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Fractal Polymer Globules: A New Insight on Prebiological Evolution

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Abstract—One of the most important problems of the origin of life, namely, the problem of the evolutionary primary carriers of selective functions in evolution that provided the required accuracy in the assembly of complex molecular structures at the prebiological stages of evolution, is discussed in this paper. In contrast to the widely abundant approaches to this problem that consider only RNA- and/or protein-like structures, we suggest that so-called fractal (crumpled) polymer globules could be the primary carriers of selective functions. The unusual structure and dynamics of fractal globules are described in this paper. It is demonstrated that although a fractal globule does not have the elements of the secondary structure of RNA and proteins, its dynamic properties are similar to those of biological molecular machines.

Keywords: prebiological evolution, fractal globules, primary molecular machines

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INTRODUCTION

Despite the wide spectrum of insights on the essence of the phenomenon of life (e.g., [1–3]), it is generally accepted that life is based on the generation of quite complex and specific molecular structures. In this regard, it is of fundamental importance that the generation of molecular structures at various stages of evolution is mostly controlled by the issue of whether or not the required accuracy of their assembly is gained by the considered stage [4–8]. This restriction is not significant at the stages of chemical evolution: the formation of relatively simple molecules follows the statistics of random events, i.e., any simple structure may appear spontaneously quite often. This requirement is fulfilled de facto for biological evolution: the generation of biological systems is performed by so-called molecular machines that provide a high accuracy of assembly of all the molecular components of a cell. However, as soon as "chemical kinetics becomes evolutionary dynamics" [8], i.e., at the stage where molecular and system objects of a chemical nature are structurally quite complex already, but are insufficiently functionally organized, the accuracy of their reproducibility becomes the major factor that limits evolutionary development. If we consider this stage as "prebiological evolution" we may discuss different scenarios of the transitional period, focusing our main attention on the problems that are related to the "primary" molecular machines, their formation in abiogenic conditions, the generation of operational systems of a chemical nature on their basis, the appearance of functional closure and acquisition of the properties of self-replicating autonomous agents by these systems, and, finally, natural selection of such systems and their evolution towards "a protocell" that bears attributes of the existing life forms. In contrast to the traditional scenarios, e.g., the well-known concept of the RNA world with the key role of RNA, or the concept of "sustained ordering" [9], in which an important role is played by ATP, the above-mentioned scenario accepts that the attributes of the *observed* form of life could be formed as a result of "evolutionary dynamics" but not "chemical kinetics."

In fact, such ideas are not novel (e.g., [10, 11]) and have been discussed together with the traditional approaches (e.g., [12]) that go back to A.I. Oparin and J. Haldane. However, the problem is that the chemical and structural peculiarities of natural molecular machines (RNA and proteins) are so tightly "adjusted" to the mechanisms of translation and transcription that it is highly debatable to consider them as prototypes of primary molecular machines. The homochirality of RNA and proteins provides a typical example [6]. A spontaneous origin of the mechanism of biopolymer assembly together with all the molecular machines that are necessary for it seems to be absolutely impossible, even in the extremely simplified version of this mechanism [13]. However, the type of structures which would have the functional possibilities of a molecular machine, but might be formed under the statistically controlled conditions by self-assembly, has not yet been found.

In this paper, we suggest a type of structures that can be candidates for the role of primary molecular machines. Such structures may be so-called fractal crumple polymer globules. In contrast to ordinary polymer globules, the polymer chain in a fractal globule occurs as a self-similar hierarchy of unknotted folds. The statement that the collapse of a long polymer chain with definite topological restrictions on unknotting may result in a thermodynamically stable hierarchy of folds was originally made in [14]. Recently, it was discovered experimentally that the spatial packing of human DNA in chromosomes has the properties of a fractal globule [15]. In contrast to research on DNA, with a probable length that reaches several billions of units, we focused our attention on relatively short chains with several hundred units, which is typical of proteins. Using computer modeling of the collapse of polymer chains with such a length, we obtained samples of fractal globules and studied their dynamic properties within the model, which provided the proper concept of a molecular machine [16, 17]. We discovered that according to their dynamic properties fractal globules were very similar to molecular machines.

