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Review

The Supramolecular Matrix Concept

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Abstract: It has been established that dilutions of a variety of substances, when exposed to vibration in the process of their preparation, acquire not only new structural characteristics in the form of nano-associates but also new physical properties, regardless of the presence of the initial substance. One of the most important properties of these dilutions is the ability to modify the physico–chemical and biological activity of the initial substance as well as exert non-contact, "distant", effects. Here, we propose a novel hypothesis that the basis of modifying activity is the transformation of target molecules to a more harmonious (symmetrical) state supported by a supramolecular matrix, a structural unit of a structured space.

Keywords: supramolecular matrix; semantically structured space; pseudo-dilutions; released-activity; gradualized pharmacological preparations; ultra-high dilutions; holography; principle of evolutionary feasibility; antibodies

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It is thought that medicine will become a science only when a generally accepted theory of evolution appears, since biological knowledge without considering the "cosmic" role of the organism is insufficient for the development of a comprehensive medical theory.

Today, the molecular paradigm prevails in biology and in medicine—the principle of evidence, which is a necessary measure at this stage of its development. The breakthrough in the discovery of the molecular mechanisms of disease development (pathogenesis) that occurred in the last decades of the 20th century made it possible to quickly develop new drugs. However, without a unified biological and physical theory of pathology, any knowledge about the functioning of the organism is still limited. This implies the need to prove the efficacy and safety of pharmacological agents and methods of treatment.

The development of molecular methods has also affected research on ultra-high dilutions (UHD), which were known to be used as individually selected drugs for patients in alternative medicine. Starting in the 1970s, the results of the first experimental studies of UHD, carried out in accordance with at the time modern requirements, began to be published, indicating the ability of UHD to cause reproducible biological effects at the molecular and molecular–cellular levels [1–6].

Somewhat later, since 1995, our scientific team has been mainly studying the pharmacological and, to a lesser extent, physical–chemical properties of UHDs. Given the fact that we were almost the first to start fundamental research on UHDs, we managed to discover several notable phenomena, which will be discussed later in this article.

The experimental and clinical data obtained by us in accordance with modern requirements confirm that high dilutions possess activity, which drew the attention of both biologists and physicists to their study. To date, we have collected a comprehensive set of data on high dilution research: in collaboration with experts from 20 countries, we have carried out 750 experiments, including fundamental biological and physical studies, as well as more than 80 clinical trials.

After comparing the data obtained during our own research with the literature on the reproducibility of the biological effects of UHDs, we concluded that the effects of UHDs appear in two stages. In the first stage, the organism usually responds to the introduction of

UHD with reactions at the molecular level. If there is individual sensitivity to the substance from which UHD is prepared, the second stage may occur: the transformation of the molecular response to UHDs into systemic individual reactions. Current knowledge in the field of molecular immunology, which studies individual reactions, does not allow us to unambiguously determine their cause, so we assumed that they are based on a special individual-species linkage of the internal space of the organism [7]. This assumption then became the first step towards the development of the supramolecular matrix concept (see below).

In 1996, we discovered a modifying effect (ME) common to all UHDs and consisting of the ability to change the properties of the initial substance (IS) that was used for preparing these dilutions [8]. Over time, it became clear that the mechanisms of ME underlie both the biological and physical effects of UHDs [9]. The discovery of ME helped to simplify and unify the research on UHDs and to develop identity and specific activity tests for UHDs. These techniques are based on the detection of ME common to UHDs using physical–chemical and immunobiological methods (spectrophotometry, high-resolution thermography, ELISA), which allowed an objective assessment of UHD activity:

- Spectrophotometry is used to evaluate the effect of UHDs on the process of ascorbic acid autooxidation, which depends on a variety of physico–chemical factors [10]. Ascorbic acid is extremely sensitive to the environment, and the changes in the solvent structure after the addition of UHDs can alter the rate of its autooxidation [11].
- High-resolution thermography helps to evaluate changes in the structure and properties of water after the addition of UHDs by analyzing changes in the properties of the near-surface layer of an aqueous solution depending on temperature. These changes are characterized by the ratio of the dynamic constants of adsorption and desorption of the substance from the bulk phase to the surface and back [12].
- ELISA—enzyme immunoassay detects the ability of UHDs to modify their target, which leads to a change in the interaction between the target antigen and monoclonal antibodies to this antigen. The resulting antigen–antibody complexes are detected by enzyme-labeled secondary antibodies [13].

The ME is well reproduced in both biological and physico–chemical models. Its study, especially using spectroscopic methods, is a fairly routine procedure that has led to a number of publications [14–16].

We suggest that the appearance of these results largely marks the end of the phenomenological stage of UHD research, i.e., the period of gathering primary data that provide evidence of UHD activity, which began almost 50 years ago. In the future, we expect an increase in the number of studies on the influence of physical factors on the properties of UHDs. Probably, applied studies will be extended, which are focused on the development of new analytical techniques based on ME and the introduction of UHDs into technology. The possibility of improving the properties due to ME has already been shown for various materials: superconductors [17], piezo-electrics [18], petroleum products, and cement [19].

The first steps are being taken to develop a theoretical basis for UHD activity [20–27]. We believe that this article will also contribute to the systematization of views on the issue of high dilutions.

We deliberately tried to limit as much as possible the use of specific pharmacological terms in the article so that the general concept would be accessible to a wide range of readers.

The most important result, the "key" to understanding the nature of UHDs, is the fact that they acquire modifying activity during preparation, and the main technological condition without which it is impossible to obtain active UHDs is an external rhythmic mechanical effect exerted at each stage of their preparation [28–30].

Figure 1 shows a flow chart of the widely known technology of serial dilution of an IS—potentization.

