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Thermal Waves and Flow Features of Pulsed Thermally Stimulated Biochemical Reactions in Viral Particles Interaction with Cells

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Abstract: **This review considers the features of excitation, propagation over a long distance, and the action of non-dissipative high-frequency temperature waves in relation to their influence on the efficiency of the system for remote recognition of critical cells by viruses. It is shown that the action of such waves leads to screening of critical cells due to a change in their surface atomic and molecular structure, which leads to a significant change in the dispersion and other electromagnetic characteristics of these cells. This leads to a very strong weakening of the efficiency of the system of remote recognition of such cells by viruses, which corresponds to the effective "passive" self-defense of the body and blocking the activity of viruses. It is also shown that the effect of such temperature waves can be an "active" method of self-defense of the body, which reconfigures the virus recognition system to extraneous (non-critical) cells or other macrocomplexes. In this case, the result of the attack by the virus will be the mutual destruction of the "false target" and the virus due to the natural apoptosis of this non-critical object when the virus penetrates it.**

Keywords: **viruses, temperature waves, cells, apoptosis**

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Contents

1. INTRODUCTION

The wide spread of the new coronavirus infection has shown the vulnerability of the human immune system, and a significant increase in the use of antibiotics and disinfectants has already led to the formation of pathogenic microorganisms resistant to their action, which indirectly strengthens viruses. Therefore, the development of a new method for the prevention and treatment of infectious diseases is currently extremely relevant.

It has long been known that stressful effects on the body provoke the activation of a number of protective processes for its survival. Therefore, the authors of the work set themselves the task of studying the potential of an active method of self-defense against viral infections, the result of which is not only a decrease in the activity of the virus, but also the possibility of its destruction through the use of a new type of physical impact on the body.

2. THERMAL CONDITION EQUATION AND ITS SOLUTIONS FOR A SYSTEM WITH MEMORY

The traditional idea of the laws of thermodynamics is based on a reasonable assumption about the purely diffusion (incoherent and irreversible) nature of the propagation of thermal excitations. The same representations usually refer to the features of "ordinary" thermal (temperature) waves, the propagation process of which is described by the "standard" heat conduction equations, the derivation and interpretation of which is contained in any textbook on mathematical physics.

The mathematical description of these processes is based on the joint use of two basic equations – the Fourier law for a non-stationary heat flux $\vec{q}(\vec{r},t)$:

$$\rho c_v \frac{\partial T(\vec{r},t)}{\partial t} = div\vec{q}(\vec{r},t). \quad (1).$$

and the continuity equation (in fact, the law of conservation of energy for a local area), which, in the absence of distributed heat sources in the environment with bulk density ρ and heat capacity c_v, has the form:

$$\rho c_v \frac{\partial T(\vec{r},t)}{\partial t} = div\vec{q}(\vec{r},t). \quad (2)$$

From these two equations follows the classical parabolic thermal diffusivity equation for the spatiotemporal change in the temperature field:

$$\rho c_v \frac{\partial T(\vec{r},t)}{\partial t} = div\{\lambda grad[T(\vec{r},t)]\}. \quad (3)$$

The solution of this equation in a homogeneous environment in the one-dimensional case

$$\rho c_v \frac{\partial T(x,t)}{\partial t} = G\frac{\partial^2 T(x,t)}{\partial x^2},\ G=\lambda/\rho c_v \quad (4)$$

corresponds to temperature waves

$$T = Ae^{-kx}e^{i(\omega t-kx)} + Be^{kx}e^{i(\omega t+kx)}, \quad (5)$$

in which the damping coefficient is equal to the wave number. It follows from this result that such waves decay very quickly in space at a distance equal to several wavelengths.

Here $k = \sqrt{\omega/2G}$ is the attenuation coefficient, $G = \lambda/\rho c_v$ is the coefficient of thermal diffusivity.

A more detailed analysis [1-3] shows that such a "standard" way of analyzing non-stationary heat transfer processes in an approximate and implicit way is based on two important assumptions – the principle of locality and the principle of local thermodynamic equilibrium.

