works devoted to both the theoretical and experimental study of the reverse binding of  $O_2$  by myoglobin and its translational diffusion in a cell [21, 22]. The myoglobin-assisted facilitated diffusion of oxygen is especially effective at low partial pressures of the substrate, and its contribution to the diffusion flow depends on the concentration gradient of the carrier-substrate complex.

From the above review, the conclusion can be drawn that the study of the influence of radiation on diffusion processes in liquid systems is extremely important for medical-biological problems. At the same time, currently, there are no physical models that can provide reliable quantitative results concerning the parameters of diffusion processes in liquid systems under irradiation. Our article is devoted to the analysis of changes in the characteristics of facilitated diffusion processes in liquid systems under the influence of radiation, which can be induced by variations in the structural and thermodynamic properties of liquid systems.

## **2. Stationary Diffusion in Spatially Confined Medical-Biological Systems**

Today, there are a variety of approaches to describe diffusion processes. For instance, some theories use certain model representations concerning the substance structure and the interaction between parti-

cles and describe the diffusion with the help of kinetic equations; or there are phenomenological theories that describe this phenomenon in the most general way. Modern experimental and theoretical results obtained in the framework of those approaches testify that the diffusion coefficient can substantially depend on the local concentration of the particles in the system. Obviously, this circumstance cannot be taken into account in the formalism of the classical Fick's law, which has been used for a long time to determine the diffusion flow in confined systems.

In the case of facilitated diffusion, it is promising to develop a generalized theoretical model in the framework of non-equilibrium thermodynamics whose main relationships were substantiated during the last decades in the framework of the general statistical theory. As a result, now, we possess theoretical methods for the determination of the Onsager coefficients (phenomenological by nature) and can find the application limits for the linear theory. The latter is based on a quantum-mechanical description of an isolated many-particle system [23, 24]. In the framework of the indicated approach, it becomes possible to describe the facilitated diffusion in the systems that are far from the stability limits (i.e., we do not consider the region, where the equations become nonlocal with memory [25, 26]) using the physical properties of membrane systems and modeling chemical reactions as intermolecular interactions. The advantage of this model is its ability to account for the dependences of the diffusion coefficient on local concentrations and pressures.

The described approach was earlier used to study the stationary diffusion of a substance in a plane-parallel layer confined between two semipermeable walls (membranes); in the layer, substance 1 diffuses in an  $m$ -component solution [27, 28]. At the same time, the following assumptions were adopted.

- The walls are permeable only for substance 1. Under such conditions, there is only the flow of substance 1, whereas the flows of other substances are absent,

$$J_1 \neq 0, \quad J_2 = J_3 = \dots = J_m = 0.$$

- The system is far from its stability limits, which eliminates the necessity to use nonlocal equations with memory.

- The concentration gradient of the diffusing substance is maintained by maintaining its constant con-

centration at the boundaries,

$$\begin{cases} x_1(z=0) = x_0, \\ x_1(x=l) = x_l, \\ x_0 > x_l, \quad x_l \neq 0. \end{cases} \quad (1)$$

- The semipermeability of the walls leads to the appearance of osmotic phenomena in the system, which dictates a necessity to consider the pressure-induced changes in the chemical potentials of the components. The osmotic pressure makes it possible to explain the absence of the diffusion for the substance that is located between the semipermeable walls and has a concentration gradient different from zero.

- In all equations, the dependences of chemical potentials on both the concentrations and pressure are taken into account. In essence, information about the equation of state of the system is used.

- The stationary process of diffusion in the absence of external fields and at a constant temperature is considered. Cross-effects are not taken into consideration. The stationary character of the process makes it possible to correctly get rid of the second derivative in the diffusion equation. Nevertheless, the possibility of finding the flow magnitude dependence on the concentration difference survives.

- The model is one-dimensional, and the flow of the diffusing substance is perpendicular to the walls of the membrane system.

