Ultrametric theory of conformational dynamics of protein molecules in a functional state and the description of experiments on the kinetics of CO binding to myoglobin

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The paper is devoted to a systematic account of the theory of conformational dynamics of protein molecules. As an example of application of this theory, we provide a complete analytical description of experiments on the kinetics of CO binding to myoglobin, which were carried out by the group of Frauenfelder more than 30 years ago and acquired the status of base experiments for studying the properties of the fluctuation dynamic mobility of protein molecules. As early as 2001, the authors could demonstrate that, within the model of ultrametric random walk with a reaction sink, the experimental curves of CO binding to myoglobin can be reproduced in the high-temperature region. Later, in 2010, the authors proposed a modified model and, based on its numerical analysis, demonstrated that this model can reproduce the experimental results over the whole temperature range covered in the experiment. In the present study, based on the previously proposed model, we formulate a rigorous mathematical theory of conformational dynamics of protein molecules. We demonstrate that the proposed theory provides not only a complete description of the experiment over the whole temperature range of \((60 \div 300) \, \text{K}\) and in the observation time window of \((10^{-7} \div 10^{2}) \, \text{s}\) but also a unified picture of the conformational mobility of a protein molecule, as well as allows one to realize the fact that the mobility changes in a self-similar way. This specific feature of protein molecules, which has remained hidden to date, significantly expands the ideas of dynamic symmetry that proteins apparently possess. In addition, we show that the model provides a prediction for the behavior of the kinetic curves of the experiment in the low-temperature range of \((60 \div 180) \, \text{K}\) at times not covered by the experiment (more than \(10^{2} \, \text{s}\)).

I. INTRODUCTION

According to the “protein-machine” concept \[1\], protein does not speed up but, conversely, slows down elementary chemical acts (the formation or breaking of a chemical bond, charge transfer, and so on). The slow conformational dynamics of a protein molecule along a distinguished degree of freedom controls the behavior of an elementary act in the active center of a protein molecule on a large time scale from nanoseconds to hundreds of milliseconds and plays the key role in the fermentative function \[1,3\]. This feature imparts to protein the properties of a “machine” that can manipulate individual charges, atoms and molecules, against the background of thermal fluctuations (the slower protein works, the lower the probability of error). This leads to the necessity of studying conformational dynamics on large time scales. Taking into account this concept, Frauenfelder et al. \[1,5\] carried out experiments on photodissociation and subsequent binding of a CO molecule to myoglobin. In these experiments, the authors obtained nontrivial results, which, unfortunately, could not be consistently explained within the existing theories. To explain the conformational dynamics of protein, Frauenfelder put forward the idea of the ultrametricity of the energy landscape – the hypersurface of the potential energy of a protein molecule. These ideas were suggested by the studies of Parisi \[6\] and Ramal, Toulouse, and Virasoro \[7\]. It is interesting that recent studies on this subject – the 2010 microreview by Frauenfelder \[8\] and the 2015 paper by K. Nienhaus and G. Nienhaus \[9\] – remained at the previous level of theoretical understanding. As a result, an opinion has been formed about the kinetics of CO binding to myoglobin that the states of myoglobin at physiological and low temperatures differ quite significantly and that it is impossible to construct a unified description of the binding kinetics within a single physical model in the temperature range from 60 to 300 K. As for the ultrametricity of conformational states of protein, in fact, this idea dropped out of discussion (see, for details, our paper \[10\], where we discuss in detail the model formulas proposed for these experiments and explain their problematic aspects).

Possibly, it is the lack of theoretical understanding that is responsible for the eventual fading of interest in experiments of this kind. The emergence of good femtosecond experimental setups turned the interest of researchers to the study of small regions of protein molecules (as a rule, the active center of protein) on femtosecond scales. It is this period when interest in the models of small fragments of protein molecules and the computer simulation of these models arose. Such an approach leads to certain success and, for a proper choice of potentials, may give good agreement with experiments (see, for example, \[11–13\]). Nevertheless, it is worth noting that it is configurational rearrangements of sufficiently large fragments of the system, including tens and hundreds of elements, that play an important role in the behavior of complex sys-
tems such as protein. As pointed out in [14], in complex systems, a “conflict” between local interactions and the constraints imposed on the system (frozen bonds) gives rise to strong ruggedness of the energy landscapes. If $N$ is the number of elements taking part in the configurational rearrangements, then, according to the estimates of [12, 16], the number of local minima of the energy landscape is on the order of $\sim N! \exp (\eta N)$, where $\eta$ is a quantity on the order of unity. It is such cases, which are most interesting from the physical viewpoint, for which the full description of energy landscapes and, hence, the study of the dynamics of the system becomes impossible due to the unfeasibility of computations. For example, a full computer reconstruction of the fundamental act of protein in which the motions of all fragments of the protein structure would be equally represented at times from $10^{-9}$ to $10^{6}$ s is impossible. Thus, to date, irrespective of the computational resources, the computer simulation of the conformational dynamics of structures comparable with proteins in complexity is limited. It can, at best, give either a relatively detailed idea about the behavior of a structure in a relatively small domain of the conformational space, or (in a strongly coarsened description) a sketchy representation of its behavior as a whole.

Fundamental difficulties of this kind force us to seek fundamentally new approaches to the description of the conformational dynamics of protein. One of such approaches, which we would like to highlight, was proposed in the works of Stillinger and Weber [17] and Becker and Karplus [18]. Although this approach was initially developed for computer simulation, it is nevertheless close to the ideas of Frauenfelder on ultrametricity in proteins. This approach is based on the representation of multidimensional strongly rugged landscapes by hierarchical graphs. The authors of [17, 18] applied the procedure of hierarchical clustering of the local minima of the energy landscape. The procedure of clustering of local minima was applied to the energy barriers between these minima. As a result of this procedure, the local minima are combined into sets hierarchically nested into each other, which are called “basins.” Such hierarchical clustering (or, in other words, the taxonomy problem) resulted in a treelike hierarchical structure of quasi-equilibrium states of protein. Here the dynamics of protein was considered as a random walk on such a hierarchical set and was described by the Kolmogorov–Feller equation (master equation). Note that, mathematically, such clustering problem is not uniquely defined. As a consequence, this leads to nonuniqueness in the definition of the hierarchical tree that describes the set of quasi-equilibrium states of the system. Moreover, this approach involves purely technical difficulties in the definition of the transfer matrix between basins of different scales. Namely, to define the elements of the transfer matrix, one should determine the energy barriers between local basins of states, as well as determine the number of states in each basin. The solution of this problem is fundamentally unattainable for real protein molecules even by the methods of modern computer experiments. As a consequence, the approach proposed in these works had no effective continuation. Nevertheless, the works [17, 18] served as a basis for the development of an ultrametric approach to the multiscale description of the conformational dynamics of protein. The ultrametric approach is based on the representation of the basins of quasi-equilibrium macrostates hierarchically nested into each other by hierarchically nested balls of some ultrametric space, for which it is convenient to take the field of $p$-adic numbers [15, 22]. This approach was developed in our previous works [10, 23–30].

The main goal of the present study is the postulative construction of a new physical theory – conformational dynamics of protein molecules in the native state. As an example of the application of this theory, we propose an analytical description of the physical experiments of [4, 8] on the kinetics of CO binding to myoglobin, which, as already mentioned, were set up for studying the properties of fluctuation dynamic mobility of protein molecules. When constructing the theory of conformational dynamics of protein, we apply an approach based on $p$-adic analysis [21]. In this paper, we try, whenever possible, to formulate our results and conclusions in a rigorous mathematical form. Within the constructed theory, we propose a mathematically formalized physical model of experiments on the kinetics of CO binding to myoglobin and show that this model provides a complete description of the experiment in a wide temperature range of $60 \div 300$ K and in an observation time window of $10^{-7} \div 10^2$ s. We also show that this theory makes it possible to build up a unified picture of the conformational mobility of a protein molecule and realize the fact that this mobility changes in a self-similar way under the change of the observation time scales. This specific feature of protein molecules, which has remained hidden to date, significantly expands our views on the dynamic symmetry that proteins apparently possess. It is also important that our model provides a prediction for the behavior of the kinetic curves of the experiment in the low-temperature range ($60 \div 180$ K). Namely, the behavior of the kinetic curves should change significantly upon the extension of the observation time window: the lower the temperature, the wider should be the observation time window in order that the behavior of the curves be changed. This fact can serve as a recommendation for possible future experiments on the kinetics of CO binding to myoglobin in an extended observation time window.