The first of these principles makes it possible to pass from the energy conservation equation in the integral form to the energy conservation equation in the differential (local) form. The second principle assumes (without sufficient justification) that the considered spatial non-equilibrium system can be represented as a set of small locally equilibrium subsystems sequentially located in space. In fact, when deriving these equations, it was assumed that with a small size of these subsystems, each of them will always have

an equilibrium distribution of particles corresponding to the same temperature. This is an erroneous assumption, since the process of establishing equilibrium is determined not by the size of the subsystem, but by the probability of elastic scattering and the number of collisions of particles (molecules, atoms) included in this subsystem, which should lead to the establishment of an equilibrium distribution.

If we consider that about 10 collisions should occur to establish such a distribution, then the minimum size of the region of such relaxation should be several times greater than the mean free path of the particle $<l>$. Based on such circumstances, it is obvious that the size of such subsystems cannot be arbitrarily small, and to establish such an equilibrium, a finite (not equal to zero) relaxation time is necessary.

In an explicit form, this circumstance manifests itself in the structure of relation (2), which can be interpreted from the point of view of simultaneous (simultaneous) changes in the thermal energy flux $\vec{q}(\vec{r},t)$ in each subsystem and changes in the locally homogeneous temperature within the same subsystem. It is obvious that the last assumption is valid only for sufficiently slow processes, when the relaxation time of each of these subsystems to the equilibrium state is significantly less than the characteristic time of a particular process that determines the characteristics of the thermal field (in particular, the duration of the thermal front for pulsed or period for periodic heat excitation processes).

In real physical systems, these requirements may not be met under certain conditions, which can lead to a very significant modification of both the initial equations and the conclusions following from them.

In our works [1-6], we first considered the influence of a finite (non-zero) local relaxation time on the nature of the spatial and temporal evolution of a thermal field (more specifically, thermal waves) and predicted the existence of undamped temperature waves. Such waves, under certain conditions, can propagate without dissipation and spatial attenuation in material media with a small but finite time of local temperature relaxation τ (the time of establishment of local thermodynamic equilibrium or, as applied to a gas or plasma, the duration of the "Maxwellization" process).

There are several mechanisms of such "Maxwellization", depending on the state of aggregation of the substance (gas, liquid, solid medium), and its duration significantly depends on the parameters of the system (density, temperature and atomic (molecular) composition).

In air, the duration of the "maxwellization" $\tau \approx 10/n_{air}\langle\sigma(v)v\rangle$ process is determined by the average cross section of elastic scattering, which, at the thermal velocity of movement of simple one- or diatomic gas molecules, is approximately equal to the geometric cross section of molecules $\langle\sigma(v)\rangle \approx 2\cdot10^{-16}$ cm^{-2}, as well as the root-mean-square current velocity $\langle v\rangle \approx \sqrt{kT/m}$ of nitrogen or oxygen molecules and the concentration of these molecules n_{air}.

At normal pressure $n_{air} \approx 3 \cdot 10^{19}$ cm^{-3} and room temperature $T = 300$ K, the relaxation time is $\tau \approx 10^{-8}$ sec. When the temperature changes, and especially the density and composition of the air (for example, in the presence of water vapor), the value can vary over a wide range ($\tau \approx 10^{-7}$-10^{-8} sec).

Accounting for a finite relaxation time and using more logical and more accurate assumptions leads to a much more correct thermal diffusivity equation:

$$\frac{\partial T(\vec{r}, t \pm \tau)}{\partial t} = G\nabla^2 T(\vec{r}, t), \quad (6)$$

which differs significantly from the "standard equation" (3). The solution of this equation in the one-dimensional case corresponds to two counterpropagating waves

$$\begin{aligned} &T(\omega, x, t) = \\ &= A_\omega \exp\left(-k\left|\cos(\omega t/2) - \sin(\omega t/2)\right| x\right) \times \\ &\times \exp\left\{i\left(\omega t - k\left|\cos(\omega t/2) - \sin(\omega t/2)\right| x\right)\right\} + \\ &+ B_\omega \exp\left(k\left|\cos(\omega t/2) - \sin(\omega t/2)\right| x\right) \times \\ &\times \exp\left\{i\left(\omega t + k\left|\cos(\omega t/2) + \sin(\omega t/2)\right| x\right)\right\}, \\ &\mathrm{k} = \sqrt{\omega/2G}, \end{aligned} \quad (7)$$

the parameters of which depend both on the frequency and on the local relaxation time τ.