In the case of a two-component system, where, inside the plane-parallel layer, there are only a diffusing substance and a carrier responsible for the facilitated diffusion process, the general system of equations describing the diffusion flows looks like

$$\begin{cases} J_1 = -2kL_1 \nabla x_1 \left\{ \left[ \frac{1}{x_1} + \frac{\partial}{\partial x_1} \ln \gamma_1 \right] + \frac{v_{10} + kT \frac{\partial}{\partial p} \ln \gamma_1}{v_{20} + kT \frac{\partial}{\partial p} \ln \gamma_2} \left[ \frac{1}{1-x_1} - \frac{\partial}{\partial x_1} \ln \gamma_2 \right] \right\}, \\ \nabla x_2 = -\nabla x_1, \\ \nabla P = -\frac{2kT \left[ \frac{\partial}{\partial x_1} \ln \gamma_2 - \frac{1}{1-x_1} \right]}{v_{20} + kT \frac{\partial}{\partial p} \ln \gamma_2} \nabla x_1. \end{cases} \quad (2)$$

The expression for the diffusion coefficient  $D(T, p, x_1)$  reads

$$\begin{aligned} D(T, p, x_1) = 2kL_1 \left\{ \left[ \frac{1}{x_1} + \frac{\partial}{\partial x_1} \ln \gamma_1 \right] + \frac{v_{10} + kT \frac{\partial}{\partial p} \ln \gamma_1}{v_{20} + kT \frac{\partial}{\partial p} \ln \gamma_2} \left[ \frac{1}{1-x_1} - \frac{\partial}{\partial x_1} \ln \gamma_2 \right] \right\}. \end{aligned} \quad (3)$$

It should be noted that expression (3) for the diffusion coefficient demonstrates its significant dependence on the parameters of the thermal equation describing the state of the examined system. It should be especially emphasized that the equilibrium and non-equilibrium properties of the system can be distinctly separated. For instance, in the general case, the parameter  $L_1$  in expression (3) is responsible for the non-equilibrium properties, which are obtained in statistical mechanics from the solutions of the Liouville equation with a non-equilibrium distribution function. At the same time, the expression in braces describes the equilibrium properties and corresponds to the equilibrium distribution function.

The considered model allows the diffusion flow of a substance in confined systems to be determined for various models of solutions [29–31]. For this purpose, it is necessary to specify the character of the interaction between the particles in the solution (i.e., the solution type) and the character of possible chemical reactions by means of the activity coefficient in the expression for the chemical potential,

$$\begin{aligned} \mu_i(T, \rho, c_1 \dots c_n) &= \\ &= \mu_{i0}(T, \rho) + kT \ln c_i \gamma_i(T, \rho, c_1 \dots c_n), \end{aligned} \quad (4)$$

where  $\mu_{i0}$  is the chemical potential of the pure  $i$ -th component, and  $\gamma_i(T, \rho, c_1, \dots, c_n)$  is the activity of the  $i$ -th component.

Today, there are a number of different solution models that describe real fluid systems. For example, these are ideal and regular solutions, or solutions with the chemical potentials of components determined by the Margules, Scatchard-Hammer, and other relations. In order to use those models in practice, it is necessary to know the phenomenological constants entering the equation for the activity coefficient in expression (4). One of the possible approaches to their determination can be an approach based on the methods of perturbation theory and applied to isobaric-isothermal ensembles [32]. In the framework of this approach, the account for various orders of the perturbation theory allows the activity coefficients to be determined for solutions of various types. For example, for systems with the non-valent interaction that are far from the critical point or the stability limit, the following expressions obtained in the second order of perturbation theory are valid [32]:

$$\ln \gamma_1 = n_2^2 \left( \Phi_{12} - \frac{1}{2} (\Phi_{11} + \Phi_{22}) - 3\Phi_{111} + 2\Phi_{112} - \right.$$

$$\left. - \Phi_{122} \right) + 2n_2^3 (\Phi_{111} - \Phi_{222} - \Phi_{112} + \Phi_{122}), \quad (5)$$

$$\begin{aligned} \ln \gamma_2 &= n_1^2 \left( \Phi_{12} - \frac{1}{2} (\Phi_{11} + \Phi_{22}) - 3\Phi_{222} + 2\Phi_{122} - \right. \\ &\left. - \Phi_{112} \right) + 2n_1^3 (\Phi_{222} - \Phi_{111} - \Phi_{122} + \Phi_{112}), \end{aligned} \quad (6)$$

where the functions  $\Phi_{ijk}$ ,

$$\begin{aligned} \Phi_{iii} &= \frac{1}{2} \int_{\langle V(T,P,N) \rangle_0} f_0(r_1, r_2, r_3) \left[ e^{-\beta \psi_{ii}(r_{12})} - 1 \right] \times \\ &\times \left[ e^{-\beta \psi_{ii}(r_{13})} - 1 \right] dr_{12} dr_{13}, \end{aligned} \quad (7)$$