The paper is organized as follows. In Section 2, we give a brief description of physical experiments on the study of the kinetics of CO binding to myoglobin. Sections 2 and 3 provide an account of the ultrametric theory of conformational dynamics of protein molecules. In Section 3, we present, at the physical level, an argumentation for the emergence of a natural ultrametric structure on the set of conformational states of protein. The important point in this argumentation is the definition of the concept of “conformational state,” which has a slightly different meaning compared to the traditional one adopted.
in biophysics. In Section 4, we present the basic principles (postulates) of the physical theory – conformational dynamics of protein – whose mathematical formalism is the analysis over the field of $p$-adic numbers. We well understand that this mathematics is not quite familiar to a part of physicists and biophysicists, but it allows one to easily formalize such a complex object as a biopolymer. Section 5 is devoted to the solution of the Cauchy problem for the equation of $p$-adic random walk with a reaction sink. It is the solution of this mathematical problem that underlies our description of physical experiments on CO binding to myoglobin at different temperatures. Section 6 is devoted to the analysis and the physical interpretation of the solutions obtained in Section 5 and to the comparison of the predictions of the model with experimental results. In Appendices A, B, and C, we present the relations and theorems that we used in Section 6 for the analysis of the asymptotic behavior of exact solutions to the problem of $p$-adic random walk with a reaction sink.

II. EXPERIMENTS ON THE KINETICS OF CO BINDING TO MYOGLOBIN

Let us give a brief overview of the experiments described in detail in [4, 5]. Myoglobin protein molecules bound to CO were irradiated by a short laser pulse. This led to photodissociation, which breaks the bond of CO to heme iron of the active center. After that, the kinetics of CO rebinding to heme iron was investigated on a large time scale of $10^{-7} - 10^2$ s and in a wide range of temperatures of $60 - 300$ K. Here only those proteins in which a CO molecule after photodissociation remains in the active center (in the so-called heme pocket) were taken into consideration. The binding kinetics for such proteins depends only on the rearrangements of the active center, and it is this kinetics that is of primary interest.

The scheme of CO rebinding to myoglobin can be represented as follows:

$$\text{Mb-}CO \xrightarrow{hv} [\text{Mb}^* \longrightarrow \ldots \longrightarrow \text{Mb}_1] \xrightarrow{CO} \text{Mb-}CO. \ (1)$$

Here the symbol $\text{Mb}^*$ denotes the conformational states in which protein can occur immediately after the dissociation of CO from heme iron, and the symbol $\text{Mb}_1$ denotes the conformational states in which myoglobin can be rebound to CO.

The concentration of proteins unbound to CO is a function $S(t, T)$ depending on time $t$ and temperature $T$. The curves of the concentration of unbound myoglobin molecules as a function of time, taken from [5], are presented in Fig. 1.

Depending on the behavior of $S(t, T)$, two regions are distinguished in the temperature interval ($60 - 300$ K): the high-temperature ($200 - 300$ K) and the low-temperature ($60 - 180$ K) regions. The dependence $S(t, T)$ experimentally determined in [4, 5] was approximated analytically in [31]. In the high-temperature region, this approximation has the form

$$S(t, T) = \frac{1}{1 + \left( \frac{t}{\tau_1} \right)^{1 - \frac{T}{T_0}}}, \ (2)$$

where $\tau_1$ is a parameter that determines the time scale. In this temperature region, an anomalous dependence of $S(t, T)$ on temperature is observed for which the rate of the binding reaction increases with decreasing temperature.

In the low-temperature region, the approximation of the dependence $S(t, T)$ in the same observation time window has the form

$$S(t, T) = \frac{1}{1 + \left( \frac{t}{\tau_2} \right)^{\frac{T}{T_0}}}, \ (3)$$

with a different parameter of the time scale $\tau_2$. This region is characterized by normal temperature dependence, for which the rate of the binding reaction decreases with decreasing temperature.

Let us give qualitative explanations for the curves in Fig.1. The left panel shows the curves of the high-temperature region ($200 - 300$ K). On these curves, we can distinguish power-law and exponential regions. At $300$ K, the binding kinetics curve is indistinguishable from the exponential law for the given time resolution. Such behavior is attributed to the fact that, at high temperatures, the characteristic time of the conformational rearrangements of a myoglobin molecule is much less than the characteristic time of CO binding to heme iron. Therefore, the limiting time is the time of CO binding to heme iron. As temperature decreases, the process of conformational rearrangements of protein naturally slows down. This leads to the fact that the characteristic times of conformational rearrangements of a myoglobin molecule increase and become comparable with the characteristic time of CO binding to heme iron. In this case, the kinetics of the whole process starts to significantly depend on the evolution of the protein concentration distribution over conformational states. This kinetics corresponds to the power-law region, which is approximated by formula (2).

The next thing that attracts our attention on the curves in the high-temperature region are the regions before the exponential decay in which the concentration of unbound molecules is almost unchanged. The reason for the presence of such regions is purely technical: the concentration curve becomes constant if, by a given point in time, a part of myoglobin proteins for which the CO molecules remain in the active center after photodissociation is exhausted. This is explained by the fact that, after photodissociation, a CO molecule may occur in different states. In the experiment under consideration, only two such states can be distinguished. The first state of a CO
molecule implies that the molecule is in the active center (or the heme pocket). The second state of the CO molecule implies that the molecule is outside the protein globule. In the latter case, the characteristic time of penetration of CO into the protein globule is much greater than both the time of conformational rearrangements of the protein molecule and the binding time of the CO molecule to heme iron. Thus, the penetration time of CO into the globule limits the rate of the binding reaction; therefore, the concentration of unbound molecules is initially almost constant and then decreases exponentially.

In the low-temperature region (Fig.1, right), the kinetic curves are not exponential either, since in this observation time window \((10^{-7} - 10^{2})\) s) we have the binding kinetics of only those CO molecules that remain in the active center (i.e., inside the protein globule) after photodissociation. No binding kinetics is observed for the CO molecules that remain outside the protein after photodissociation, because the characteristic time of penetration of a CO molecule into the body of the protein at low temperatures is much greater than the upper boundary of the observation time window, equal to \(10^{2}\) s.

The main difficulty in the description of the experiment was associated with the stepwise change, in a rather narrow temperature interval \((180 - 200)\) K, of the exponents of the power-law approximations \(2^{a}\) and \(3^{a}\) at which the temperature dependence of the binding reaction rate reverses. The authors of \(4, 5\) themselves suggested that this change in the kinetics is associated with the existence of a temperature at which the protein globule passes to the glass transition phase (see, for example, \(32\)), in which the behavior of protein is qualitatively different from its behavior at room (physiological) temperatures. In our opinion, these conclusions are incorrect for the following reason. As already pointed out above, experiments on the kinetics of CO binding to myoglobin were carried out in a wide range of temperatures \((60 - 300)\) K but in the same observation time window \((10^{-7} - 10^{2})\) s). For high-temperature curves, this observation time window is rather large and allows one to cover the whole picture of the binding kinetics. Conversely, for low-temperature kinetics (in view of the decreased rate of conformational rearrangements), the same time window is apparently insufficient for observing the full picture of the kinetics of CO binding to myoglobin. The inconsistency consists in comparing the approximating formulas in the same time window, which leads to the appearance of a change in the exponents in formulas \(2^{a}\) and \(3^{a}\) and, as a consequence, the appearance of a stepwise change in the kinetic behavior.