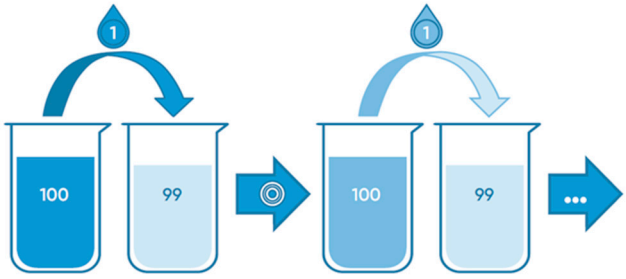


Figure 1. Flow chart of potentization using the example of one of the ways to prepare a 100-fold dilution. The first 100th dilution (C1) is prepared from 1 part of an initial substance (matrix tincture) and 99 parts of solvent. The resulting mixture is subjected to external influence (shaking). The second centesimal dilution (C2) is prepared from 1 part of the first centesimal dilution (C1) and 99 parts of solvent. The resulting mixture is subjected to external influence (shaking). Subsequent dilutions are prepared similarly (based on the European Pharmacopoeia monograph 2371 [31]).

For a long time, the idea of potentization as a process of serial dilution of an IS masked the fact that the technology of preparing dilutions is actually directed not at the IS (a decrease in the IS concentration) but at the solvent, i.e., purified water or water–alcohol solution. In fact, the potentization consists of two similar procedures: first, the vibration effect is exerted by an IS on an intact solvent, which turns the solvent into a processed solvent, and then the vibration effect on the intact solvent is exerted by the processed solvent. New properties appear in the processed solvent, probably due to the formation of a specific, long-lasting hierarchy of nano-dimensions, including homochiral structures that constantly change the symmetry.

It is known that certain structural changes can occur in water after exposure to both mechanical [29,32–35] and electromagnetic [36–38] vibration effects. Since the vibration effect during the preparation of high dilutions is mediated by the IS, specific structural rearrangements are eventually accumulated in the solvent. The specificity is manifested in the fact that processed solvent is able to exert an effect only on the IS, which is modifying by its nature. The processed solvent does not exert ME on all other substances except the IS.

Below, we will present our view on the mechanisms of potentization. Known but poorly studied phenomena may underlie potentization. For example, potentization can lead to a symmetric-asymmetric transition between molecular clusters. Ultimately, this leads to the emergence of strong van der Waals forces (Casimir effect) between new molecular clusters (see an example of this effect in [39]).

In our early publications, in order to focus on the technological aspect of the acquisition of new properties by UHDs, we used the term “released-activity”, i.e., the activity released during the technological processing of an IS [7]. However, due to the development of analytical methods for UHD analysis, we have started to also use terms, let us say, “more pharmacopeial”, that emphasize the multi-stage process of preparation of UHDs: “gradual” technology and “gradualized” preparations (GrP). We were able to validate the technology of serial dilution combined with controlled external rhythmic influence, which resulted in the development of a standard for the preparation of UHDs: a general pharmacopoeia monograph for a new class of biological preparations obtained using gradual technology (GPM 1.7.0001, Russian Federation). Thus, the term “gradual” technology has become official. Therefore, we propose to use both terms: “released-active” preparations and “gradualized” preparations (GrPs).

After the discovery of ME, which does not depend on whether IS molecules are contained in GrP or not [40], it has become obvious that the term “ultra-high dilutions” does not reflect the nature of GrP. However, this term is common, and to preserve historical continuity, we propose a modified version of this term: “pseudo-dilutions” (PDs).

The term “high dilutions” a priori implies that the dilutions go beyond the Avogadro number and, by definition, cannot exhibit any activity. We have completed several stages of GrP research, which allowed us to overcome this notion.

The most important step in the study of PDs, as we mentioned above, was the discovery that released-active preparations can exert ME on the IS. This discovery was preceded by a literature review: we found that PDs of a substance can be used to reduce toxic effects caused by toxic doses of this substance [41]. In this regard, the assumption was made that PDs may have a direct influence on the IS. We carried out a series of experiments where an IS and its "low dose" (PD) were administered to laboratory animals simultaneously [42]. In most cases, PDs of low-molecular-weight compounds, well-known pharmacological products, enhanced the pharmacological activity of the drugs and reduced their toxicity (Table 1). Additionally, clinical trials of ethanol PD and morphine PD were conducted and showed that these preparations could indeed be used for detoxification [43,44].

Table 1. Examples of modification of pharmacological effects.

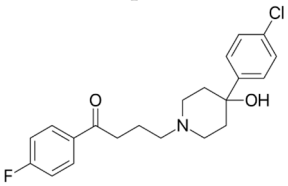
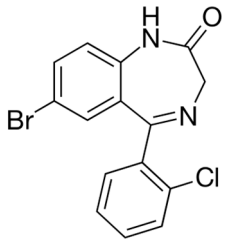
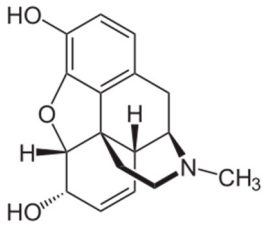
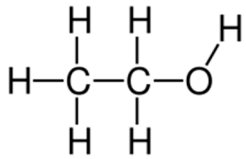
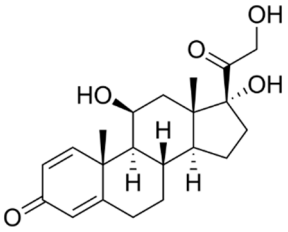
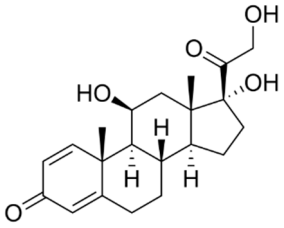
Agent	Parameter Assessed	Effect of Co-Administration of an Agent with Its Pseudo-Dilution
Haloperidol 	Behavioral reactions and electrical characteristics of command neurons of the grape snail defensive behavior	Decreased locomotion rate of an animal; depolarization shift of the membrane potential of command neurons [45]
Phenazepam 	Behavioral activity of rats in the open field test	Stimulatory effect manifested in increased horizontal and vertical activity [46]
Morphine 	The number of self-stimulation reactions of the lateral hypothalamus in the morphine withdrawal syndrome in rats	Relief of the morphine withdrawal syndrome manifested in the decrease in the number of self-stimulation reactions of the lateral hypothalamus to baseline values, i.e., prior to morphinization [47]
Ethanol 	The content of biogenic monoamines and ethanol metabolism in rat tissues subjected to alcoholization	Multidirectional changes in the level of biogenic monoamines in the brain and in the whole blood, increased alcohol dehydrogenase activity, and delayed elimination of ethanol from the blood [48]