We note that the choice of the fractal globules for our investigations was not random. Theoretical analysis [18–20] of a large database on the kinetics of binding of CO by myoglobin [21] and spectral diffusion in globular proteins [22] showed that the energy landscapes of globular proteins should have the property of hierarchic self-similarity. In addition it was assumed that such a property might be typical of a fractal polymer globule with a hierarchically self-similar structure of folds [23].

Since fractal globules represent an unusual globular state of a polymeric chain, we introduce a description of the main results with a brief characterization of this issue. We then describe the methods of modeling and investigation of fractal globule dynamics, and finally discuss the results of our study. A direct comparison of the dynamic properties of the fractal globules obtained in this study with the previously determined typical dynamic properties of molecular machines [16, 17] demonstrates their clear consistency. In conclusion, we discuss the perspectives that fractal globules open for scenarios of prebiological evolution.

FRACTAL POLYMER GLOBULES

It is known that the "non-phantom character" of a polymer chain results in two types of interactions: a volume interaction that disappears for infinitely thin chains and topological interactions that are observed even in chains with a zero thickness. At quite high temperatures (in a "good solvent"), a polymer molecule has a strongly fluctuating coile structure without a reliable thermodynamic state. At temperatures below some critical value θ (in a "poor solvent"), a polymer of N units each of l-length collapses into a weakly fluctuating globular structure with a size of $R \sim lN^{1/3}$. It has been demonstrated in classical studies (e.g., [24]) on the statistical theory of the coil-to-globule transition that the conformation of a chain in the globular phase without accounting for topological interactions is similar to the trajectory of Brownian random motion. However, with account for topology, due to the additional repulsion of folds, chain packing may be different [14]. In particular, at a temperature below the θ-point, unknotted conformations may be characterized by some critical length, g*, that depends on temperature and volume interactions, so that the chain fragments exceeding g* collapse. In the case of quite long chains, these fragments of g* units may play the role of new "monomeric blocks" (or folds of the first level). The chain fragments containing several successive folds-blocks may collapse "in its own volume" forming a fold of the second level, then folds of the second level form a fold of the third level, etc. (Fig. 1a). The process of hierarchical folding of the entire chain will be finished when all fragments of g* units in the chain are inside one common fold. A specific peculiarity of such a "crumpled" (also called "fractal") globule is that if the knotting is prohibited for all levels of folds, the hierarchical structure of folds is not destroyed and provides thermodynamic equilibrium.

It is reasonable to describe the state of a unit in a crumpled polymer conformation by its belonging to certain folds, rather than its position in space. In particular, the unit state can be characterized by a set of indexes that defines which fold of the first level (occurring in a definite fold of the second level, which in turn occurs in a definite fold of the third level, etc.) the given unit is located. Such index sets are uniquely matched with the paths on a tree-like graph (Cayley tree) from the roots of a tree to its "leaves" (nodes at the tree boundary). Each path from the top of the tree to a definite "leaf" describes a hierarchy of folds that contain the considered unit (Fig. 1b). In such a description, the branching index of Cayley tree, p, sets the number of folds embedded in to the fold of the higher level of hierarchy. Each sub-tree of the Cayley tree represents a fold of a definite scale, whereas a set of "leaves" at the Cayley tree boundary sets the space of states S_F for chain units in the crumpled conformation.