III. \(p\)-ADIC MODEL OF CONFORMATIONAL DYNAMICS OF PROTEIN

In this section, we provide a physical substantiation of a \(p\)-adic model for the conformational dynamics of protein and formulate the basic principles of the model.

The configuration space \(M\) of a protein molecule is a smooth manifold defined by a set of generalized coordinates \(q = \{q_i\}, i = 1, \ldots, \dim M\), corresponding to all microscopic degrees of freedom of the molecule in the native state. Accordingly, the phase space \(P\) of a protein molecule is a smooth manifold defined by a set of generalized coordinates and generalized momenta, \(z = \{q_i, p_i\}\). The Hamiltonian of the system \(H = H(q, p)\) is a function of its kinetic \(K = K(q, p)\) and potential \(U = U(q)\) energies. At a given temperature \(T\) of the medium, protein executes thermal motion, which represents a random walk on \(M\) or on \(P\). The description of this random walk of protein within the Langevin or the Fokker–Planck approaches requires a precise description of all degrees of freedom of the protein and of the function \(U(q)\), which is hardly implementable at present. Therefore, one needs new unconventional approaches to describe the conformational dynamics of protein.

In 1987, Frauenfelder \(33\) put forward the idea of ultrametricity of proteins. Namely, to explain the experiments on the kinetics of CO binding to a myoglobin molecule, he suggested that a protein molecule has a set of quasi-equilibrium conformational states that are associated with the local minima of the potential energy. He also suggested that these conformational states can be combined into sets of states hierarchically nested into each other and that this nesting is determined by
the value of the activation energy barrier separating any two such states. These assumptions immediately imply that the set of quasi-equilibrium states of protein can be mapped to the vertices of some hierarchical three, which is what is meant by the ultrametricity of protein.

Even before Frauenfelder’s paper, as well as in the first works appeared after its publication, relatively simple models of ultrametric random processes were proposed (see, for example, [34 35]); however, these models turned out to be hardly applicable to the description of the distribution function over the phase space $P$. By contrast to this, the random walk of protein over the set of basins. By maximum of the function $U$ into subsets – elementary basins (or attraction basins). A $p$-adic approach to the conformational dynamics of protein appeared as a development of the ideas of [15 33] with the use of the parametrization of the set of quasi-equilibrium states of protein by subsets from the set of $p$-adic numbers. Note that the approach of [15] was originally aimed at a precise determination of the structure of basins by molecular dynamics methods followed by the numerical simulation of the random walk of protein over the set of basins. By contrast to this, the $p$-adic approach was designed from the very beginning as an analytical theory of random walk on an ultrametric space and was considered as an adequate approximation to describe the conformational dynamics of protein.

According to the general idea of [15 18], the configuration set $M$ can be divided (up to a set of measure zero) into subsets – elementary basins (or attraction basins). Each elementary basin is associated with a local minimum of the function $U(q)$ and is defined as an open subset of points each of which satisfies the following condition: on $M$, there exists a continuous path $q = q(s)$ from this point to a point of local minimum such that, at each point of this path $\frac{dq}{ds} = -\nabla U(q)$.

Denote by $B$ the set of all elementary basins. The conformational state (conformation) $C = C(B)$ of a protein, corresponding to some basin $B \in B$, is the process of random walk of protein over the phase space $P$ with distribution function equal to the equilibrium distribution function in this basin,

$$f(q,p) = \begin{cases} Z_B^{-1} \exp \left( -\frac{H(q,p)}{kT} \right), & q \in B, \\ 0, & q \notin B, \end{cases}$$

where $k$ is the Boltzmann constant and $Z_B$ is the partition function over the subset $P$ bounded by the basin $B$. Any such state is also called a quasistationary state of the protein in the basin $B$. Denote the set of all conformational states by $\mathcal{U}$.

We stress that the conformational state $C(B)$ of protein at a given time $t$ is not identified with the location of the protein at this time at a point $q \in B$, because the conformation state is determined by the distribution function rather than by a point of the configuration space. The system is in some conformational state during some random time interval starting from the time when the distribution function of the protein becomes quasi-equilibrium in the elementary basin $B$ and ending at time when the protein leaves the basin $B$. The average transition time between two conformational states $C(B')$ and $C(B'')$ corresponding to two elementary basins $B'$ and $B''$ is $\Delta t = \tau(B',B'') + \tau(B'')$, where $\tau(B',B'')$ is the mean transition time from the basin $B'$ to the basin $B''$ along some path $\Gamma \subset M$ connecting two points of the basins $B'$ and $B''$ and $\tau(B'')$ is the mean relaxation time to the quasi-equilibrium state in the basin $B''$. Denote by $t(B)$ the average residence time of the protein in the conformation $C(B)$. Then it is natural to assume that $\tau(B') \ll t(B)$ and $\tau(B',B'') \ll \{t(B'), t(B'')\}$. The first condition follows from the very fact of the existence of quasistationary states. The second condition follows from the following fact. The transition path $\Gamma$ connecting two elementary basins is unlimited; it may directly connect two basins (this is possible if the basins have a common boundary); however, it may also pass through other basins different from $B'$ and $B''$. In the first case, $\tau(B',B'') = 0$. In the second case, one or several other intermediate basins may lie on the transition path. Suppose that the system, during its transition from $B'$ into $B''$, passes through some intermediate elementary basin $B_{int}$ and relaxes to the quasi-equilibrium state. This is only possible if, for a given motion in the basin $B_{int}$, the mean value of the velocity of the system on its transition path is much greater than the rms value of its velocity in the conformational state $C(B_{int})$. Only in this case the system in a short time goes outside $B_{int}$ and reaches some other basin with high probability. In this case, the transition time through the intermediate basin $B_{int}$ is much less than the average residence time of the system in the state $C(B_{int})$. In view of the aforesaid, we assume that $\tau(B',B'') + \tau(B'') \ll \{t(B'), t(B'')\}$ for any two elementary basins $B'$ and $B''$. This means that the dynamics of the random evolution of the protein over the set of conformational states can be described by Markov’s stepwise random process, which takes into account only the residence time of protein in the conformational states. In this case, the distribution function $f_C(t)$ of the protein over the set of conformational states $\mathcal{U}$ satisfies the Kolmogorov–Feller equation (master equation) [44]

$$\frac{df_C(t)}{dt} = \sum_{C' \in \mathcal{U}} \left( P_{CC'} f_{C'}(t) - P_{C'C} f_C(t) \right), \quad (4)$$

where $P_{CC'}$ is the matrix of transition probabilities (in unit time) between conformations.

On the set of basins $B$, we can introduce a distance function (metric). To this end, for any two elementary basins $B'$ and $B''$, we define a function $E(B',B'')$ whose
value is equal to the minimum of all the numbers $E$ satisfying the following condition: there exists a path $\Gamma \subset M$ connecting the points $q_{1}^{\prime}$ and $q_{2}^{\prime}$ of the basins $B^{\prime}$ and $B^{\prime \prime}$ such that $E = \max_{q \in \Gamma} U (q)$. The value of the function $E (B^{\prime}, B^{\prime \prime})$ will be referred to as the value of the potential barrier between the basins $B^{\prime}$ and $B^{\prime \prime}$. Introduce a function

$$d (B^{\prime}, B^{\prime \prime}) = h (E (B^{\prime}, B^{\prime \prime})),$$

where $h$ is an arbitrary positive increasing function. We can show that the function (5) is ultrametric on the set of basins $B$ (see, for example, [2]). Since there is one-to-one correspondence $C = C (B)$ between conformational states and elementary basins, the set of conformational states is also an ultrametric space with ultrametric $d (C (B^{\prime}), C (B^{\prime \prime})) = d (B^{\prime}, B^{\prime \prime})$.