Table 1. *Cont.*

Agent	Parameter Assessed	Effect of Co-Administration of an Agent with Its Pseudo-Dilution
Prednisolone 	Development indicators of arthritis induced by Freund's adjuvant in rats	Anti-inflammatory effect manifested in reduced growth of the inflamed paw edema, reduced number of stomach ulcers and number of animals with ulcers [49]
Cyclophosphamide 	Characteristics of tumor growth in the Lewis lung carcinoma model in mice	Decreased incidence of metastasis [50]

Next, we found that ME was not a feature unique to the organism and could indeed be reproduced using relatively simple models, for example, hydrolysis [51] or inversion voltammetry [52].

These results clearly indicate that ME cannot be determined by the residual content of the IS molecules in dilutions. Adding a few IS molecules, which may be contained in PDs, to the "standard" dose of an IS should not notably change its properties and, moreover, reduce its toxicity. This was also confirmed by the fact that ME was exhibited by dilutions of up to 10^{-24}, theoretically containing a notable number of the IS molecules, as well as by higher dilutions [40,45]. Some scientists who studied PDs [53–55] offered reconciling explanations of the PD phenomenon: the retention of IS molecules in the wall zone, the flotation effect on microbubbles, etc. However, these hypotheses did not shed any light on the mechanisms of ME of PDs, which ultimately must be explained at the level of supramolecular chemistry/physics. As the presence of ME does not depend on the concentration of IS in released-active dilutions, the traditional division into high and ultra-high dilutions has no practical meaning.

Subsequently, we rather accidentally came up with the idea of using PDs of antibodies when we investigated the mechanisms of ME in the context of neurobiological phenomena using antiserum to the brain-specific S100 calcium-binding protein B (S100B) [56]. PDs of antiserum to this protein were found to modify the effect of the native antiserum. Then, the assumption was made and further confirmed that released-active dilutions of any antibody can exert ME not only on the IS, but also on the respective antigen [57]. Interactions of antibodies and antigen in usual doses are highly specific (selective) and therefore are an adequate model for ME studies.

Later, we mainly focused on the study and practical implementation of PDs of antibodies in medicine [58,59] with more than 15 drug products licensed to date [60].

To study the mechanisms of ME, as a main model we chose the effect of PDs of antibodies to interferon-gamma (IFN-γ) on its antigen, IFN-γ. PDs of antibodies to IFN-γ are by far the most studied GrP [40,61–67]. Using this preparation, we discovered that ME is based on conformational changes in the target molecule, in this case, its antigen, IFN-γ [68], and influences the antigen's hydration shell [69]. As a result, the interaction of IFN-γ present in the organism (endogenous) with its target (IFN-γ receptor) is activated, which initiates sequential molecular events that are proposed to result in the therapeutic effect of this drug product [68]. Studies of PDs of antibodies to IFN-γ in clinical trials have

also repeatedly proven that the magnitude of the molecular effects caused by GrP (the first stage of the organism's response to PDs) is quite sufficient to provide a therapeutic effect.

The two-stage effect of PDs with induction of the individual reactions of the organism on PD administration was also obscured by the fact that the individual response to released-active dilution, unlike the response to the usual dose of a substance, is specific. For example, a patient with a high innate sensitivity to arsenic responds to the administration of arsenic PD as if poisoned with toxic doses of arsenic [70] (a "pseudo-intoxication" reaction, which in a reduced, safe form reproduces the symptoms of poisoning with toxic doses and is the goal of individual selection of treatment options). As mentioned above, current knowledge allows us to attribute the mechanisms for the development of the second stage of response to PD to immunology, since it is immunology that considers individual reactions, such as Quincke's edema, anaphylaxis, and allergic reactions. Individual reactions are based on hypersensitivity mechanisms described in experimental immunology, but their mechanisms of initiation are currently unknown. A common feature of individual reactions in immunology is that they are typical (proceeding similarly). A range of pharmacological drugs can induce Quincke's edema of the same type in terms of clinical manifestations [71]. Quincke's edema or anaphylaxis can be attributed to paradoxical reactions of the organism because they can lead to fatal outcomes. Since non-random, non-genetically determined reactions are possible in the organism, these individual reactions can be assumed to benefit the whole population, and not an individual, i.e., they are evolutionarily feasible. Paradoxical reactions can, for example, also include such a phenomenon as apoptosis (programmed cell death). We will return to paradoxical reactions later in this article when considering the concept of uniformity.

In medicine, all substances are divided mainly into endogenous and exogenous classes, i.e., contained or not contained in the organism. It is known that most elements of Mendeleev's periodic table are present in the body in micro-doses, which can be targets for the action of the PD of these elements. At the same time, there are no targets in the body for drugs of plant origin.