The scale of folds is the only parameter that defines the metrics on the S_F space. The scale of a fold of the γ level for a regularly branching tree is p^γ. For any two units i and j, there are always one and only one smallest fold of the γ level that contains the units i and j and only two *largest disjoint folds* of the $(\gamma - 1)$ level that contain the units i and j, respectively. The scale of the

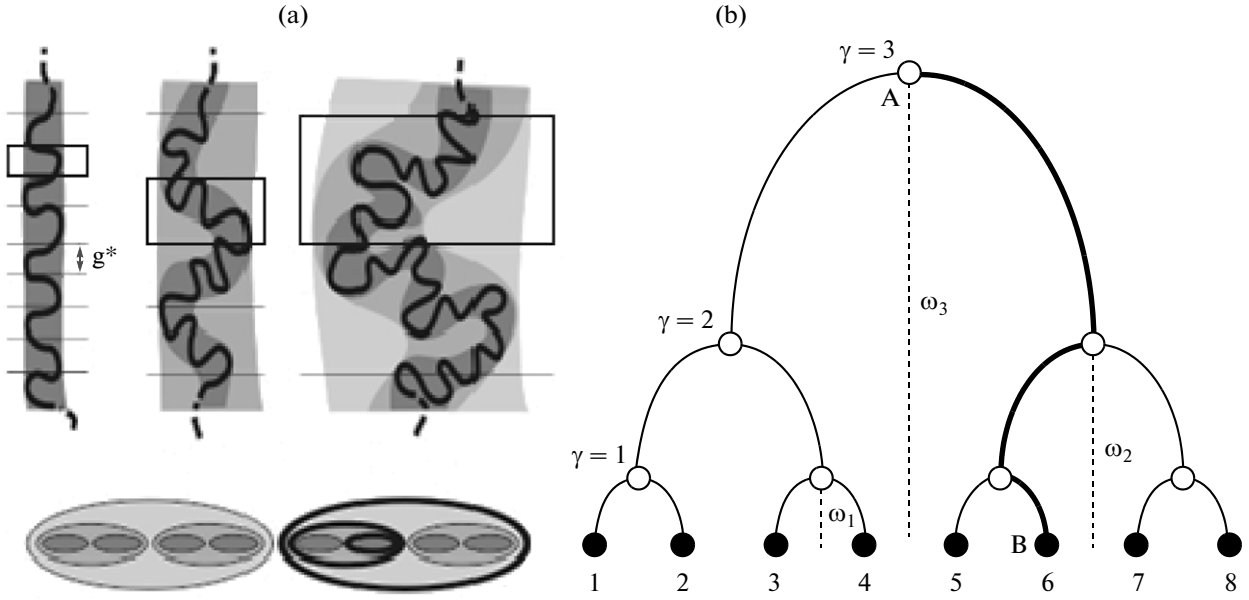

Fig. 1. (a) The hierarchy of the stages in the formation of a folded (fractal) globule. (b) Representation of a space of conformational states of a fractal globule by a branching tree of folds.

largest fold separating two states may be understood as "the conformational distance" in the S_F space that specifies the "conformational barrier" that should be passed by the chain in order to transit from one fold to another.

Note that the distance determined in such a manner obeys the strong triangular inequality, i.e., it is "ultrametric." Replacement of three-dimensional Euclid space with the ultrametric space that accepts only equilateral and isosceles triangles (with a lower base) assumes the presence of topological restrictions that distinguish only crumpled conformations among all possible conformations of a polymer chain. An ultrametric (conformational) distance between the states in S_F can be determined as $p^{\gamma(i,j)}$, where $\gamma(i, j)$ is the level on which the paths on the Cayley tree from the "leaves" i and j to the root are joined.

Within the given description, the crumpled conformation of an N-unit polymer chain is related to the random sequence of states from S_F indexed along the polymer chain, i.e., with the trajectory of random walk on the Cayley tree boundary. Let us determine such a random process explicitly. Let $\varphi(i, s)$ be the transition function of a random process, i.e., the probability of finding the end of the chain with a length of s in the state i, assuming that the beginning of the chain occurs in some preset state i_0. The value of the $\varphi(i, s)$ function defines the measure of all s-step trajectories (crumpled conformations of a length of s) that start and finish at the points i_0 and i, respectively. Assuming that the walk at the Cayley tree boundary is a homogeneous Markov process, let us subordinate the transition function $\varphi(i, s)$ the Kolmogorov–Feller equation:

$$\frac{d\varphi(i,s)}{ds} = \sum_{j\neq i} w(j|i)\varphi(j,s) - \sum_{j\neq i} w(i|j)\varphi(j,s), \quad (1)$$

where the probability of a transition (per time unit) between the states i and j depends only on the ultrametric distance between them: $w(i\,|\,j) \sim p^{-2\gamma(i,j)}$ (e.g., [5]). As an explanation, we should note that such a dependence of the probability of a transition from the ultrametric distance includes the Arrhenius probability of the transition through the "conformation barrier" of a scale $p^{\gamma(i,j)}$ and the probability of the selection of one of the possible states in a new fold of the same scale $p^{\gamma(i,j)}$.

Equation (1) describes conformations of a crumpled globule with a well-defined ground state, because all non-zero eigenvalues of the operator in the right-hand-side of Equation (1) are known to be negative (e.g., [21]).

Let us consider the destruction of the fold hierarchy. We should introduce an additional repulsion between chain units in the globular phase depending on the ultrametric (conformational) distance and temperature:

$$\frac{d\varphi(i,s)}{ds} = \sum_{j\neq i} w(j|i)\varphi(j,s) - \sum_{j\neq i} w(i|j)\varphi(j,s) + \frac{T-\theta}{\theta}\sum_{i\neq j} w(i|j)\varphi(i,s). \quad (2)$$

Using the p-adic Fourier transform, we can easily calculate the eigenvalues of an operator in the right-hand-side of Equation (2):

$$\lambda_\gamma(T) = -p^{-\alpha\gamma} + \frac{T-\theta}{\theta}\left(-p^{-\alpha\gamma} + \frac{1-p^{-1}}{p^{\alpha}-p^{-1}}p^{-\alpha}\right). \quad (3)$$

The solution of the equation $\lambda_\gamma(T) = 0$ determines the hierarchy of critical temperatures $T_1 < T_2 < T_3 < \ldots < T_{\max}$ at which the eigenvalues of the operator in the right-hand-side of Equation (2) become positive, i.e., the folds lose their stability. At $T \le \theta$, all $\lambda_\gamma(T)$ values are negative and all folds are stable. Folds are successively destroyed above the θ-point: at the minimal critical temperature T_1, the largest fold is destroyed, but folds of the lower levels that form the large fold remain stable. When $T_2 > T_1$, the folds of the next level are destroyed, but folds of the lower levels remain stable, etc., until the maximal critical temperature at which folds of the first level are destroyed. In the reverse process, with decreasing temperature, below the θ-point, a hierarchy of folds is formed successively, level by level, in accordance to passing the critical temperatures in the reverse order. We should emphasize that such pattern of the formation and destruction of folds is correct only if the conformational space remains ultrametric, i.e., the topological restrictions favoring the formation of a fold hierarchy are valid within the entire area of temperature variation. Otherwise, all folds become unstable [25] and the chain collapses into an ordinary globule.

MODELING OF THE FORMATION OF A FRACTAL POLYMER GLOBULE AND ITS DYNAMICS

The considerations given above were applied for modeling of polymer chain collapse using the Monte Carlo dynamic continual method (e.g., [26]) in order to obtain a fractal crumpled globule. A polymer chain was represented by beads (centers of the potential application) connected by continuous flexible links. Interaction between beads was controlled by a standard set of potentials accounting for rigidity of the chain and bulk interactions. A block–hierarchic potential $U(\gamma)$ was added to the standard potentials of the form of the Parisi matrix, which imposed constraints forming an ultrametric tree of states for chain units. In our simulations, the model potential $U(\gamma)$ was applied only between the definite (representative) beads of the chain. An example of a folded structure presented below was obtained for the potential $U(\gamma) \sim \gamma^{-1}$. However, we should note that the specific dependence of the potential $U(\gamma)$ on the level γ of hierarchy is not important. The basic role of a hierarchic potential is to provide a quite long life-time for the folds, which allows us to consider them as stable structural subunits formed upon chain collapse. For example, this may be achieved if we place the polymer chain into the cotracting field $U_i \sim r_i$, where r_i is the distance from the i-link to the mass center of the structure. The contracting field forcing the polymer chain to collapse more rapidly than the process of swallowing of intermediate folds by other ones.