To describe the dynamics of protein by Eq. (4), we need exact parameterization of all conformations and the definition of the matrix of transition probabilities $P_{CC^{\prime}}$. This description requires serious simplifications of the model.

The first simplifying assumption is that $U$ is assumed to be a homogeneous ultrametric space. Recall that an ultrametric space is homogeneous if, for any ball, the number of maximal subballs nested into it is the same. We will call the set of conformations the ultrametric distance between which does not exceed $r$ a ball of radius $r$ on the space of conformations $U$. As applied to our model, this assumption implies that any ball $B \subset U$ of radius $r_{i}$ is a union of an equal number $p \geq 2$ of balls $B_{i-1,a} \subset U$ $(a = 1, 2, \ldots, p)$ of radius $r_{i-1}$ nested into it; i.e., $B_{i} = \bigcup_{a=1}^{p} B_{i-1,a}$.

This assumption allows us to perform a $p$-adic parameterization of the space of conformations, i.e., to map this space to the field of $p$-adic numbers $\mathbb{Q}_{p}$. Since in $\mathbb{Q}_{p}$ every ball of radius $r = p^{i}$ is a union of $p$ subballs of radius $r_{i-1} = p^{i-1}$ nested into it, it is natural to assign a $p$-adic ball of given radius $r = r_{0}$ to each conformation. Without loss of generality, we can take the value of $r_{0}$ equal to 1. Thus, any conformational state of protein can be parameterized by a certain $p$-adic ball $B_{0}$ of unit radius. In this case, any point $x \in B_{0}$ is the center of this ball and can be used for identifying the conformation corresponding to the ball $B_{0}$.

The ultrametric distance between two conformations $C$ and $C^{\prime}$ corresponding to two $p$-adic balls $B_{0} \subset \mathbb{Q}_{p}$ and $B_{0}^{\prime} \subset \mathbb{Q}_{p}$ of radii $r_{0} = 1$ is the $p$-adic distance $d (x, y) = |x - y|_{p}$ between arbitrary points $x \in B_{0}$ and $y \in B_{0}^{\prime}$. It is exactly equal to

$$|x - y|_{p} = r_{j},$$

where $r_{j} = p^{j}$ is the radius of the minimal ball in $\mathbb{Q}_{p}$ that contains both balls $B_{0}$ and $B_{0}^{\prime}$. In this $p$-adic parameterization of the conformational space, we will describe the state of a protein ensemble by the distribution function $f (x)$, $x \in \mathbb{Q}_{p}$. Here $f (x)$ is assumed to be a locally constant function with radius of local constancy equal to $r_{0} = 1$ (i.e., for any $x \in \mathbb{Q}_{p}$ and $x^{\prime} \in \mathbb{Z}_{p}$, where $\mathbb{Z}_{p} = \{ x \in \mathbb{Q}_{p} : |x|_{p} \leq 1 \}$, the equality $f (x) = f (x + x^{\prime})$ holds).

The following simplifying assumption concerns the matrix of transition probabilities in unit time between conformations, $P_{CC^{\prime}}$. We adopt that $P_{CC^{\prime}}$ is completely determined by the value of the potential barrier between the basins $B$ and $B^{\prime}$, which correspond to the conformations $C$ and $C^{\prime}$, i.e.,

$$P_{CC^{\prime}} = W (d (C, C^{\prime})) = W (|x - y|_{p}),$$

where $W$ is a function, $x \in B_{0}$ and $y \in B_{0}^{\prime}$, and the $p$-adic balls $B_{0} \subset \mathbb{Q}_{p}$ and $B_{0}^{\prime} \subset \mathbb{Q}_{p}$ parameterize the conformations $C$ and $C^{\prime}$, respectively.

Having adopted the above assumptions, we can formulate the following basic principles of the $p$-adic model of the conformational dynamics of protein.

1. The set of all possible conformational states of protein of all levels is parameterized by a set of $p$-adic balls of unit radius of the field of $p$-adic numbers $\mathbb{Q}_{p}$.

2. The dynamics of protein on the set of conformational states is represented by a random walk on the field $\mathbb{Q}_{p}$, which is described by a Markov random process $\xi (t, \omega) : \Omega \times \mathbb{R} \to \mathbb{Q}_{p}$. The density of the distribution function $f (x, t)$ of such a process is assumed to be a locally constant function with radius of constancy equal to one (i.e., for any $x$ and $x^{\prime}$, $|x|_{p} \leq 1$, the equality $f (x) = f (x + x^{\prime})$ holds), and it is a solution of the equation of $p$-adic random walk (the Kolmogorov–Feller equation on the field of $p$-adic numbers):

$$\frac{\partial f (x, t)}{\partial t} = \int_{\mathbb{Q}_{p}} W (|x - y|_{p}) (f (y, t) - f (x, t)) \, dy.$$  (6)

The following principle is necessary to reproduce the power-law relaxation functions observed in a number of experiments in the $p$-adic model of conformational dynamics of protein.

3. Equation (6) is covariant with respect to the scaling transformations

$$\begin{cases} x \to x^{\prime} = \lambda x, \\
t \to t^{\prime} = |\lambda|^{-\alpha} t, \\
f (x, t) = f^{\prime} (x^{\prime}, t^{\prime}) = |\lambda|^{-1} f \left( \lambda x, |\lambda|^{-\alpha} t \right), \end{cases}$$

where $\lambda \in \mathbb{Q}_{p}$ is the transformation parameter and $\alpha \in \mathbb{R}_{+}$.

Assumption 3 imposes a stringent constraint on the choice of the kernel $W (|x - y|_{p})$ of the integral operator in Eq. (6). Namely, under this condition, the kernel of this operator coincides up to a factor with the kernel of the Vladimirov operator [20]:

$$W (|x - y|_{p}) \sim \frac{1}{|x - y|_{p}^{\alpha + 1}}.$$  (8)
The parameter \( \alpha \) can be given a physical meaning if we set
\[
\alpha = \frac{E_0}{kT}
\] (9)
and write
\[
\frac{1}{|x - y|_p^\alpha} = \exp \left( - \frac{E_0 \log (|x - y|_p)}{kT} \right),
\] (10)
where \( T \) is temperature, \( k \) is the Boltzmann constant, and \( E_0 \) is a parameter with the dimension of energy. In this representation, expression (10) can be interpreted as the Boltzmann factor defining the probability that the system overcomes the potential barrier
\[
E(x, y) = E_0 \log |x - y|_p
\] (11)
between two basins that correspond to a conformation containing the points \( x \) and \( y \). In this case, the additional factor \( \frac{1}{|x - y|_p} \) in (5) is inversely proportional to a combinatorial factor equal to the number of conformations whose basins are separated by the potential barrier (11) from the basin of the conformation containing the point \( x \).