For our research, it is extremely important that individual sensitivity to any exogenous substance is determined by a complex set of linked phenotypic traits (markers). One individual trait is not pathognomonic (not indicating the presence of sensitivity to a particular drug) and may be present in different patients, sensitive to different ISs. Various traits can act as phenotypic markers: morphological, behavioral, psychological, and modal (reaction to various environmental factors). Only in the presence of markers of individual sensitivity to a certain substance does the body respond with an individual reaction of "pseudo-intoxication" to PD. In fact, an indicator of individual sensitivity to any substance is the individual hierarchy of phenotypic markers that the physician identifies for each patient.

At the same time, let us once again draw attention to the fact that the organism does not have specific, pre-existing target molecules for such drugs. There is no doubt that the linkage of completely different phenotypic traits with sensitivity to an exogenous substance absent in the body is evolutionarily determined.

We used the phenomenon of association of phenotypic traits for the development of the concept of a semantic molecular ensemble, which is a target for highly diluted exogenous substances in the organism. Any molecule of the organism, like letters combined into words, can be involved in many semantic molecular assemblies. The "force" that links the body molecules into semantic molecular ensembles is represented by the intermolecular bonds within a separate, long-living spatial molecular formation, the structure of which coincides with the structure of a substance absent in the body.

Intermolecular interactions in the organism, between regulatory protein molecules, are non-covalent. Therefore, we have chosen supramolecular chemistry as a prototype that is closest to the issue. From the standpoint of supramolecular chemistry, proteins (in their secondary and tertiary folding) are supramolecular structures [72]. Proteins regulate many functions in the organism realized by structurally simpler low-molecular-weight compounds and ions and, in fact, link them into functional supramolecular ensembles. By

analogy, we have assumed that semantic assemblies can also be attributed to supramolecular formations generated by supramolecular matrices, which are not biological, but physical and objectively existing in reality.

Certainly, the supramolecular matrix concept developed when analyzing the biological effects of PDs is a challenge to theoretical physics. This idea is rather isolated from cosmological concepts, and at the current stage, it does not take into account the scale and stages of development of the universe to which it can be extended. Let us note that the universe itself can be considered a linked ensemble of galaxies.

Continuing to analyze the PD features, we increased the complexity of the model. First, the arrangement of semantic molecular assemblies, which are structural and functional elements of the organism, is close to the concept of "holography". Since the same supramolecular target in all cases determines both a primary molecular response to PDs common to all representatives of the species and a secondary individual systemic response, we assumed that the supramolecular ensemble has a species–individual and therefore complex linked spatial structure, which may be considered holographic. Figuratively speaking, two straight lines pass through any two points in the body: one is common to all representatives of this species and the other is individual. By the complex linked system, we mean a system where each element interacts with all other elements at each moment of time, which makes the system perfectly symmetrical in terms of geometry and open to interaction with other conditionally holographic structures (Figure 2).

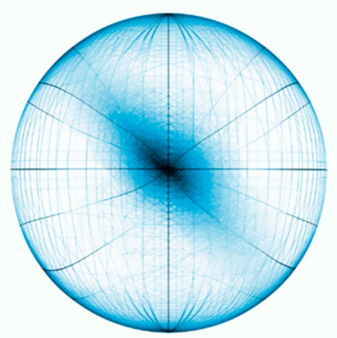


Figure 2. Ideally symmetrical holographic sphere.

Second, GrPs themselves are conditionally holographic structures. The transformation of an IS into a conditionally holographic formation occurs during its technological processing, and the main condition of this process is, again, a repeated rhythmic influence exerted on the solvent. A seemingly simple vibration processing of the solvent is a combination of serial dilution of the IS and sequential intermittent external effects occurring simultaneously, which is a unique event. The probability that these two factors familiar to us can be combined in living nature is too small. Both factors are modally identical in relation to intermittence. Perhaps this identity is the reason for the multiparametric addition of macroscopic fluctuations of PDs induced by external rhythmic effects into a complex linked state, which we conditionally call holographic. A similar phenomenon called tidal bore can occur in nature: a tidal sea wave entering a narrow river mouth in the delta sometimes transforms into a standing wave that propagates upstream.

From a thermodynamic point of view, we can assume that external rhythmic influences transform the system from one nonequilibrium stable state to another, more harmonious holographic state.

From the idea that a semantic molecular assembly with a holographic structure is an element of the body in terms of structure and function, it follows that the organism itself has a holographic structure. The holographic arrangement of biological systems is formed by the DNA of fused female and male gametes, the zygote (or its analogs in the simplest organisms). A special double helix structure of DNA provides two processes simultaneously: the capability of replication (duplication) and the transition of the zygote

into a holographic state. The "screw"-like arrangement of DNA creates conditions for interrupting DNA self-oscillations and their subsequent interference in the holographic structure. As a result, on the one hand, all events in the body are spatially interconnected and subordinated to a single, i.e., central, regulation, and on the other, the body is open to direct communication with a holographically organized space.

We have earlier hypothesized that evolution is based on the philosophical principle of unity and the struggle of opposites: at least two opposites with different space-time algorithms are fighting for the right to occupy space [73]. As a result, evolution comes down to increasing the complexity of space.

An attempt to bring a unifying principle of the universe into its every possible locus leads to the fact that space, in parallel with the increase in complexity, is subjected to structuring (curvature) —fractalization. In each fractal (locus), both the geometric characteristics of the given locus itself and the general geometric characteristics of a "correct" symmetrical, homogeneous space corresponding to a single algorithm of the world order are linked, which together constitute the semantic content of each locus (Figure 3).