$$\begin{aligned} \Phi_{ijj} (ijj) &= \frac{1}{2} \int_{\langle V(T,P,N) \rangle_0} f_0(r_1, r_2, r_3) \times \\ &\times \left\{ \left[ e^{-\beta \psi_{ij}(r_{12})} - 1 \right] \left[ e^{-\beta \psi_{ij}(r_{13})} - 1 \right] + \right. \\ &\left. + 2 \left[ e^{-\beta \psi_{ii}(r_{12})} - 1 \right] \left[ e^{-\beta \psi_{ij}(r_{13})} - 1 \right] \right\} dr_{12} dr_{13}. \end{aligned} \quad (8)$$

depend only on the temperature and pressure. Expressions (5)–(8) are the known empirical Margules relations [33]

$$\begin{aligned} \ln \gamma_1 &= \frac{a_1}{2} n_2^2 + \frac{a_2}{3} n_2^3, \\ \ln \gamma_2 &= \frac{a_1 + a_2}{2} n_1^2 - \frac{a_2}{3} n_1^3, \end{aligned} \quad (9)$$

where

$$\begin{aligned} a_1 &= 2\Phi_{12} - \Phi_{11} - \Phi_{22} - 6\Phi_{111} + 4\Phi_{112} - 2\Phi_{122}, \\ a_2 &= 6(\Phi_{111} + \Phi_{122} - \Phi_{112} - \Phi_{222}). \end{aligned} \quad (10)$$

Equations (5)–(10) make it possible to consider changes occurring in the interparticle interaction, which are observed in liquid systems at certain irradiation energies [34]. At the same time, changes in the magnitude of the diffusion flow can be observed, even if only entropy contributions to the thermodynamic potential of the binary system are taken into consideration. The latter can be seen by analyzing the facilitated diffusion in a membrane system in the framework of the ideal-solution model (in this model, at the mixing, the contribution of entropic factors to thermodynamic potentials dominates over the energy contribution, so that the latter can be neglected. Accordingly, the contribution of the activity coefficient

to expression (4) identically equals zero). In this approximation, the chemical potential is given by the expression

$$\mu_1(T, p, x_1) = \mu_{10}(T, p) + kT \ln x_1. \quad (11)$$

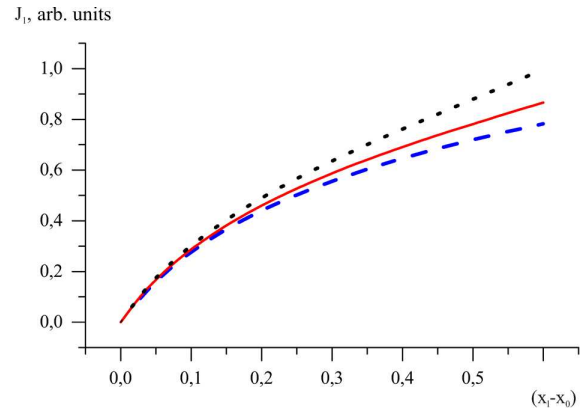
In Fig. 1, the calculation results obtained earlier [31] for the dependence of the diffusion flow on the concentration difference  $(x_l - x_0)$  across the membrane in the absence of irradiation are exhibited. The figure demonstrates a considerable nonlinearity of the depicted dependences. It is of interest that such behavior is observed only for an ideal solution, i.e., if only the entropic contribution to the change in the thermodynamic potential at the mixing is taken into consideration. It should be emphasized that the deviation from the classical linear dependence was revealed due to the correct account for the dependence of the diffusion coefficient on the field variables of the system in the transport equations.

The analysis of the presented results testifies that an almost linear dependence of the flow is observed at low  $(x_l - x_0)$ -values. But, as the difference  $x_0 - x_l$  increases, the dependence  $J_1(x_l - x_0)$  substantially deviates from linearity. An appreciable stabilizing effect is observed, which manifests itself in that the flow magnitude weakly depends on the difference between the diffusing substance concentrations at the membrane system boundaries.