IV. SOLUTION OF THE CAUCHY PROBLEM FOR THE EQUATION OF \( p \)-ADIC RANDOM WALK WITH A REACTION SINK

Formally, the kinetics of CO binding to myoglobin is described by a Cauchy problem of the form [10, 24]
\[
\begin{aligned}
\frac{\partial f(x, t)}{\partial t} &= -\tau^{-1}D^\alpha f(x, t) - \lambda \Omega((|x|_p)f(x, t), \\
f(x, 0) &= N_r|x|^{-\beta}_p(\Omega(|x|_p^{-\tau}) - \Omega(|x|_p)).
\end{aligned}
\] (12)
Here \( \alpha > 1, \beta > 1, \tau > 0, \lambda > 0, \) and \( D^\alpha \) is the Vladimirov pseudodifferential operator [20]
\[
D^\alpha \varphi(x) = \frac{1}{\Gamma_p(-\alpha)} \int_{Q_p} \frac{\varphi(y) - \varphi(x)}{|x - y|_p^{\alpha+1}} dy,
\]
\[
\Gamma_p(-\alpha) = \frac{1 - p^{-\alpha - 1}}{1 - p^2}
\]
is a \( p \)-adic analog of the gamma function, and the function \( \Omega(\xi) \) is defined as
\[
\Omega(\xi) = \begin{cases} 
1, & \xi \leq 1, \\
0, & \xi > 1.
\end{cases}
\]
In addition, \( N_r = \left( \frac{p}{p - 1} \right) \frac{p^{\beta - 1} - 1}{1 - p^{-(\beta - 1)r}} \) in (12) is the normalization factor, which is determined by the requirement
\[
\int f(x, 0) dx = 1.
\]
The Vladimirov operator \( D^\alpha \)
is defined on the class of functions \( W^\alpha \), \( 0 \leq \alpha < \beta \) (i.e., on complex-valued functions \( \varphi(x) \) on \( Q_p \) that satisfy the following conditions: (1) \( |\varphi(x)| \leq C (1 + |x|_p) \), \( C \in \mathbb{R}_+ \), and (2) there exists an \( l(\varphi) \in \mathbb{N} \) such that, for any \( x \in Q_p \) and any \( x' \in Q_p \), \( |x'|_p \leq p^l \), the equality \( \varphi(x + x') = \varphi(x) \) holds.

The physical meaning of the Cauchy problem (12) is quite transparent. The function \( f(x, t) \) is the concentration, normalized to unity, of protein molecules unbound to CO that are in the conformational state parameterized by a point \( x \in Q_p \) at time \( t \). We can see from the scheme of CO rebinding to myoglobin that, after photodissociation, the protein passes to the state \( Mb^* \), which is described by the initial condition of the Cauchy problem. Note that, based on the available experimental data, we can say nothing about the actual distribution of protein molecules over conformational states immediately after photodissociation; hence, this distribution can only be a model distribution. The domain of conformational states \( Mb_1 \) in which the reaction of CO molecule binding to protein takes place is mathematically described by a domain \( \mathbb{Z}_p \subset Q_p \) containing the reaction sink. This sink corresponds to the term \(-\lambda \Omega(|x|_p)f(x, t)\) in Eq. (12) and describes a decrease in the concentration of unbound proteins due to their binding to CO. The conformational transitions \( Mb^* \rightarrow ... \rightarrow Mb_1 \) are described by the term with the Vladimirov pseudodifferential operator in Eq. (12), which is responsible for the ultrametric diffusion of protein through conformational states. In Eq. (12), the parameter \( \tau \) defines the time scale \( t \), the parameter \( \alpha \) is related to temperature by formula (9), the parameter \( \lambda \) is the rate of CO binding to myoglobin in unit time, and the parameter \( \beta \) characterizes the initial distribution of unbound myoglobin over conformations.

To match the model with experiment, we impose the requirements \( \alpha > 1 \) and \( \beta > 1 \). In theoretical calculations, we set \( \tau = 1 \); thus, \( \lambda, \tau, t, \) and \( f \) are dimensionless parameters.

**Theorem 1.** A solution of the Cauchy problem (12) in the class of \( f(x, t) \in W^\alpha \cap L^1(Q_p, dx) \cap C^1(\mathbb{R}_+) \) exists and is unique.

**Proof.** The Cauchy problem (12) in terms of Fourier transforms has the form
\[
\begin{aligned}
\frac{\partial \hat{f}(k, t)}{\partial t} &= -|k|^\alpha p \hat{f}(k, t) - \lambda \int_{Q_p} \Omega(|k - q|_p) \hat{f}(q, t) dq, \\
\hat{f}(k, 0) &= N_r \left( \frac{1 - p^{-\alpha - 1}}{p^{\beta - 1} - 1} \left( \Omega(|k|_p) - \Omega(|k|_p^{-\beta}) \right) - \frac{1 - p^{-\beta}}{p^{\beta - 1} - 1} \left( \Omega(|k|_p) - \Omega(|k|_p^{-\beta}) \right) \right),
\end{aligned}
\] (13)
If $|k|_p > 1$, then $\hat{f}(k,t) \equiv 0$; this follows from the Fourier transform of the initial condition $\hat{f}(k,0) = 0$, $|k|_p > 1$. If $|k|_p \leq 1$, then we have

$$\frac{\partial}{\partial t} \tilde{f}(k,t) = -|k|_p^{\alpha} \tilde{f}(k,t) - \lambda \int_{Z_p} \tilde{f}(q,t) dq.$$  \hspace{1cm} (14)$$

Let us show that there exists a Laplace transform for the function $\tilde{f}(k,t)$. In view of the inequality

$$|\tilde{f}(k,t)| \leq \int_{Q_p} |f(x,t)| dx < \infty,$$

the function $\tilde{f}(k,t)$ is bounded on $\mathbb{Z}_p$; moreover, it is continuous with respect to the variable $k$. With respect to the variable $t \in \mathbb{R}_+$, the function $\tilde{f}(k,t)$ is continuous and differentiable. Let us integrate Eq. (14) over $\mathbb{Z}_p$. Then we have

$$\frac{\partial}{\partial t} \int_{Z_p} \tilde{f}(k,t) dk = -|k|_p^{\alpha} \tilde{f}(k,t) dk - \lambda \int_{Z_p} \tilde{f}(q,t) dq,$$

which implies

$$\left| \frac{\partial}{\partial t} \int_{Z_p} \tilde{f}(k,t) dk \right| = \left| \int_{Z_p} |k|_p^{\alpha} \tilde{f}(k,t) dk + \lambda \int_{Z_p} \tilde{f}(q,t) dq \right| \leq \left| \int_{Z_p} |k|_p^{\alpha} \tilde{f}(k,t) dk \right| + |\lambda| \left| \int_{Z_p} \tilde{f}(q,t) dq \right| .$$

Denoting $S_{Z_p}(t) = \int_{Z_p} \tilde{f}(k,t) dk$, we write

$$\left| \frac{\partial}{\partial t} S_{Z_p}(t) \right| \leq |(1 + \lambda) S_{Z_p}(t)| \text{ or } -(1 + \lambda) dt \leq \frac{dS_{Z_p}(t)}{S_{Z_p}(t)} \leq (1 + \lambda) dt,$$

whence we obtain $S_{Z_p}(t) \leq A \exp[(1 + \lambda) t]$ for some $A$. From the last inequality we obtain $\int_{Z_p} \tilde{f}(k,t) dk \leq A \exp[(1 + \lambda) t]$, which implies that $\tilde{f}(k,t) \leq M \exp[s_0 t]$. This upper bound of the function $\tilde{f}(k,t)$ proves that, for this function, there exists a Laplace transform, which we denote by $\tilde{F}(k,s)$.