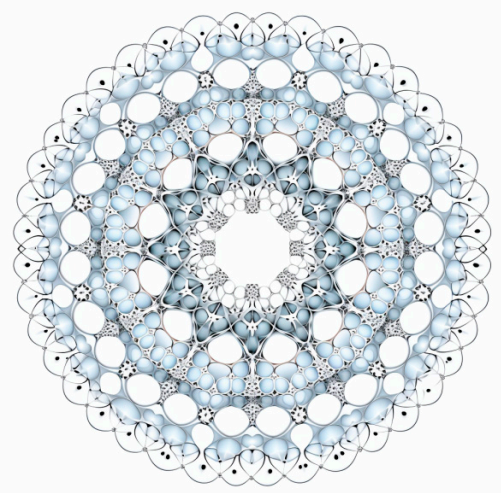


Figure 3. An artistic representation of a fractal.

As we understand it, the supramolecular matrix is a unique curvature of space that, according to its geometric characteristics, sets a certain level of complexity. Therefore, all structural and functional processes occurring at this level of complexity, both inside and outside the body, have a single spatio–temporal linkage, which ensures their homogeneity. Together, all dually organized fractals form a semantically structured space. Within each locus, the "common" (uniform geometric characteristics of the entire space) are protected by the "unique" (geometric characteristics of a single locus).

Within a fractal, it is easier to control whether the uniformity is maintained. Postulating the fragmentation (anisotropy) of space to retain its original geometric integrity, we come into conflict with the generally accepted use of the term "uniformity" in physics, implying the identity of the properties of space at all its points. Perhaps it is more correct to speak not about uniformity but about coessentiality.

Within a locus, space may have different types of organizational complexity, but its level is always the same. Each molecule is just one of the linkage options within the framework of its "coding" locus. If, in physical terms, loci (fragments) of space can be considered fractals, then in biological terms they represent phenotypic traits of the organism.

Our studies demonstrated that PD can be produced not only from an IS, but also from an electromagnetic signal, and ME of PD can be directed not only at the IS, but also at the "function"—the electrophysiological activity of the brain. Using a device for processing and transforming potentials, we passed an electromagnetic signal modulated by an ideal human electroencephalogram through the liquid and then obtained a released-active drug

that modulated the EEG of experimental animals [74]. This experiment demonstrates that not only molecules but also "functions" have patterns in the semantically structured space.

At some stage of the evolutionary "exploration" of space, there was a transition (hypostasis) of the linkage of space into molecules. An indirect confirmation of this assumption is given by some regularities at the "molarity threshold". A centesimal scale is commonly used for potentization: each previous dilution is diluted 100 times by volume. As a result, dilutions from 9 to 12 are at the "molarity threshold": based on various calculations, they should not contain any IS molecules. Some qualitative changes were found to occur in PDs beyond this "molarity threshold" (Figure 4). Thus, the formation of nano-associates in solution of GrP of antibodies to IFN-γ occurs only after the 11th centesimal dilution [61]; gold nanoparticles in the near-surface layers pass into a new stationary state at a similar stage of dilution [54].

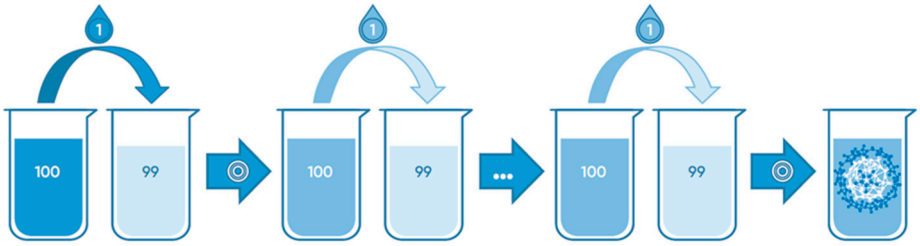


Figure 4. Nano-associate formation during preparation of dilutions.

For the sake of controlling complexity in the process of the evolution of the universe, not only the process of separation of complexity into its individual elements—fractals, but also its "rupture"—distribution into ranges (orbits) of complexity could occur, which required an additional control apparatus in the form of a single integrative matrix capable of "correctly" combining all fractals of certain ranges (orbits) of complexity. Thus, common (species-specific) for the whole range of complexity super-matrices such as DNA (or RNA for simply organized species) could appear, i.e., the evolution (fragmentation) of space in order to control complexity has reached the biological level. Supramolecular matrices of biological systems have a dual species–individual organization, which explains the possibility of individual reactions to PDs. Spatial matrices of a certain range combine general (species) and individual architectonics into a single whole. The DNA molecule of each individual has a level of spatial complexity corresponding to the level of complexity range of the species and, simultaneously, a unique individual organization (Figure 5). As a result, DNA is able to merge the loci of a structured space into a unique phenotype of an individual. Meanwhile, phenotypic traits simultaneously belong to an infinitely large number of biological systems.

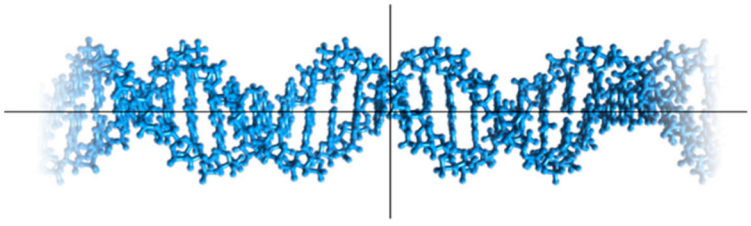


Figure 5. Double symmetry of DNA molecule. Visualization performed using the Opensource package Avogadro.

The unique individual organization of the zygote DNA molecule is sufficient to determine the space–time orientation of morphogenesis in the process of individual (ontogenetic) development of an organism (morphological integration into the space–time continuum). In ontogeny, communication of DNA with a structured space promotes an attachment to a certain set of loci (phenotypic traits), and all of them are linked in accordance with

the individual DNA structure of a particular organism into its unique phenotype. Since phenotypic traits are distributed across ranges (orbits) of complexity, a certain number of phenotypic traits "belong" to each species of living organisms. The higher the level of organization of a species, the greater the hierarchy of its phenotypic traits.