As one can see from the analysis of the results, modifications in the equilibrium part of the diffusion coefficient (3) can lead to substantial changes in the magnitude of the diffusing substance flow. Thus, when determining the influence of radiation on diffusion processes in medical-biological fluid systems, structural changes induced by a stationary irradiation can play an essential role in the variation of the diffusion flow characteristics.

### 3. Influence of Irradiation on the Structural and Thermodynamic Properties of Medical-Biological Fluids

One of the possible mechanisms affecting the structure and the thermodynamic properties of liquid systems under the influence of external factors is the deviation of the particle velocity distribution function from the Maxwellian distribution, which is typical of the equilibrium state [35]. The basis of this mechanism is the transfer of momentum from “active” in-



**Fig. 1.** Dependences of the normalized diffusion flow  $J_1$  on the concentration difference  $(x_l - x_0)$  between the membrane boundaries in the framework of the ideal solution model for various values of the ratio  $\frac{v_{10}}{v_{20}} = 0.01$  (dashed curve), 0.2 (solid curve), and 0.5 (dotted curve)

coming particles to those that form the liquid. Therefore, the irradiation changes the values of the coefficients  $A$  and  $\phi$  that they have for the Maxwellian distribution in the equilibrium state,

$$f(p) = A \exp(-\phi p^2), \quad (12)$$

where  $p$  is the momentum of a particle in the system.

It should be noted that similar mechanisms of parameter changes are inherent to various systems. For example, there are works, where the properties of non-equilibrium systems are studied in the framework of an approach with the non-equilibrium distribution function [36, 37], or where the momentum expansion of distribution functions about a local Maxwellian distribution is used [38]. One of such problems is the study of the gas behavior in a plane Couette flow, which can be solved by modifying the Maxwellian distribution function with the Sonine polynomials. Another problem is to determine the specific features of the gas involved in chemical reactions. To solve it, it is necessary to account for the changes in the velocity distribution function [39]. Such a system has a lot in common with a liquid system under irradiation, because the radiolysis generates a significant number of new interacting particles in liquids [40].

A separate group of studies deals with the deviations from the Maxwellian distribution for systems in a stationary state. For example, this is the power-law distribution of velocities in granular gases [41] or the

non-Maxwellian distribution of velocities observed in fluids in a stationary state in an external field [42–44].

Earlier, we already considered the mechanism described above. Namely, in the framework of the formalism of the Bogolyubov–Born–Green–Kirkwood–Yvon (BBGKY) chain of equations, an approach was developed to determine the variations in the thermodynamic properties and the structure of liquid systems due to the action of a stationary isotropic irradiation [45]. It should be noted that this approach has certain restrictions on the irradiation character. In the classical approach, the chain of Bogolyubov equations is applied to describe a liquid system just under the thermodynamic equilibrium condition [46,47]. At the same time, under certain other conditions, it can also be used to determine the structure of a non-equilibrium system.

Let us consider what happens in a liquid system subjected to stationary irradiation. The energy transfer from incoming particles to the particles composing the liquid system drastically changes the velocity of the latter. This means that the phase volume varies so that the application of Hamiltonian mechanics to describe such a system becomes incorrect. Obviously, this circumstance makes also invalid the application of the chain of Bogolyubov equations to describe the process. The situation is somewhat different, if the complicated process of the system evolution from a purely non-equilibrium state (immediately after the irradiation was started) to a stationary non-equilibrium state is not considered in detail. In this case, the system passes through a number of intermediate states that are characterized by their own sets of relaxation times. In the general case, a perturbed system evolves to an equilibrium state. If we include a permanent energy source, then the permanent irradiation does not allow the liquid system to transit into the equilibrium state so that the latter remains in a certain stationary non-equilibrium state.

Proceeding from Bogolyubov’s ideas [48], it can be asserted that, after a certain time interval sufficient for several collisions to happen, the movement of particles becomes chaotic. Afterward, a quasi-equilibrium velocity distribution among the molecules is achieved, and the system evolution can be governed by changing macroscopic parameters and external factors. Hence, the model aimed at determining the parameters of a liquid system in a stationary non-equilibrium state under the irradiation on the basis

of the Bogolyubov equations is applicable to the case where the system state is not determined by the path used to achieve this state, but by macroscopic parameters and the principle of minimum entropy production under a fixed external influence prohibiting the system from the transition into the equilibrium state [23, 49, 50]. Then the chain of Bogolyubov equations can be used provided that the time,  $t$ , dependence of the non-equilibrium distribution function of the  $n$ th order  $F_n(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n, \mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_n, t)$  is taken into account via the  $t$ -dependences of macroscopic parameters,

$$F_n(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n, \mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_n, t) = F_n(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n, \mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_n, \rho(t), T(t), Ext(t)), \quad (13)$$

where  $\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_n$  are the coordinates of the particles,  $\mathbf{p}_1, \mathbf{p}_2, \dots, \mathbf{p}_n$  are their pulses, and  $Ext(t)$  is the influence of external factors.