The collapse of a polymer chain into a crumpled globule was modeled in a box using the standard Metropolis algorithm, i.e., the new conformation of a chain was produced from the previous one by a random shift of the randomly selected bead of the chain in the box volume. A typical example of a model sample of a crumpled globule is shown in Fig. 2.

The dynamics of crumpled globular structures that were obtained by the methods described above were studied in terms of the model of an elastic network [15]. The essence of the model is as follows. The molecular structure is considered as an undirected graph (network), namely, as a set of nodes $i = 1, 2, \ldots, N$ located in space and undirected elastic links between them, which may stretch and shrink elastically. The topology of a graph is specified by an adjacency matrix A, the element a_{ij} is 1 if there is a link between the i and j nodes; it is 0 if there is no link. It is considered that all links have the same elasticity coefficient. In a overpdamped approximation (the node rate is proportional to active elastic forces), the dynamic equations that describe the relaxation of network nodes to the equilibrium are written as

$$\frac{d\mathbf{R}_i}{dt} = \sum_{j=1}^{N} a_{ij}\frac{\mathbf{R}_i - \mathbf{R}_j}{|\mathbf{R}_i - \mathbf{R}_j|}\left(|\mathbf{R}_i - \mathbf{R}_j| - |\mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}|\right),$$

where $\mathbf{R}_i \equiv \mathbf{R}(t)$ is the current position of the i-node and $\mathbf{R}_i^{(0)}$ is its equilibrium state. At a small deviation of $\mathbf{r}_i = \mathbf{R}_i^{(0)} - \mathbf{R}_j^{(0)}$ from equilibrium, Equation (1) may be linearized:

$$\frac{d\mathbf{r}_i}{dt} = -\sum_j \Lambda_{ij}\mathbf{r}_j,$$

where the elastic stress tensor Λ_{ij} is an element of the linearization matrix Λ of the initial system of dynamic equations (4) with a size of $3N \times 3N$. Thus, in the model of an elastic networks, the system dynamics near the equilibrium is described by the sum of independent (normal) relaxation modes $\mathbf{r}_i(t) = \sum_{k=1}^{3N} r_{ki}(0)\mathbf{e}_k \exp(-\lambda_k t)$, where $\lambda_k > 0$ and $\mathbf{e}_k$ are the nonzero eigenvalues and eigenvectors of the linearization matrix Λ. The system dynamics far from the equilibrium are described by the system of nonlinear equations (4).

Of special interest for our study are the results of [16], in which the model of an elastic network