It is possible that, in the process of evolutionary increase in space complexity, together with the component loci, the phenotype of a certain species is linked to DNA of other fractals of a certain range that are not phenotypic traits. As a result of joint "materialization", phenotypes and loci of the same level of complexity after "hypostatization" constitute its ecological niche. Biological and "geological" "materialization" occur in parallel, which is close to Vernadsky's ideas about the simultaneous appearance of the bio-geosphere [75]. In addition, along with the species, its "communications" probably materialize, including language and language-related thinking as well as algorithms of interpersonal relationships. These were reflected in a number of humanitarian concepts (Naom Chomsky's generative grammar [76], the Sephir–Worth hypothesis [77], and Jung's collective unconscious [78]).

At all stages of ontogeny, DNA, according to its own structural and spatial uniqueness, encodes the synthesis of proteins or polypeptides, which also have an individual spatial arrangement corresponding to this organism and control almost all processes in the body. Thus, DNA encodes not phenotypic traits but individually organized controllers of traits. It is noteworthy that polypeptide controllers have a more complex spatial structure than their polynucleotide matrix.

Each organism has an individual hierarchy of phenotypic traits that must "fit" into the general hierarchical relationships of a semantically structured space. Perhaps by linking phenotypic traits stochastically, DNA prevents their accidental "foreign" linkage and retains the spatial harmony (symmetry) of the evolutionary process, and this spatial association is the evolutionary role of biological systems. Therefore, we consider pathological processes in the body to be evolutionarily determined. Their goal is to maintain the uniformity of the internal space of the organism. Such paradoxical phenomena as death from anaphylaxis or Quincke's edema, no matter how unfavorable they may be for an individual, are evolutionary feasible. The organism is prohibited from responding to "foreign" influences that can disrupt the uniformity of its spatial organization and potentially lead to "foreign" linkage of phenotypic traits. The same reason underlies the mechanism of the individual response to PDs. If the structure of the molecules of a substance from which PD is prepared coincides with the individual structure of the body, the latter cannot evaluate the holographic "image" of the influencing factor in terms of uniformity and has to scale it for the subsequent analysis.

As mentioned above, individual reactions in the body are the prerogative of the immune system, which regulates uniformity at the level of the whole organism using complex mechanisms of molecular recognition. For the first time, the idea that the immune system is responsible for the genetic integrity of the body was expressed by M. Burnet [79]. This process is so important for the body that mutations are allowed in the genetic apparatus of the immune system cells for its sake, and the principle of "one gene–one protein" is violated: the molecules responsible for the recognition of "foreign" or "non-self", i.e., antibodies and T-cell receptors, consist of several polypeptide chains, which allows them to take any spatial conformation and function in 3D mode. We consider it possible to contrast the term "uniformity" with the term "foreignness" accepted in immunology, a concept applied in immunology to an antigen, usually a protein or part of it. If the antigen is foreign, then it is so different from the body in species or individual terms that it poses a threat to the genetic integrity of the organism and, as a result, causes a protective immune response. It is noteworthy that the immune response is initiated not simply by the structure of the molecule (antigen), but by its extreme deviations from certain norms of uniformity, i.e., how much "self" differs from "non-self" [80]. The concept of foreignness in medicine is subject-related, implying a separation of one organism from another based on the self/non-self principle. To explain the effects of PDs, we have expanded the use of the term "foreignness" to "foreign" on a single space–time continuum.

With cybernetics riding a wave of popularity in physiology, systematic approaches were developed to explain the principles of the body's vital activity. On the example of motor activity [81] and behavior [82,83], it was shown that the functioning of biosystems at every moment of time is subject to a certain single "beneficial" result of activity, and the desire to achieve it leads to a constantly changing pairing of various performance indicators. We believe that, from the point of view of the principle of evolutionary feasibility, the "beneficial" result of the activity of any system, both biological and physical, is to maintain homogeneity while increasing the complexity of the functioning system.

The thermodynamic approach is also often used to analyze systemic phenomena in medicine [84]. In our opinion, the self-organization of dissipative systems in the form of irreversible transitions to a new level of complexity may also be based on the tendency of systems towards uniformity.

The self-organization of released-active dilutions was studied in a series of experiments carried out by the A.I. Konovalov group [85–87] and other researchers, who have shown that PDs differed in a number of characteristics depending on the level of dilution: pH [61,88,89], surface tension [61,90], electrical conductivity [61,88–92], electrical resistance [91,93], concentration of dissolved gases [88,94,95], content of ROS and free radicals [32,88], etc.

Apparently, differences in the connection (self-organization) of various physical–chemical criteria of GrPs determine the polymodal dependence of the extent of the effects of released-active preparations on the level of nominal dilution, as shown by E. Burlakova and other authors [6,96,97].

The capability of self-organization of PDs has also been demonstrated in a well-known article by L. Montagnier [98], which is difficult for us to comment on because of its technical complexity.

Data are accumulating, indicating that the self-organization of released-active preparations depends on the characteristics of the vibration impact used in their preparation [33,55,99].

We assume that the dependence of PD activity on the extent of technological processing and, in fact, on the modes of vibration effect is determined by the properties of semantically structured space. Perhaps one of the mechanisms underlying the retention of uniformity is the self-oscillation (wave) process inherent in the semantically structured space. The constant deviations of its elements, fractals, from a certain ideal (symmetrical) state allow determination of the risks of the appearance of "foreignness" by the degree of deviation and restoring the ideally symmetrical state of supramolecular matrices by negative feedback (Figure 6).

Figure 6. An example of feedback in biology—neurofeedback.