In terms of $\tilde{F}(k,s)$, the Cauchy problem (12) is rewritten as

$$s \tilde{F}(k,s) = \tilde{f}(k,0) - |k|_p^{\alpha} \tilde{F}(k,s) - \lambda \int_{Z_p} \tilde{F}(q,s) dq,$$

whence we have

$$\tilde{F}(k,s) = \frac{\tilde{f}(k,0)}{s + |k|_p^{\alpha}} - \frac{\lambda}{s + |k|_p^{\alpha}} G(s),$$  \hspace{1cm} (15)$$

where

$$G(s) = \int_{Z_p} \tilde{F}(q,s) dq.$$  \hspace{1cm} (16)$$

Integrating (15) with respect to $k \in \mathbb{Z}_p$, we obtain

$$G(s) = \int_{Z_p} \tilde{F}(q,s) dq.$$  \hspace{1cm} (17)$$

The calculation of the integrals in (17) yields

$$G(s) = \frac{J(s) + h_r(s) - H_r(s)}{1 + \lambda J(s)},$$  \hspace{1cm} (18)$$

where

$$J(s) = (1 - p^{-1}) \sum_{n=0}^{\infty} \frac{p^{-n}}{s + p^{-\alpha n}},$$

$$h_r(s) = \frac{p^{-(\beta-1)r}}{1 - p^{-(\beta-1)r}} \sum_{n=0}^{r-1} \frac{p^{-n}}{s + p^{-\alpha n}},$$

$$H_r(s) = \frac{1}{1 - p^{-(\beta-1)r}} \sum_{n=0}^{r-1} \frac{p^{-\beta n}}{s + p^{-\alpha n}}.$$
this function on the extended complex plane. To this
end, we define it at removable points \( s = -p^{-\alpha k} \), \( k = 0, 1, 2, \ldots \), where it is not defined but has finite limits
\[
\lim_{s \to -p^{-\alpha k}} G(s) = \frac{1}{\lambda} \left( 1 + \frac{p^{-\alpha k}}{1 - p^{-\alpha k}} - \frac{1 - p^{-\beta}}{1 - p^{-\alpha k}} p^{-(\beta - 1)k} \right)
\]
for \( k \leq r - 1 \) and
\[
\lim_{s \to -p^{-\alpha k}} G(s) = \frac{1}{\lambda}
\]
for \( k > r - 1 \). Then the function \( G(s) \) is holomorphic on the entire extended complex plane except for the points \( s = -\lambda_k \), \( k = -1, 0, 1, 2, \ldots \), where it has simple poles determined from the equation
\[
1 + \lambda J(s) = 0.
\] (19)
It is easily seen that the values \( \lambda_k \) satisfy the inequality
\[
p^{-\alpha(k+1)} < \lambda_k < p^{-\alpha k}, \quad k = 0, 1, 2, \ldots, \lambda_{-1} > 1.
\]

The function \( G(s) \) is not meromorphic since \( s = 0 \) is an essentially singular point at which the poles are condensed. Notice that \( \lim_{s \to 0, \text{Res}_s} G(s) = \frac{1}{\lambda} \) and \( \lim_{s \to \infty} G(s) = 0 \) uniformly with respect to \( \arg s \). Let us change the variable: \( s \to z = \frac{1}{s} \). Then the auxiliary function \( G \left( \frac{1}{z} \right) = \Phi(z) \) is meromorphic; moreover,
\[
\lim_{z \to \infty} \Phi(z) = \frac{1}{\lambda} \quad \text{and} \quad \lim_{z \to 0} \Phi(z) = 0.
\]
Since \( |\Phi(z)| \leq A|z|^n \) for \( z \to \infty \), Mittag–Leffler’s simple pole expansion theorem implies that \( \Phi(z) \) can be represented as a uniformly convergent (except for a countable number of simple poles) series \( \Phi(z) = \sum_{k=-1}^{\infty} \frac{a_k}{z + \lambda_k} \). Thus, the function
\[
G(s) = \Phi \left( \frac{1}{s} \right)
\]
can also be represented as a uniformly convergent series
\[
G(s) = \sum_{k=-1}^{\infty} \frac{b_k}{s + \lambda_k},
\] (20)
where \( b_k \) are the residues of the function \( G(s) \) at the poles \( s = -\lambda_k \), given by
\[
b_k = \text{Res}_s G(s) = \frac{1}{\lambda^2 |J'(-\lambda_k)|} + \frac{h_r (-\lambda_k) - H_r (-\lambda_k)}{-\lambda |J'(-\lambda_k)|}.
\] (21)

Thus, the solution in terms of Fourier transforms has the form
\[
\hat{f}(k, t) = \hat{f}(k, 0) \exp \left( -|k|_p^\alpha t \right) -
\]
\[
\lambda \exp \left( -|k|_p^\alpha t \right) \sum_{n=-1}^{\infty} \frac{b_n}{\lambda_n - |k|_p^\alpha} \left( 1 - \exp \left[ - \left( \lambda_n - |k|_p^\alpha \right) t \right] \right).
\] (22)

We can show by direct substitution of Eq. (22) into Eq. (13) that this solution is a solution of the Cauchy problem in terms of Fourier transforms. Similarly we can show that the function
\[
f(x, t) = \int_{Q_p} \hat{f}(k, t) \chi(-kx) \, dx
\]
satisfies Eq. (12), i.e., that a solution exists. The coefficients \( b_n \) are determined uniquely for a given initial condition; this implies the uniqueness of the solution. The theorem is proved.

V. ANALYSIS OF THE SOLUTIONS AND RELATION TO EXPERIMENT

The concentration \( S(t) \) of myoglobin molecules that are not bound to CO at time \( t \) is
\[
S(t) = \int_{Q_p} f(x, t) \, dx.
\]

If we integrate Eq. (12) with respect to \( Q_p \), we arrive at the equation
\[
\frac{\partial S(t)}{\partial t} = -\lambda S_{Z_p}(t),
\] (23)

where
\[
S_{Z_p}(t) = \int_{Z_p} f(x, t) \, dx.
\]
is the concentration of proteins in the conformational states \( Mb_1 \) and \( \lambda \) is the rate of CO binding to myoglobin. The function \( S_{Z_p}(t) \) is the Laplace transform of the meromorphic function \( G(s) \); it can be represented as an infinite series:
\[
S_{Z_p}(t) = \sum_{k=-1}^{\infty} b_k \exp(-\lambda_k t) \neq G(s) = \sum_{k=-1}^{\infty} \frac{b_k}{s + \lambda_k},
\] (24)
where \( \lambda_k \) and \( b_k \) are, respectively, the poles and residues of \( G(s) \). Then, taking into account that \( G(0) = \frac{1}{\lambda} \), from Eq. (23) and (24) we obtain
\[
S(t) = \lambda \sum_{k=-1}^{\infty} \frac{b_k}{\lambda_k} \exp(-\lambda_k t).
\] (25)
Let us represent (25) as

\[ S(t) = \sum_{k=0}^{\infty} b_k \exp(-\lambda_k t), \]

where

\[ \tilde{S}(t) = \sum_{k=0}^{\infty} b_k \exp(-\lambda_k t). \]  

Taking into account (A7) and (B6)–(B12), we write

\[ S_1(t) < \tilde{S}(t) < S_2(t), \]

where \( S_1(t) \) and \( S_2(t) \) have the following structure:

\[
S_1(t) = A_1 \sum_{k=0}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t) + B_1 \sum_{k=0}^{r-1} p^{-(\beta-1)k} \exp(-p^{-\alpha} t) + C_1 \left( p^{(\alpha-\beta)r} - 1 \right) \sum_{k=r}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t)
\]

\[
- D_1 p^{-(\beta-1)r} \sum_{k=0}^{r-1} p^{-(\beta-1)k} \exp(-p^{-\alpha} t) - E_1 \left( p^{(\alpha-1)r} - 1 \right) \sum_{k=r}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t), \]

\[
S_2(t) = A_2 \sum_{k=0}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t) + B_2 \sum_{k=0}^{r-1} p^{-(\beta-1)k} \exp(-p^{-\alpha} t) + C_2 p^{\alpha r} \left( 1 - p^{-\beta r} \right) \sum_{k=r}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t)
\]

\[
- D_2 p^{-(\beta-1)r} \sum_{k=0}^{r-1} p^{-(\beta-1)k} \exp(-p^{-\alpha} t) - E_2 p^{\alpha r} \sum_{k=r}^{\infty} p^{-(\alpha-1)k} \exp(-p^{-\alpha} t). \]

In (27) and (28), the coefficients \( A_i, B_i, C_i, D_i, \) and \( E_i \) depend only on the parameters \( \lambda, \alpha, \) and \( \beta \), and their explicit form is unimportant for our further analysis.