Therefore, it is possible to formulate the main points that made it possible to develop the indicated approach and to determine the influence of external factors on liquid systems [51, 52]:

- stationary irradiation of a liquid system changes the momentum distribution function of its particles;
- variations in the momentum distribution function affect the system structure; namely, they modify the radial distribution functions;
- changes in the thermodynamic parameters of a non-equilibrium liquid system in a stationary state under the irradiation is a consequence of structural changes in the system.

As one can see from the last item, in order to determine the characteristics of a liquid system in a stationary non-equilibrium state under the irradiation, it is necessary to find a relation between the changes in the radial distribution functions of the system and the changes of its thermodynamic properties.

In the framework of the approach described in work [45], the following expression was obtained for the modified BBGKY chain for a one-component system in a stationary non-equilibrium state:

$$\begin{aligned} & - \frac{\partial g_2(\mathbf{r}_1, \mathbf{r}_2)}{\partial \mathbf{r}_1} \int \frac{\mathbf{p}_1}{m} f_2(\mathbf{p}_1, \mathbf{p}_2) \partial \mathbf{p}_1 \partial \mathbf{p}_2 + \\ & + \frac{\partial \Phi(|\mathbf{r}_1 - \mathbf{r}_2|)}{\partial \mathbf{r}_1} g_2(\mathbf{r}_1, \mathbf{r}_2) \int \frac{\partial f_2(\mathbf{p}_1, \mathbf{p}_2)}{\partial \mathbf{p}_1} \partial \mathbf{p}_1 \partial \mathbf{p}_2 + \\ & + \rho \int \frac{\partial \Phi(|\mathbf{r}_1 - \mathbf{r}_3|)}{\partial \mathbf{r}_1} g_3(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3) d\mathbf{r}_3 \times \end{aligned}$$

$$\times \int \frac{\partial f_2(\mathbf{p}_1, \mathbf{p}_2)}{\partial \mathbf{p}_1} \partial \mathbf{p}_1 \partial \mathbf{p}_2 = 0. \quad (14)$$

We introduce a new parameter  $T_{\text{eff}}$  which allows the equation to be written in the form

$$kT_{\text{eff}} \frac{\partial g_2(\mathbf{r}_1, \mathbf{r}_2)}{\partial \mathbf{r}_1} + \frac{\partial \Phi(|\mathbf{r}_1 - \mathbf{r}_2|)}{\partial \mathbf{r}_1} g_2(\mathbf{r}_1, \mathbf{r}_2) + \rho \int \frac{\partial \Phi(|\mathbf{r}_1 - \mathbf{r}_3|)}{\partial \mathbf{r}_1} g_3(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3) d\mathbf{r}_3 = 0, \quad (15)$$

where the equality

$$kT_{\text{eff}} \int \frac{\partial f_2(\mathbf{p}_1, \mathbf{p}_2)}{\partial \mathbf{p}_1} d\mathbf{p}_1 d\mathbf{p}_2 = - \int \frac{\mathbf{p}_1}{m} f_2(\mathbf{p}_1, \mathbf{p}_2) d\mathbf{p}_1 d\mathbf{p}_2. \quad (16)$$

is taken into account.

The analysis of Eqs. (14)–(15) showed that, in the case of a homogeneous liquid system in a stationary state, there appears a new parameter  $kT_{\text{eff}}$  in them instead of the thermodynamic temperature, which is associated with the modified momentum part  $f_2(\mathbf{p}_1^k, \mathbf{p}_2^l)$  of the two-particle distribution function [51–53]. The structural similarity of Eqs. (14)–(15) and the BBGKY equations in the case of equilibrium systems allowed us to assume that the parameter “effective temperature”  $kT_{\text{eff}}$  will play the role of the thermodynamic temperature governing the structural and thermodynamic properties of a non-equilibrium liquid system in a stationary state under the irradiation. However, the parameter “effective temperature” differs from the genuine thermodynamic temperature of the system and is equal to the temperature of an equilibrium system whose structure and thermodynamic properties are similar to those of the non-equilibrium system. The analysis of the results also showed that the only reason for the difference between the “effective” and thermodynamic temperatures is the changes in the momentum distribution function.