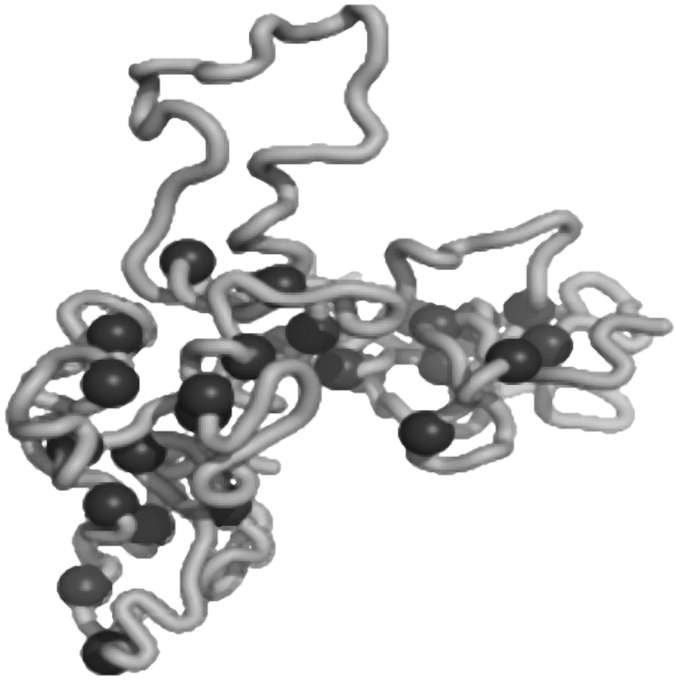

Fig. 2. A typical example of an anisotropic fractal folded globule obtained by the method of the collapse of a relatively short polymeric chain in the field of the hierarchic potential (the chain length is 200 links). Spheres show the representative links of a chain that underwent the influence of the hierarchic potential; tubes denote other fragments of a chain.

described above was applied to the study of the dynamic properties of functional subunits of molecular motors. It was found that the natural (biological) molecular machines had two characteristic signs: (1) a wide spectral gap that separates the one (or two) slowest relaxation modes from the other ones, and (2) a low-dimensional manifold embedded in the multidimensional dynamic space to which all dynamic trajectories started from large attractive basin are repidly focused. In other words, as a response to local excitation, a molecular machines first rapidly relax to a low-dimensional attracting manifold formed by the one (or two) slowest degrees of freedom and then slowly migrate to the equilibrium, while performing some function during the slow migration. We considered the presence/absence of such dynamic properties in the structure as a criterion of whether a structure could potentially be a molecular machine or not.

Figure 3 shows the results of similar investigations, which we performed for the samples of a crumpled globule obtained by the method of polymer-chain collapse under the action of the hierarchic potential $U(\gamma) \sim \gamma^{-1}$. It is clearly evident that the spectrum of normal modes of a fractal globule contains a large gap separating the slowest relaxation mode from the others ($\lambda_2/\lambda_1 \approx 7$). As is shown in Fig. 3a, this peculiarity distinguishes a fractal globule from a common polymer globule. Such a feature is reflected in the dynamics of the fractal globule as well (Fig. 3b). It is shown that at first the structure rapidly relaxes to a low-dimensional (one-dimensional for the given example) attracting manifold and then, remaining on it, slowly migrates to the equilibrium.

Note that the dynamic properties typical of the molecular machine were observed only for strongly anisotropic fractal globules. The probability of the formation of such structures as a result of the collapse of a polymer chain with a length of several hundred links in the field of a hierarchic potential was estimated as 0.10 ± 0.05. The number of individual slow modes was different in various samples. In particular, we observed two and even three distinguished slow modes. Consequently, the low-dimensional attracting manifold was two- and three-dimensional for such structures.

The dynamic properties of the molecular machine were observed for the samples of folded globules that were obtained in the field of a focusing central symmetric potential $U_i \sim r_i$ as well. In these computer simulations, we also observed structures with a distinguished slow mode and low-dimensional attracting manifold with a large basin of attraction (Fig. 4). It is interesting that the phase (dynamic) space of crumpled structures obtained by the focusing field was richer than that of the structures that were obtained in the field of the hierarchic potential. In particular, they are less anisotropic and their low-dimensional attracting manifolds are often characterized by several (quasi-) stationary states (shown by points in Fig. 4b),