Let us find asymptotic estimates for (27) and (28) in the high-temperature and low-temperature regimes. In our model, we assume that all values of the temperature parameter \( \alpha \) that satisfy the following condition correspond to the high-temperature region:

\[ \alpha_1 \beta. \]

Accordingly, the low-temperature region is described by the inequality

\[ \alpha > \beta. \]

In the high-temperature region (29), we can consider two cases. In case 1, we deal with large observation times such that \( t \gg p^{\beta r} \). In case 2, we deal with intermediate observation times such that \( 1 \ll t \ll p^{\beta r} \).

Consider case 1 and find the asymptotic behavior of (27) and (28) for a fixed \( r \) as \( t \to \infty \). Using Theorem 1 in Appendix C, we find that the main contribution to the asymptotic behavior of (27) and (28) is given only by the sums multiplying the coefficients \( A_i, C_i, \) and \( E_i \), which have the following asymptotic estimates as \( t \to \infty \):

\[ S_1(t) > a_1 t^{-\alpha-1} \frac{1}{\alpha} (1 + \omega(t)), \]

\[ S_2(t) < a_2 t^{-\alpha-1} \frac{1}{\alpha} (1 + \omega(t)), \]

where \( a_i \) are some coefficients independent of \( t \) and the symbol \( \omega(t) \) denotes functions, not explicitly shown, that are infinitesimal as \( t \to \infty \).

In case 2, we should consider the behavior of (27) and (28) as \( t \to \infty \) and \( r \to \infty \) under the condition that \( p^{-\beta r} t \to 0 \). In this case, the terms with coefficients \( C_i, D_i, \) and \( E_i \) do not contribute in the limit as \( r \to \infty \).

From Theorems 1 and 2 in Appendix C, for the sums multiplying the coefficients \( A_i \) and \( B_i \), respectively, we find that, for \( \alpha < \beta \), a contribution to the asymptotic
estimates \( S_1 (t) \) and \( S_2 (t) \) is made only by the sums multiplying the coefficients \( A_i \). In this case, we again obtain asymptotic estimates in the form \( S_1 \) and \( S_2 \) but with different coefficients \( a_i \).

Thus, for \( \alpha < \beta \), we obtain estimates \( \alpha \) and \( \beta \) both for intermediate observation times \( (1 \ll t \ll p^{3r}) \) and for large observation times \( (t \gg p^{3r}) \); these estimates completely agree with formula \( \beta \), which approximates the experimental dependence in the high-temperature region \( (T \sim 190 – 300 \, \text{K}) \) region:

\[
S (t) = \frac{1}{1 + \left( \frac{t}{1} \right)^{1 - \frac{\alpha}{\beta}}} \sim \left( \frac{t}{\tau_1} \right)^{\frac{\alpha - 1}{\alpha}}. \tag{33}
\]

This means that the behavior of \( S (t) \) in the high-temperature region is universal and does not depend on the observation time window. Our result shows that the behavior of \( S (t) \) is independent of the form of the initial condition, i.e., of the parameter \( \beta \), which parameterizes the density of the distribution function of proteins over conformations after photodissociation. This is explained by the fact that the random walk at high temperatures is rather intense. Hence, within relatively small times compared with the observation time \( (10^2 \, \text{s}) \), the concentration of unbound molecules, first, is uniformly distributed over the domain \( B \), and then is distributed over \( Q_p \setminus B \). It is the random walk over the domain \( Q_p \setminus B \), which is sufficiently far from the domain \( Z_p \), and contains the sink, that determines the law \( \beta \). The anomalous dependence of the binding reaction rate on temperature (i.e., the increase in \( \frac{dS (t)}{dt} \) with decreasing temperature) is explained equally easily. Indeed, the higher the temperature, the further the random trajectory from the support of the initial distribution in the space \( Q_p \), and the more time it takes to reach the sink region.

In the low-temperature region, we have \( \alpha \). Here we can also consider two cases: case 1 – large observation times \( (\text{or } t \gg p^{3r}) \) and case 2 – intermediate observation times \( (1 \ll t \ll p^{3r}) \).

In case 1, repeating precisely the arguments for case 1 in the high-temperature region \( \alpha \), we obtain the same result \( \alpha \) and \( \beta \) from \( \alpha \) and \( \beta \). Nevertheless, the result in case 2 will be different. It is this case that corresponds to observation times of \( 10^{-7} \div 10^2 \, \text{s} \) in the experiment at low temperatures \( (T \sim 60 – 180 \, \text{K}) \). Indeed, consider \( \alpha \) and \( \beta \) as \( t \to \infty, \, r \to \infty \) under the condition \( p^{3r} t \to 0 \). In this case, the terms with the coefficients \( C_i \), \( D_i \), and \( E_i \) do not contribute in the limit as \( r \to \infty \). Using Theorems 1 and 2 in Appendix C for the sums multiplying the coefficients \( A_i \) and \( B_i \), we find that, for \( \alpha > \beta \), only the sums multiplying the coefficients \( B_i \) contribute to the asymptotic estimates for \( S_1 (t) \) and \( S_2 (t) \). As a result, we obtain

\[
S_1 (t) > a_1 t^{\frac{\beta - 1}{\alpha}} (1 + \omega (t)), \tag{34}
\]

\[
S_2 (t) < a_2 t^{\frac{\beta - 1}{\alpha}} (1 + \omega (t)). \tag{35}
\]

We can see that, in the low-temperature region for intermediate observation times \( 1 \ll t \ll p^{3r} \), the asymptotic behavior of \( S (t) \) significantly depends on the parameter \( \beta \), which appears in the initial distribution. Note that \( \alpha \) and \( \beta \) agree with the approximating function \( \beta \) if we set \( \beta = 2 

\[
S (t) = \frac{1}{1 + \left( \frac{t}{\tau_2} \right)^{1 - \frac{\alpha}{\beta}}} \sim \left( \frac{t}{\tau_2} \right)^{\frac{\alpha - 1}{\alpha}}, \tag{36}
\]

VI. DISCUSSION

We have shown that the model considered reproduces the asymptotic behavior of functions approximating the dependence of the concentrations of unbound molecules in the experiments on CO binding to myoglobin. In spite of the fact that the functions approximating the experimental curves in the high-temperature \( (T \sim 190 – 300 \, \text{K}) \) and low-temperature \( (T \sim 60 – 180 \, \text{K}) \) regions have different forms, the time dependence of \( S (t) \) for unbound molecules is described in our model by a universal function in the entire range of temperatures from 60 K to 300 K.

The most important consequence of our description of the behavior of \( S (t) \) in the low-temperature region is that, upon the extension of the observation time window, the behavior of \( S (t) \) is changed. This follows from the fact that, for sufficiently large times \( t \) in the low-temperature region \( \alpha \), we pass to case 1 \( (t \gg p^{3r}, \text{see Section 6}) \). Therefore, for increasing observation times in the low-temperature region, the temperature dependence of \( S (t) \) should change, and, instead of the dependence \( \alpha \), we should observe the same dependence \( \beta \) as that for the high-temperature region. This is the main non-trivial prediction of our theory, which can immediately be checked in possible future experiments on CO binding to myoglobin in extended observation time windows of \( > 100 \, \text{s} \), which were not covered in the experiments of \( \alpha \).

An interesting question is that why precisely the choice of the initial condition in the form

\[
f (x, 0) \sim |x|^{-\beta} \left( \Omega \left(|x|p^{\beta t_r}\right) - \Omega (|x|) \right) \tag{37}
\]

leads to agreement with experiment for \( \beta = 2 \) in the low-temperature region.