Therefore, the polymodal (sinusoidal) dependence on the degree of dilution shown for the PD effects is determined by the resonant interactions of PD with the dynamic deviations of its supramolecular matrix from the equilibrium state. The effect of PD of an IS on the same IS and its hydrate shell is also a process of restoring the ideal symmetry of the IS structure.

The relationship between such parameters as symmetry and conformation with functional activity is not in doubt, but it should be noted that symmetrical structures are characterized by greater stability [100], i.e., lower mobility, and, therefore, symmetry break-

ing can serve as the trigger that will lead to a change in hydration shells as a result of ME [69] (Figure 7).

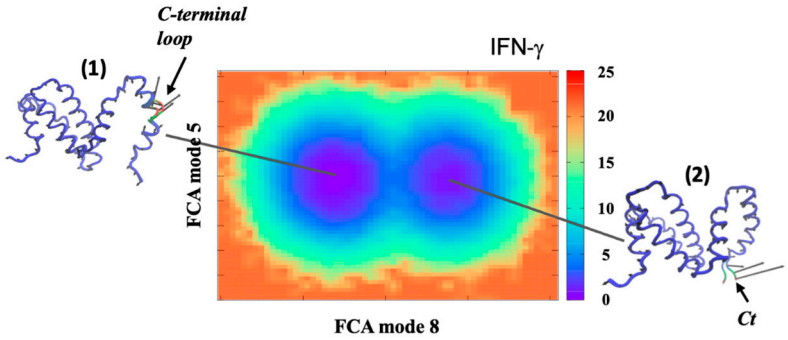


Figure 7. Free energy surface derived from the full correlation analyses of the molecular dynamics trajectory of IFN-γ in a mixed water–ethanol solvent. The representation of each conformation ((1)—"conformation 1" and (2)—"conformation 2") illustrates the dominant motion within the minimum of the energy surfaces, where regions colored in red show greater mobility and regions colored in blue have less mobility [69].

Since PDs are dispersed-spatial structures that do not have a discrete carrier of activity, they do not have the fairly strict dependence of the effect on the dose, which is characteristic of conventional pharmacological preparations.

At any level of conditional dilution and, consequently, association of criteria of PDs, their effect is adaptive [73]. For example, PDs of antibodies to erythropoietin increase the reduced level of erythropoietin and reduce the increased level [101]. This fact indirectly emphasizes that PDs have an ideal structure and activate the transition of the target molecule to an ideal symmetrical state.

In some dilutions, association of the criteria common to PDs does not occur [61,91], which can be explained by a prohibition on self-organization due to the threat of losing the uniformity of supramolecular matrix in this vibration-wave range.

A unique property of GrPs underlying both the biological and physical activity of released-active drugs is the ability to transfer the linkage of their constituent elements to a neutral medium, which changes its structure and turns into a carrier of PD activity. For instance, we found that exposure to released-active antibodies to IFN-γ (without an additional vibration treatment) changes the structure of any neutral carrier, i.e., water/water–alcohol mixture [61,62], lactose [67,102–104] and its aqueous solution [104–106], as well as triglycine sulfate, a crystalline ferroelectric [107]. If we define information as a combination of features characterizing a material object or process, then the interactions of released-active drugs with a neutral medium can be considered informational.

It is known that released-active preparations can be obtained without the dilution process as such, for example, as a result of serial trituration of an IS in lactose [4,108,109]. Therefore, the idea that GrPs can be prepared only with the use of a solvent in which nano-associates appear is not entirely correct. Traditionally, much attention is paid to nano-associates as a factor that determines the activity of PD [55,90,110–112].

In our opinion, nano-associates formed during the preparation of PDs and traditionally considered the cause of their effects [85] are a consequence of the technologically driven activity of GrPs and are short-lived, but linked by the structure of IS molecules (absent in dilutions), dynamic, renewed associations of molecules of a liquid or solid phase. In this regard, the relaxation time of certain nano-dimensions that appear in dilutions during technological processing is not important [113], since the hierarchy of spatial linkage of nano-associates is preserved for a long time.

We can assume that a key role in the formation of nano-associates in the liquid phase is played by the hydration shell of IS molecules, which has been shown to play a role in the development of ME [69].

For solid carriers of released-activity, nano-associates are obviously combined into the least connected dynamic elements, most likely at the electron level.

To provide a specific (corresponding to the structure of the IS molecule) linkage of transition to a conditionally holographic state, the solvent requires an external rhythmic effect, but the long-term retention of conditionally holographic linkage is maintained by the supramolecular matrix of the IS, which is a natural property of the semantically organized space.

The conditionally holographic structure of PDs can probably explain the ability of PDs to exhibit a limited distant effect (i.e., without direct contact with their target at a distance of up to several centimeters), recently discovered using released-active antibodies to IFN-γ as an example [62,114–117].

An important detail is that, using released-active antibodies to IFN-γ and PD of sodium sulfate, we have previously discovered that released-active dilutions produced from high-molecular-weight substances had a more pronounced ability to exhibit the distant effect [14,62,114–116]. The main regulators of functions in the organism are proteins capable of intermolecular interactions [118].

The ability of GrP to cause a distant effect allows us to assume that the conditionally holographic structural organization of GrP goes beyond the solvent, and released-active preparations can be considered as a spatially isolated material object—a conditionally holographic "sphere" that is associated with the solvent, has limited dimensions, and, possibly, will be characterized by certain physical quantities in the future.

Since the activity of PDs is determined by the technology of their preparation, we investigated various physical factors that could potentially affect the process of PD preparation and came to the conclusion that the vibrational effect is the key technological condition.

Due to the complexity and extent of the required experimental studies, we have not yet had the opportunity to study in detail all the factors that can affect the technological process of gradualization as well as the properties of GrPs, such as the dependence of non-contact interactions on distance and electromagnetic field, solvent polarity, temperature, and for how long the modifying activity is retained. We plan to continue this research in the future.