Later, the results were generalized in a natural way onto multicomponent systems. In this case, for the effective temperatures, we may write [45]

$$kT_{\text{eff}}^{kl} = - \frac{\int \frac{\mathbf{p}_1^k}{m_k} f_2(\mathbf{p}_1^k, \mathbf{p}_2^l) d\mathbf{p}_1^k d\mathbf{p}_2^l}{\int \frac{\partial f_2(\mathbf{p}_1^k, \mathbf{p}_2^l)}{\partial \mathbf{p}_1^k} d\mathbf{p}_1^k d\mathbf{p}_2^l}, \quad (17)$$

$l, k = 1 \dots M,$

where  $f_2(\mathbf{p}_1^k, \mathbf{p}_2^l)$  is the momentum part of the two-particle distribution function of the components  $l$  and  $k$ . The cross terms in Eq. (17) do not depend on the component order, i.e.,  $T_{\text{eff}}^{kl} = T_{\text{eff}}^{lk}$ .

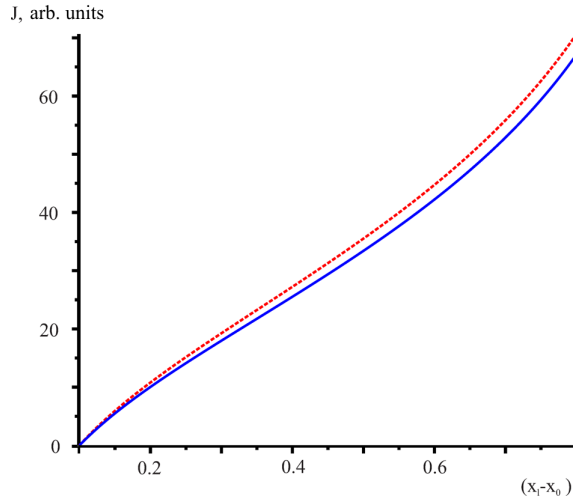
Note that Eq. (17) determines several “effective temperatures” of subsystems  $1l, 2l, \dots$ . Such qualitative results correspond to the results of the statistical theory of relaxation processes for systems consisting of weakly interacting subsystems [23], for which several different temperatures are acceptable.

The obtained theoretical results were later confirmed in a computer experiment, where the behavior of water under the influence of  $\alpha$ -particles with energies in an interval of 0.05–0.25 KeV/particle was studied using molecular dynamics methods [54]. It was shown that the dependence of the self-diffusion coefficient on  $T_{\text{eff}}$  corresponds to the literature data for its dependence on the thermodynamic temperature. Such a coincidence confirmed the assumption about the physical meaning of the “effective temperature”.

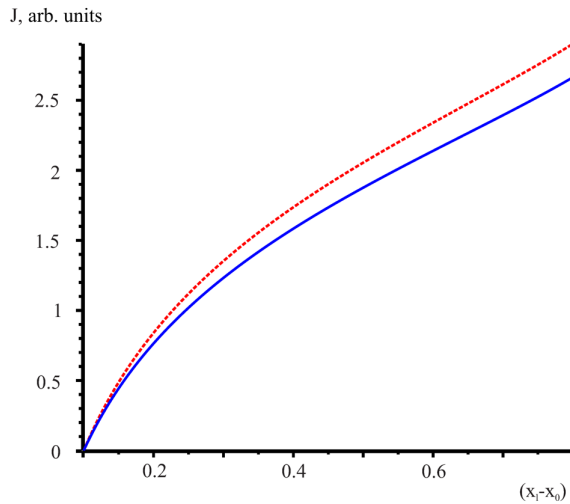
#### 4. Transfer Processes in Liquid Systems under Irradiation. Entropic Effects

As was already mentioned, the irradiation effect on the transport processes in liquid systems can be divided into two parts. One of them is the entropic contribution, which can be described by introducing a new temperature of the system [Eq. (17)] which can affect the flows, if the thermodynamic temperature is substituted by the effective one in Eqs. (2) and (3). The other is the energy contribution; in the case of irradiation, it can arise, for example, owing to changes in the parameters of the interaction between particles, and modify the chemical potentials of the components. In the general case, the irradiation of a liquid system brings about the emergence of both entropy and energy contributions to the thermodynamic potential.