Obviously, in the limiting case , this solution coincides with the solution of the initial approximate thermal diffusivity equation (4).

The absorption coefficient for thermal waves defined by equation (6) is equal to:

$$\delta = k\left|\cos(\omega t/2) - \sin(\omega t/2)\right|, \; k = \sqrt{\omega/2G}. \quad (8)$$

It follows from this formula, that under this condition

$$\omega_n = (n + 1/2)\pi/\tau, \; n = 0, 1, 2, \ldots \quad (9)$$

such waves have a form:

$$T(\omega_{opt}, x, t) = A_{\omega_{opt}} \exp\{i(\omega_{opt} t - k\sqrt{2}x)\} +$$
$$+ B_{\omega_{opt}} \exp\{i(\omega_{opt} t + k\sqrt{2}x)\},$$

and will propagate in space without attenuation. In air, the minimum frequency of such an undamped wave depends on temperature, humidity, and air pressure and, under normal parameters, is equal to:

$$\omega_0 \approx 75...85 MHz. \quad (10)$$

In our experiments [1–6], we generated such waves due to the formation on the surface of a closed chamber, inside which water cavitation occurred, of very short thermal pulses, the Fourier spectrum of which contains components at allowed frequencies (9). In these experiments, we reliably recorded heat waves with this and higher allowed frequencies at several meters (this distance was limited only by the size of the laboratory). The structure of the recorded thermal wave and the spectrum of these waves are shown in **Fig. 1.**

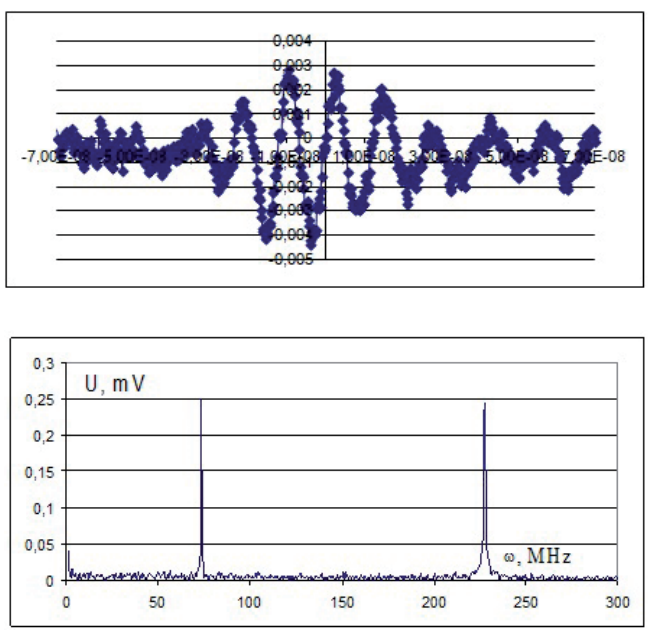

Fig. 1. *Spatial structure and spectrum of undamped thermal waves generated by water cavitation and recorded at a distance of 2 meters.*

For comparison, we point out that the size of the attenuation region of thermal waves of this frequency, if they are considered based on the solution of the "standard" theory (4) with the attenuation coefficient $k = \sqrt{\omega / 2G}$, does not exceed several microns.

3. INFLUENCE OF THERMAL WAVES ON BIOLOGICAL OBJECT

Let us consider the features of the influence of such waves on biological objects.

First of all, let us recall the basis of standard ideas about the role and influence of heat on the vital processes of living organisms.

It is well known that heat and the heat-stimulated biochemical (as well as directly related physiological processes) associated with it form the basis of the kinetics of biochemical reactions that determine most of the features of the vital activity of all micro- and macroorganisms.

The main patterns of direct or indirect effects of temperature on such objects are associated with a very significant effect both on the rate of metabolic processes and on regular (deterministic) and random (non-deterministic) processes for the synthesis of simple and complex organic molecules, such as, for example, the breakdown of proteins into amino acids or DNA replication with the possible random formation of tautomeric compounds that violate the pattern of formation of AT and GC nucleotide pairs.