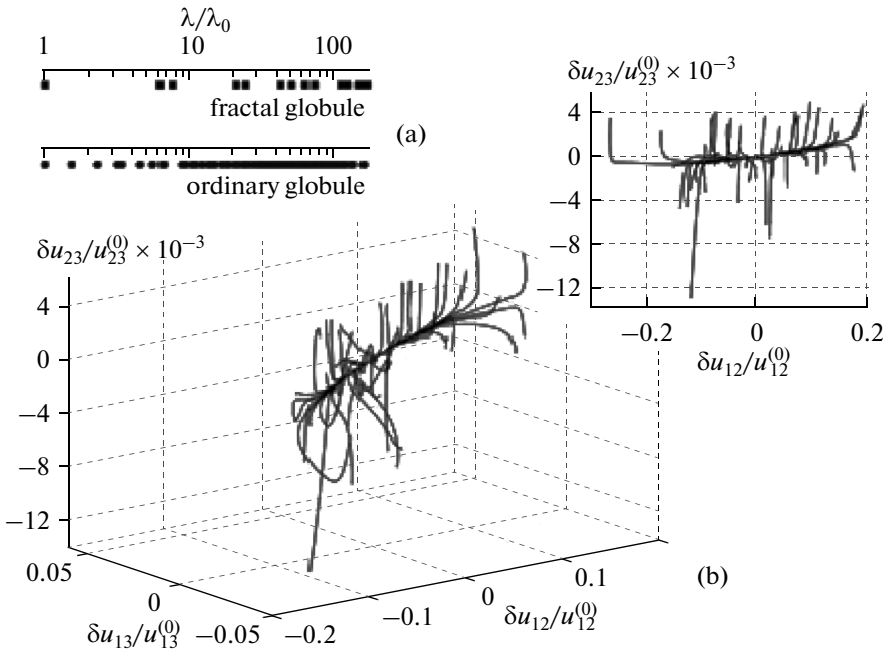

Fig. 3. The dynamic characteristics of an elastic network of a fractal folded globule that were obtained by the method of the collapse of a polymeric chain in the hierarchic potential $U(\gamma)$: (a) the spectrum of the proper values of the linearization matrix Λ related to the least nonzero proper value (given in comparison with the spectrum of equilibrium globule); (b) a three-dimensional representation of multi-dimensional dynamic trajectories in relation to the two slowest relaxation modes ($\sim\delta u_{12}$; $\sim\delta u_{13}$) and one rapid mode ($\sim\delta u_{23}$). The inset shows the projection of dynamic trajectories to the plane ($\sim\delta u_{12}$; $\sim\delta u_{23}$).