Consider the simplest case with entropy contributions. Assume that the irradiation energy is low enough so that the system does not undergo radiolysis. (For example, from the literature data for the water irradiation with  $\alpha$ -particles [55], one can see that these are energies lower than 1 KeV/particle. The differential ionization cross-section almost vanishes at such energies, and the probability of inelastic collisions with the formation of secondary electrons is



**Fig. 2.** Dependences of the diffusion flow  $J_1$  on  $(x_l - x_0)$  for an ideal solution with  $\frac{v_{10}}{v_{20}} = 0.1$  for various  $T_{\text{eff}}^{ij}$ :  $T_{\text{eff}}^{11} = T_{\text{eff}}^{22} = T_{\text{eff}}^{12} = 300$  K (solid curve); and  $T_{\text{eff}}^{11} = 320$  K,  $T_{\text{eff}}^{22} = 300$  K,  $T_{\text{eff}}^{12} = 310$  K (dashed curve)



**Fig. 3.** Dependences of the diffusion flow  $J_1$  on  $(x_l - x_0)$  for an ideal solution with  $\frac{v_{10}}{v_{20}} = 0.01$  for various  $T_{\text{eff}}^{ij}$ :  $T_{\text{eff}}^{11} = T_{\text{eff}}^{22} = T_{\text{eff}}^{12} = 300$  K (solid curve); and  $T_{\text{eff}}^{11} = 320$  K,  $T_{\text{eff}}^{22} = 300$  K,  $T_{\text{eff}}^{12} = 310$  K (dashed curve)

quite low. On the basis of the above results, it can be assumed that elastic collisions prevail in the energy transfer process in the selected interval of irradiation energies, and water remains a one-component system.) This assumption is essential, because it allows us to use the equations for the fluxes of diffusing substances in a two-component system at all stages. Since we are interested in the entropic con-

tributions, we use the ideal-solution model (11). Taking into account that three new parameters appear in the description of the structural and thermodynamic properties of a two-component system under the irradiation [see Eq. (17)], the system of equations (2) can be rewritten in the form

$$\begin{cases} J_1 = -2k \frac{L_1}{T_{\text{eff}}^{12}} \frac{dx_1}{dz} \left\{ \frac{T_{\text{eff}}^{11}}{x_1} + \frac{v_{10}}{v_{20}} \frac{T_{\text{eff}}^{22}}{1-x_1} \right\}, \\ \frac{dx_2}{dz} = -\frac{dx_1}{dz}, \\ \frac{dp}{dz} = \frac{2kT}{v_{20}} \frac{1}{1-x_1} \frac{dx_1}{dz}. \end{cases} \quad (18)$$

Then, after the integration under condition (1) for the flux, we obtain the expression

$$J_1 = -\frac{2kL_1}{lT_{\text{eff}}^{12}} \left( \ln \frac{x_l T_{\text{eff}}^{11}}{x_0} - \frac{v_{10}}{v_{20}} \ln \frac{(1-x_l) T_{\text{eff}}^{22}}{1-x_0} \right). \quad (19)$$

The derived dependences of the diffusion flux on the concentration difference for the model quantities  $T_{\text{eff}}^{11}$ ,  $T_{\text{eff}}^{22}$ , and  $T_{\text{eff}}^{12}$  are shown in Figs. 2 and 3.

As can be seen from the analysis of Figs. 1–3, the irradiation reduces the stabilizing effect in the facilitated diffusion phenomenon in confined systems. This is manifested in a smaller deviation of the diffusion flux from the linear dependence, when the concentration difference between the membrane boundaries increases as compared with the absence of irradiation. As a result, the flow of the diffusing substance increases at large concentration gradients, which can explain the lower oxygen content in tissues, when using FLASH therapy in comparison with the classic approach. Under the pulsed irradiation, the system relaxes between the pulses, and, accordingly, the diffusion saturation of tissues with oxygen decreases owing to the stabilizing effect. In the classical approach with permanent irradiation, although the irradiation intensity is lower, the average value of the oxygen diffusion flux is larger. This can lead to a growth of the oxygen concentration in healthy tissues, which increases the risk of negative consequences [7].