According to the laws of equilibrium thermodynamics, an increase in temperature leads to a rapid increase in the rate of reactions. Based on the fundamental laws of physics, this effect is associated with the need to overcome the reaction threshold, which is usually due to the presence of a sufficiently high intermolecular or interatomic potential barrier. At the same time, a significant difference between purely chemical and biochemical reactions is that in a living organism, chemical processes occur, as a rule, with the participation of complex enzyme systems that locally lower this threshold, the activity of which, in turn, also depends on temperature.

These features are considered in detail in our works [7,8] as applied to controlled DNA self-repair after a double-strand break of the double helix.

For any biological system, there is an area of optimal temperature, a departure from which (increase) leads either to the death of the organism due to the disintegration of enzymatic reactions, or (if it is lowered) to inhibition of metabolic processes up to a complete stop of these processes. The same ideas fully apply to the cell cycle, which includes a deterministic sequence of events from the formation of a daughter cell in the process of division of the mother cell to its fundamental transformation through stages corresponding to the mode of cell activity with a change in acidity and ATP concentration, to the onset of mitosis and its subsequent division into two daughter cells.

The envelope of some types of viruses, as a rule, consists of fragments of the cytoplasmic membranes of the host cell, but also contains viral transmembrane proteins and glycoproteins. Such shells are called supercapsids, since in addition to the inner protein shell (or, in fact, the capsid) surrounding the DNA or RNA of

the virus, they contain an outer lipoprotein shell. The viral envelope is used to facilitate entry of the virus into the host cell. Glycoproteins on the surface of the envelope serve to identify and bind the virus to a specific cellular receptor on the cell membrane. Later, the viral envelope fuses with the host membrane, allowing the capsid and viral genome to enter and infect the host cell.

Viral particles of the SARS-CoV-2 coronavirus also form supercapsids and carry glycoproteins on the surface of their envelope. These proteins are referred to as S-proteins or S-glycoproteins (Spike-glycoproteins). S-proteins form homotrimers and, thus, form rather large protein complexes, which are called peplomers or spikes. Each S protein consists of two functionally distinct regions: S1 interacts with a receptor on the cell surface, and S2 triggers the fusion of the viral envelope with the cell membrane. Surface proteins are highly glycosylated as a result of the reaction of a non-enzymatic compound of glucose with amino groups of the protein, which helps the virus to hide from the body's defense systems.

Infection is initiated by binding of the virus to ACE2 receptors on the cell surface, followed by fusion of the virus and cell membranes to release the viral genome into the cell. After binding to the membrane, the S protein is post-translationally cleaved, in this case by furin. It is assumed that activation of the fusion after binding to the receptor involves the exposure of the second proteolytic site (S2'), the cleavage of which is necessary for the release of the fusion peptide providing the formation of the endosome, which includes the virus.

Obviously, the success of the subsequent evolution of the virus depends on the properties of the membrane of the cell it attacks, such as its elasticity. In other words, the more difficult it is to deform the membrane during virus penetration, the less likely it is that the virus will be able to infect the cell.

This complex process is influenced by several key factors:

- geometrical parameters of proteins and peptides that realize the fusion (their spatial arrangement determines how these proteins will interact with the membrane);
- acidity of the environment, affecting the structure of proteins;
- the presence of large molecular complexes (rafts) in the volume of the lipid membrane, moving relatively freely along the semi-liquid cell membrane, violating its integrity, and thereby helping the virus to penetrate the cell.

It is important that the role of rafts in penetration has long been proven by the example of the human immunodeficiency virus. In addition to it, a similar mechanism is used by hepatitis viruses, Ebola, influenza, etc.

In this sense, the relevance of the problem under consideration can hardly be overestimated - if we know in detail how the virus merges with the cell, we can find a means to prevent penetration. Of course, the developed model describes the whole process in theory, but it will tell experimenters what to focus on in studies of the interaction of viruses and cells.

For example, when a cell is attacked by a virus, to which it is enough to say: "Open Sesame!", then the lipid envelope of the virus merges with the plasma membrane. In this case, the so-called fusion pore is formed, and viral RNA begins to be realized inside the cell.

Heat is the basis of the kinetics of chemical reactions that make up the vital activity of an organism. Therefore, temperature conditions turn out to be one of the most important environmental factors affecting the intensity of metabolic processes. Temperature is one of the permanent factors; its quantitative expression is characterized by wide geographic, seasonal and daily differences.