To date, there are conflicting data on the role of electromagnetic fields (EMF) in the appearance of GrPs' activity in the course of their preparation. According to some data, EMF does not affect the process of PD preparation in the first days when water samples are incubated under hypo-magnetic conditions, but it manifests itself later [93]; according to other studies, ME is not formed under hypo-magnetic conditions, or it is weakly expressed [61,98,99]. It is known that EMF is not fundamentally different from mechanical vibration in its ability to influence the formation and maintenance of GrP activity [93,99]. This circumstance indirectly indicates that EMF is not a predominant factor in the mechanisms of PD activity acquisition. But on the other hand, it is also known that PDs possess increased sensitivity to external electromagnetic effects [99,114,115].

There is some evidence that released-active dilutions can be prepared only using polar solvents [119–121].

According to empirical data, PDs can retain their activity for a long time: it is retained better in water–alcohol solutions than in aqueous solutions. The activity is retained for the longest time in solid dosage forms (powders and tablets). Additional vibration treatment can restore activity in them [28].

PDs retain the ability to be used for ME even at temperatures up to 700 °C [18], but liquid forms of PDs lose their activity upon freezing (according to empirical data).

The dependence of PDs' distant effect on the distance to the "target" is still poorly understood.

In the course of the research, it was found that with "delicate" (without external rhythmic influence) preparation of PDs, they do not have activity [99,115].

Not only mechanical shaking [88,92] but also microfluidic technology, a modern unified version of rhythmic mechanical action, can be used as vibration treatments [122].

It should be noted that, according to theoretical calculations, during a horizontal rotation on the vortex, used by us instead of vertical mechanical shaking during the most recent experiments, the solution is heated only by hundredths of a degree (0.06 °C). Therefore, the amount of energy released during such heating will definitely be insufficient to initiate qualitative and quantitative changes in the physico–chemical properties of the prepared solution. Thus, the changes that occur in the solution during technological processing in combination with external rhythmic influence are caused by the very fact of rhythmic influence, and not by its energy contribution.

It is also known that singlet oxygen is formed under high-intensity exposure to an IR laser [123]. Recently, a publication appeared stating that rhythmic shaking, the energy of which is not comparable to the energy of an IR laser, is sufficient to generate singlet oxygen in water [88]. This paradoxical result should be deeply comprehended, but we can first assume that the transition to a stable nonequilibrium state in a conditionally holographic system, unlike thermodynamic systems, does not encounter "resistance" and does not require additional energy. Let us also pay attention to the following detail: at each stage within the framework of the potentiation process, intermediate dilutions require vibration treatment. However, when PDs are transferred to a new environment, they can have a modifying action without shaking.

When preparing PDs, we studied both horizontal and vertical mechanical shaking of test vials, and we obtained active PDs in both cases. However, our preliminary results indicate that the activity of PDs may decrease moderately if the symmetry of technological procedures is violated during their preparation. For example, with horizontal preincubation of test tubes and their horizontal rotation on the "vortex", the activity remains at the usual level, but it decreases with a combination of horizontal preincubation and vertical mechanical shaking. The role of the symmetry factor was also noted by other authors [113,124].

The amplitude and frequency of vibration are important in the preparation of PDs [33].

Recently, it was found that PDs of antibodies have their own emission in the IR and GHz parts of the radio range [14,62,117,125]. Emission has also been detected in undiluted antibodies [125] and concentrated solutions of salts [126]. Therefore, at this stage, the available data are insufficient to draw a conclusion on the role of emission in the mechanisms of action of released-active preparations. A more fundamental point is that the nature of emission and its intensity also depend on vibration. In addition, it has been shown that the shaking process, under conditions of a magnetic field comparable to the geomagnetic background, also leads to a decrease in the emission of samples in the IR range [115].

We did not set out to determine the minimum number of shakes during the preparation of GrP, but experimentally determined that 10 shakes or 10 s of horizontal rotation are enough for PDs to be active. Such a minimum set of necessary conditions indirectly indicates that ME may be a manifestation of a property not of dilutions of IS, but of the IS molecule itself. The molecule exposed to an external rhythmic effect may transform into a conditionally holographic state.

To test this assumption, we conducted two experiments, the results of which are currently being prepared for publication. In the first experiment, the substance (antibodies) after vibration treatment was directly added to an intact (not subjected to external influences) antigen (biological target) solution. In another group, antibodies after vibration treatment were distantly combined with a solvent (purified water, also not subjected to vibration treatment), i.e., two test tubes were placed close to each other, and then the solvent after this interaction was directly added to the intact (not subjected to external influence) antigen solution. Indeed, it turned out that a substance subjected to vibration treatment acquires the ability to have an ME, which can be realized directly or through an intermediate link—a solvent. Consequently, ME is caused by structural transitions of the molecule itself (within a supramolecular matrix).

In the follow-up experiment, we established that, during joint vibration treatment of a substance and a solvent, when both participants—not only the substance but also the solvent—are subjected to vibration, their distant interaction is possible (with the mutual influence of the substance and solvent on each other). This result provides another solid piece of evidence of the ability of the substance itself, and not its dilutions, under conditions of external rhythmic influence to acquire new physical properties. Already at the next technological stages, the activity acquired during vibration treatment (provided that the vibration effect is maintained) can be transferred from the substance to its PDs, which leads to an increase in the ME.

Historically, the activity of dilutions subjected to vibration, used in medicine and which were the prototype for our research, was first empirically discovered, and only recently it was established that under conditions of external rhythmic influence the substance itself acquires new properties.

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Conflicts of Interest: Oleg Epstein is a founder of the OOO "NPF "MATERIA MEDICA HOLDING", which produces and markets drugs based on the ultra-high dilutions of antibodies. The author declares no other conflict of interest.

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