From the analysis of the obtained data, one can see that the reduction of the ratio between the partial molar volumes of the substance diffusing through the membrane, and the solvent enhances the effect of irradiation. This behavior testifies to the importance of the revealed effect for biological systems, in which the



ratio  $\frac{v_{10}}{v_{20}}$  is extremely small due to the facilitated diffusion of biologically active substances through membranes (for example, the facilitated diffusion of oxygen in the myoglobin or hemoglobin solutions).

It is worth emphasizing once more that the effect analyzed in the work has an exclusively entropic origin and is invoked by the growth of the effective temperature of a non-equilibrium system in a stationary state. In order to obtain a complete picture of this phenomenon, it is necessary to engage more complicated models that make allowance for energy contributions.

## 5. Conclusions

A possible influence of the irradiation on diffusion processes in confined medical-biological liquid systems has been studied. A relation of the changes in the structural and thermodynamic properties of liquid systems under the irradiation to the specific features of diffusion processes is considered. Namely, the model developed earlier in the framework of non-equilibrium thermodynamics for the description of the stationary diffusion in confined systems is extended to the case where the system is subjected to the irradiation. The new variant allows the changes in the structural characteristics of the system as a result of the irradiation to be taken into account, which made it possible to study the influence of the irradiation (for example, the irradiation with electron beams or heavy ions) on the magnitude of the diffusing substance flow. A relation between the changes in the diffusion flux and the effective temperatures characterizing the thermodynamic properties of a non-equilibrium system in the stationary state under the irradiation is determined.

The analysis of the obtained data leads us to the following conclusions:

- the account for the dependence of the diffusion coefficient on the concentrations and pressure in the processes of stationary facilitated diffusion leads to the emergence of the stabilization and saturation effects in the diffusion flow magnitude, unlike the models with constant diffusion coefficients;
- the irradiation of a liquid system reduces the stabilization effect observed at the facilitated diffusion in confined systems in the absence of irradiation; if the concentration difference across the membrane is substantial, the diffusion flux increases in comparison with that in the absence of irradiation;

- the influence of the irradiation of a liquid system on the parameters of the facilitated diffusion becomes stronger, as the ratio between the partial molar volumes of the substance diffusing through the membrane and the solvent increases;

- the irradiation-induced growth of the flux of the diffusing substance can contribute to the increase of the oxygen concentration in the biological tissues under a permanent irradiation (the classical approach) in comparison with FLASH therapy and, accordingly, increase the probability of negative effects for healthy tissues during radiation therapy;

- the account for the changes in the parameters of diffusion processes in medical-biological fluids under the irradiation is mandatory when developing new irradiation methods in medicine, biology, and so forth.

*The authors are grateful to Professor V.M. Sysoev for the fruitful discussion of the ideas that underlie the research presented in this paper. The work was partially sponsored in the framework of grant 22K-04-12 of the target program of scientific research of the National Academy of Sciences of Ukraine.*

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Received 14.06.23.

Translated from Ukrainian by O.I. Voitenko

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#### ВПЛИВ РАДІАЦІЙНОГО ОПРОМІНЕННЯ НА ПАРАМЕТРИ ПОЛЕГШЕНОЇ ДИФУЗІЇ МОДЕЛЬНОЇ МЕДИКО-БІОЛОГІЧНОЇ СИСТЕМИ

В рамках нерівноважної статистичної термодинаміки розвинено теоретичну модель дифузії в обмежених багатокомпонентних рідинних системах за наявності радіаційного опромінення, що дозволяє визначати стаціонарні дифузійні потоки з урахуванням спричинених опроміненням змін у рівноважній частині коефіцієнта дифузії. Для низки модельних розчинів проведено оцінку ентропійних внесків у рівноважну частину коефіцієнта дифузії, спричинених зміною термодинамічних властивостей рідинних систем під впливом радіаційного опромінення. Показано, що опромінення медико-біологічних рідинних систем в неперервному режимі може призводити до збільшення насичення тканин киснем за рахунок зменшення стабілізаційних ефектів, що спостерігаються при полегшеній дифузії за відсутності опромінення.

*Ключові слова:* полегшена дифузія, коефіцієнт дифузії, радіаційне опромінення, біологічна система, ідеальний розчин.