Temperature variability entails corresponding changes in the rate of exchange reactions. Since the dynamics of the body temperature of poikilothermic organisms is determined by changes in the temperature of the environment, the intensity of metabolism is also directly dependent on the external temperature. The rate of oxygen consumption, particularly during rapid changes in temperature, follows these changes, increasing as it rises and decreasing as it falls. The same circumstances apply to other physiological functions: heart rate, digestion intensity, etc. In plants, depending on temperature, the rate of water and nutrients intake through the roots changes: an increase in temperature to a certain limit increases the permeability of the protoplast to water. It has been shown that when the temperature drops from 20 to 0°C, the absorption of water by plant roots decreases by 60–70%. As in animals, an increase in temperature causes an increase in respiration in plants.

The most general pattern of the effect of temperature on living organisms is expressed by its effect on the rate of metabolic processes. According to the van't Hoff rule common to all chemical reactions, an increase in temperature leads to a rapid (linear or faster (up to exponential)) increase in the reaction rate. The difference lies in the fact that in a living organism, chemical processes always take place with the participation of complex enzyme systems, the activity of which, in turn, depends on temperature. As a result of enzymatic catalysis, the rate of biochemical reactions increases and its dependence on external temperature changes quantitatively.

The magnitude of the temperature acceleration of chemical reactions is conveniently expressed by the coefficient Q_{10}, which shows how many times the reaction rate increases with an increase in temperature by 10°C:

$$Q_{10} = K_{T+10^0C} / K_T, \quad (11)$$

where K_T is the reaction rate at temperature T.

The coefficient of thermal acceleration Q_{10}, which is equal to 2 for most chemical reactions of an abiotic nature, in the reactions of living systems varies over a wide range even for the same processes occurring in different temperature ranges. This is because the rate of enzymatic reactions is not a linear function of temperature.

So, in tropical plants at temperatures below 10°C, the Q_{10} coefficient is approximately equal to 3, but it decreases significantly with increasing temperature above 25÷30°C. In the Colorado potato beetle, oxygen consumption in the range

of 10÷30°C is characterized by Q_{10} = 2.46, and at a temperature of 20÷30°C Q_{10} = 1.8. The dependence of the metabolism of fish and many other aquatic animals on temperature is expressed in a change in the Q_{10} value from 10.9 to 2.2 in the temperature range from 0 to 30°C.

In the same organism, the magnitude of the thermal acceleration of biochemical reactions is not the same for different processes.

These general patterns are associated with the specifics of temperature processes. The very concept of temperature, based on its classical definition, characterizes the root-mean-square velocity of particles (molecules, atoms, ions) and automatically assumes that this value corresponds to a completely equilibrium state of a particular micro- or macrosystem, consisting of a very large number of particles.

The formation of such an equilibrium state requires a large (relative to the time scale characterizing local interparticle interactions or local quantum processes) time necessary for multiple interactions of the particles of this system with each other. This circumstance was taken into account when creating classical thermodynamics due to the fact that it actually considers only such processes that correspond to slowly changing (compared to the time of this relaxation) thermal fields or waves. Because of this fundamental reason, the equations (1)-(4) of classical thermodynamics are fundamentally unsuitable for describing fast thermal processes, the characteristic change time of which is comparable to or less than the relaxation time. Such processes, in particular, correspond to the process of penetration of the viral capsid with the genome into the cell.

The situation with the action of high-frequency temperature waves is fundamentally different from the standard slowly changing temperature field. This is due to the fact that very fast heating and the same fast cooling periodically occur in the zone of action of such waves. In the heating phase, the particle or molecular complex gains more energy and can very effectively overcome the potential barrier, which subsequently provides a significantly different force field near the surface.

The possible influence of temperature waves on the process of interaction of viral particles with cells can be as follows.

The mechanism of remote identification of a host cell by a virus is realized due to the mechanism of recognition of this cell by glycoproteins located on its surface (a specific mechanism is associated with the remote interaction of these glycoproteins with cell receptors located on the host cell membrane).

The remote recognition process can be disrupted if there is a significant modification of the surface of the virus or the surface of the cell that the virus attacks. This modification of the surface takes place under the successive action of very short thermal field pulses. The fundamental difference between such high-frequency heating, which is combined with the same high-frequency cooling at each period of the temperature wave, does not lead to the destruction or destruction of viruses and cells, but leads to a very significant change in the dispersion characteristics of these objects, which leads to suppression of the remote recognition mechanism.