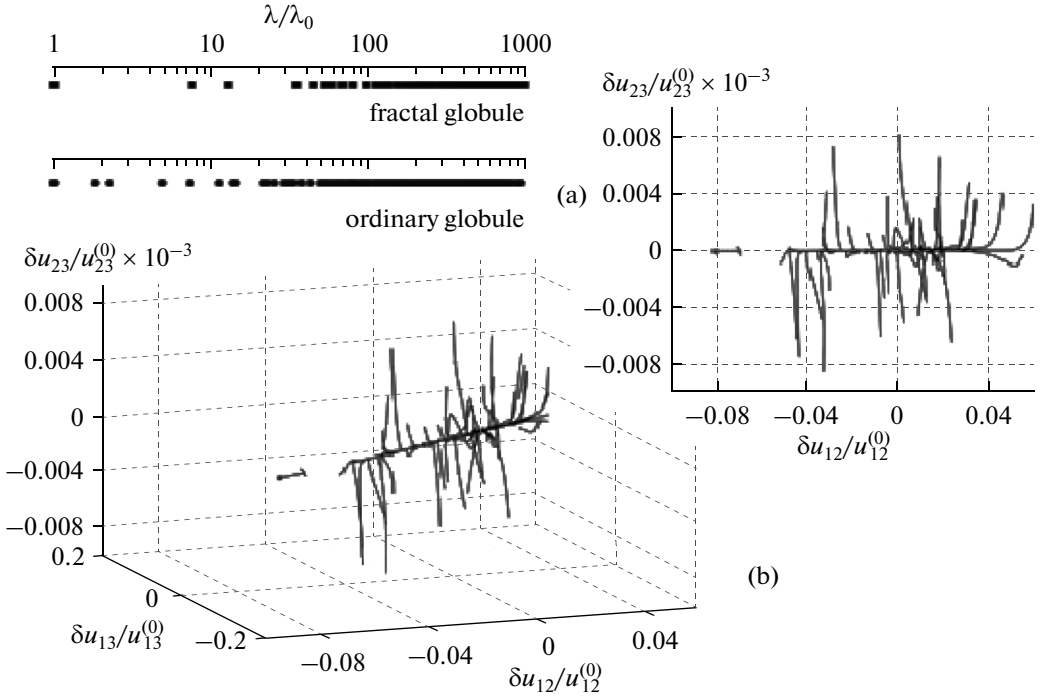

Fig. 4. The relaxation characteristics of a folded structure obtained by the method of collapse in the central symmetric potential: (a) the proper values of the linearization matrix Λ for the samples of a folded structure and equilibrium globule related to the least (nonzero) proper value; (b) a three-dimensional representation of the relaxation trajectories of a folded structure in relation to the two slowest relaxation modes ($\sim\delta u_{12}$; $\sim\delta u_{13}$) and one rapid mode ($\sim\delta u_{23}$). The inset shows the projection of the relaxation trajectories to the plane ($\sim\delta u_{12}$; $\sim\delta u_{23}$).

which constrict the dynamic trajectories. However, the common dynamic behavior of crumpled globules is the same as that of molecular machines.

Finally we should note that the examples of fractal polymer globules given above are only particular representatives of a quite wide family of folded structures with the properties of a molecular machine. The variability of such structures mostly concerns the number of separated slow modes and, consequently, the dimension of an attracting manifold, on which the quasimechanical motion of the structure proceeds. We observed one-, two, and rarely, three-dimensional attracting manifolds corresponding to one, two, and three distinguished slow modes. Thus, fractal polymer globules that act as molecular machines admit functional variability without the fundamental change of the structure type. In other words, the same type of structure may generate a wide family of functionally different molecular machines. This quality seems to be the most important one for primary operational systems.

CONCLUSIONS

In our attitude to the problems of prebiological evolution, we proceed from fundamental restrictions, which are defined by "the error catastrophe" on the accuracy of the assembly of complex molecular structures that are involved in the processes of natural selection and directed evolution. We assume that these restrictions should be necessarily overcome in the prebiological transition period. In our opinion, they could be overcome only by primary molecular machines and/or primary operational systems (molecular assemblers) of the nonbiological type, since such functional structures and systems should "spontaneously" appear in the abiogenic environment. We suggest that the specific function, rather than the specific structure, should be in the core of the theory of prebiological evolution.

It seems to us that the absence of clear progress in the theory of prebiological evolution is mostly given by biochemical stereotypes. Prebiological evolution is usually understood as a "higher" stage of chemical evolution, at which the main components of cell biochemistry were formed. Such an understanding of the content of prebiological evolution, which formed almost 100 years ago, is quite doubtful now. A cell, even if it is much "simplified," always remains an operational system with "functional closure" providing the properties of self-replicating autonomous agents. However, proper functional closure is an attribute of only a quite specific and very narrow class of operational systems. The requirement of functional closure is excessive for the primary operational systems. It could appear as a result of the proper evolution. Most likely, because of this, all the structural and chemical peculiarities of RNA and proteins that control functional closure in biological systems are excessive for the primary molecular machines as well.

The role of "primary" molecular machines in prebiology might be played by fractal polymer globules, which, as was demonstrated above, may appear in means of the rapid collapse of polymer chains under not very specific physical conditions. This structural archetype could generate quite a wide family of molecular machines with different functions, which is important for the next evolutionary step, namely the formation of primary operational systems of a chemical nature on the basis of primary molecular machines.

Certainly, the hypothesis that fractal polymer globules really can be molecular machines requires experimental support. However, we suggest that the results that were obtained in this study provide an optimistic prediction for the development of scenarios of prebiological evolution in which primary operational systems of a chemical nature are removed from the context of biochemistry and the beginning of biological evolution is related to the moment of the appearance of the first autonomous agents with functional closure.

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