Therefore, one of the potentially effective methods of blocking the activity of viruses consists in high-frequency periodic heating and cooling of either viruses or cells that may be the target of these viruses. This heating:

- stimulates the passage of molecules and ions dissolved in the liquid until direct contact with the capsid or cell surface and its irreversible shielding, as well as a significant change in their dielectric constant, which leads to the disabling of the remote identification of the host cell by the virus and, accordingly, the mechanism of remote recognition;
- does not adversely affect the environment and the functioning of cells in a living organism.

In this case, we have the phenomenon of deactivation of the remote recognition mechanism by the virus and the phenomenon of cell screening without disturbing the normal functioning of the organism.

High-frequency temperature waves, along with other methods of influence, make it possible to implement such a scenario. The action of such intermittent pulsed heating changes the properties of the liquid for a short time, which leads to a change in the balance of forces near the surface of the virus and potentially leads to a short-term decrease (or even elimination) of the potential barrier. For the surrounding molecules and ions, this is a "window of opportunity" and at these moments there is adhesion to the surface of the capsid and blocking it.

4. CONCLUSION

The considered mechanism qualitatively describes a possible "passive" method of protecting the host organism from the virus, which is associated with a decrease in the efficiency (deactivation) of the long-range remote recognition system in the virus. In other words, in this case, a kind of screening of critical cells occurs due to a change in their surface structure, which leads to a corresponding change in the dispersion and other electromagnetic characteristics of these cells and a kind of deception of the remote recognition system.

There is every reason to believe that under the action of such temperature waves, another ("active") method of protecting the body is also possible, which "reconfigures" the virus recognition system to extraneous (non-critical) cells or other macrocomplexes.

The essence of such an "active" defense is that in the process of changing the dispersion and other electromagnetic characteristics of non-critical cells, they begin to be perceived by the virus recognition system precisely as those objects that need to be attacked. This is a "false" goal method, the result of which is:

- switching the interest of the virus to these false objects;
- the possibility of destroying the virus if the result of the attack of the decoy is the mutual destruction of the decoy and the virus due to apoptosis.

REFERENCES

1. Vasylenko AO, Vysotskii VI, Vassilenko VB. Heat transfer equation with delay for media with thermal memory. *International Journal of Sciences: Basic and Applied Research* (IJSBAR). 2013, 12(1):160-166.
2. Vysotskii VI, Vassilenko VB, Vasylenko AO. Generation and propagation of undamped temperature waves under

pulse action on a target surface. *Journal of Surface Investigation: X-ray, Synchrotron and Neutron Techniques,* 2014, 8(2):367-373.

3. Vysotskii VI, Kornilova AA, Vasylenko AO, Tomak VI. Detection and investigation of undamped temperature waves excitation under water jet cavitation. *Journal of Surface Investigation: X-ray, Synchrotron and Neutron Techniques*, 2016, 8(6):1186-1192.
4. Vysotskii VI, Kornilova AA, Vasilenko AO. Observation and investigation of X-ray and thermal effects at cavitation. *Current Science,* 2015, 108(4):608-613.
5. Vysotskii VI, Kornilova AA, Vasilenko AO, Krit TB. The prediction, observation and study of long-distant undamped thermal waves generated in pulse radiative processes. *Nuclear Instruments and Methods in Physics Research B,* 2017, 402:251-255.
6. Vysotskii VI, Kornilova AA, Vasilenko AO, Krit TB, Vysotskyy MV. On the long-range detection and study of undamped directed temperature waves generated during the interaction between a cavitating water jet and targets. *Journal of Surface Investigation: X-ray, Synchrotron and Neutron Techniques*, 2017, 11(4):749-755.
7. Vysotskii VI, Pinchuk AA. Pecularities of long-range interaction between the nucleotides after DNA demage. *Bioelectrochemistry and bioenergetics,* 1999, 48(2):329-331.
8. Pinchuk AA, Vysotskii VI. Long-range intermolecular interaction between broken DNA fragments. *Physical Review E*, 2001, 63(3):31904-31910.