The experiments carried out do not allow us to make any conclusions about the distribution of unbound protein molecules over conformational states immediately after photodissociation. It is known that, before the experiment, the test sample was kept for a rather long time.
at a certain temperature ($T \sim 300$ K). In this case, the equilibrium is reached in the protein ensemble. After that, at time $t_0$, the temperature is reduced to some value $T_1 < T$. Starting from time $t_0$ until the time of photodissociation $t_1$, the protein ensemble does not yet have time to completely reach the equilibrium state. At time $t_2$ after photodissociation (the interval $t_2 - t_1$ is the same for all experiments with different temperatures $T_1$), the concentration of unbound protein molecules is measured. The initial condition (37) is the distribution of unbound protein molecules at time $t_2$. Naturally, it is impossible to explain the origin of this initial condition within the present model. Nevertheless, we can go beyond the model and try to imagine some hypothetical scenario that would justify to some extent the choice of the initial condition (37).

We can assume that, by the time $t_0$ when the temperature is reduced to $T_1$, the nonequilibrium distribution of protein over conformational states is described by the distribution function with support in the neighborhood of $Z_p$. Suppose also that the variation of the distribution function is described by the equation of $p$-adic random walk

$$\frac{\partial f(x,t)}{\partial t} = -r^{-1}D^\alpha f(x,t)$$

and that photodissociation hardly changes the distribution of proteins over conformational states. In this case, the distribution of unbound molecules at time $t_2$ should be a solution of the Cauchy problem for the given equation with the initial condition on a compact set. It is known that the solution of this Cauchy problem is estimated by a function $\frac{C}{|x|^{\alpha + 1}}t$ as $\frac{t}{|x|^\alpha} \to 0$ (see, for example, [21, 25]). If $t = t_2 - t_0$ is time passed from the beginning of cooling of the sample to temperature $T_1$ to the moment of observation, then, for small $t$, the main part of molecules are located near $Z_p$ and are rapidly bound to CO molecules. The remaining small part of protein molecules that are not bound to CO, which are the object of observation in the experiment, are distributed with respect to $Q_p$ by the law $\frac{Ct_2}{|x|^{\alpha + 1}}$, where $\alpha = \frac{T_0}{T}$ is a temperature parameter (see [19]). The value $T_0$ of the temperature scale corresponds to the maximum temperature of the experiments, which coincides with the preparation temperature of the samples $T_0 \sim 300$ K. For $T_0 = 300$ K, the value of $T = 300$ K corresponds to the value $\alpha = 1$. Therefore, the initial distribution should have the form $\sim |x|^{-2}$, which means $\beta = 2$.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and its supplementary material. All other relevant source data are available from the corresponding author upon reasonable request.

Appendix A: Estimate of $\lambda_k$.

Taking into account that $\lim_{\lambda \to 0} \lambda_k = p^{-\alpha(k+1)}$, it is convenient to use the following representation for $\lambda_k$:

$$\lambda_k = p^{-\alpha(k+1)} + p^{-\alpha k} (1 - p^{-\alpha}) \delta_k.$$  \hfill (A1)

From the graphical solution of the equation $1 + \lambda J(s) = 0$, we can show that $0 < \delta_k < 1$. Then (A1) implies the following estimate for $\lambda_k$:

$$p^{-\alpha k} - p^{-\alpha} < \lambda_k < p^{-\alpha k}.$$  \hfill (A2)

The data supporting the findings of this study are available within the article and its supplementary material. All other relevant source data are available from the corresponding author upon reasonable request.

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which also follows from (A3). From (A5) we obtain
\[ d\delta_k^2 = (1 + b_\alpha + d_k) \delta_k + 1 < 0, \] (A6)
where \( d_k = \frac{p^2}{p-1} \frac{p^\alpha - 1}{p^\alpha} \frac{1 - (\alpha - 1)k}{\lambda} \) and \( b_\alpha = \frac{p^\alpha}{p^\alpha} - 1 \).
Solving (A6) and performing straightforward transformations, we obtain
\[ \delta_k < \frac{1 - p^{-\alpha+1}}{1 + p}. \]
Finally, we write
\[ 1 - p^{-\alpha+1} = \delta_{\text{min}} < \delta_k < \delta_{\text{max}} = p^{-1}. \] (A7)

**Appendix B: Estimate of \( b_k \).**

Let us rewrite formula (21) as
\[ b_k = b_k^{(1)} + b_k^{(2)} - b_k^{(3)}, \]
where
\[ b_k^{(1)} = \frac{\lambda^{-2}}{P(\lambda_k)}, \]
\[ b_k^{(2)} = \frac{1 - p^{-\beta}}{1 - p^{-\beta(1)+1}r} \frac{R(\lambda_k, \alpha, \beta, r)}{P(\lambda_k)}, \]
\[ b_k^{(3)} = \frac{1 - p^{-\beta}}{1 - p^{-\beta(1)+1}r} \frac{R(\lambda_k, \alpha, 1, r)}{P(\lambda_k)}, \]
\[ P(\lambda_k, \alpha, \beta, r) = \sum_{n=0}^{r-1} \frac{p^{-\beta n}}{\lambda_k - p^{-\alpha n}}. \]

Using the inequalities
\[ \sum_{n=0}^{\infty} \frac{p^{-n}}{(p^{-\alpha n} - \lambda_k)^2} > \frac{1}{(1 - p^{-\alpha})^2 \delta_k^2}, \]
\[ \sum_{n=0}^{\infty} \frac{p^{-n}}{(p^{-\alpha n} - \lambda_k)^2} < \sum_{n=0}^{k} \frac{p^{-n}}{(p^{-\alpha n} - \lambda_{n-1})^2} + \sum_{n=k+2}^{\infty} \frac{p^{-n}}{(p^{-\alpha n} - \lambda_k)^2} \]
\[ < \frac{p^{(2\alpha - 1)k}}{(1 - p^{-\alpha})^2 \delta_k^2} \frac{1}{p(1 - p^{-\alpha})^2 \delta_k^2} \frac{p^{2\alpha - 1} - 1}{p^{2\alpha - 1} - 1} \]
and, taking into account (A7), we can obtain the following structure of the upper and lower bounds for \( P(\lambda_k, \alpha) \):
\[ U_1 p^{(2\alpha - 1)k} < P(\lambda_k, \alpha) < U_2 p^{(2\alpha - 1)k} \] (B1)
where the coefficients \( U_i \) are independent of \( k \).
To find the structure of the estimates \( R(\lambda_k, \alpha, \beta, r) \) for \( k \ll r - 1 \), it is convenient to single out the term with \( n = k \) in the sum:
\[ R(\lambda_k, \alpha, \beta, r) = \sum_{n=0}^{k-1} \frac{p^{-\beta n}}{p^{-\alpha n} - \lambda_k} \]
\[ < \sum_{n=0}^{k-1} \frac{p^{(\alpha - \beta)n}}{(1 - p^{-\alpha})(1 - \delta_k)} + \frac{p^{(\alpha - \beta)k}}{(1 - p^{-\alpha})(1 - \delta_k)} \] (B2)
It follows from (B2) that
\[ R(\lambda_k, \alpha, \beta, r) < \sum_{n=0}^{k-1} \frac{p^{-\beta n}}{p^{-\alpha n} - \lambda_k} + \frac{p^{-\beta k}}{p^{-\alpha k} - \lambda_k} \]
where \( U_i \) are independent of \( k \).
for $k \leq r - 1$ and $\alpha < \beta$, and
\[
g^{(2)} \left( p^{(\alpha-\beta)r} - 1 \right) p^{-(2\alpha-1)k} < b^{(2)}_k
\]
\[
< h^{(2)} \left( 1 - p^{-\beta r} \right) p^{\alpha r} p^{-(2\alpha-1)k}
\]  \hspace{1cm} (B11)
\[
g^{(3)} \left( p^{(\alpha-\beta)r} - 1 \right) p^{-(2\alpha-1)k} < b^{(3)}_k
\]
\[
< h^{(1)} \left( 1 - p^{-\beta r} \right) p^{\alpha r} p^{-(2\alpha-1)k},
\]  \hspace{1cm} (B12)
for $k > r - 1$. The coefficients $g^{(i)}$, $h^{(i)}$, $i = 1, 2, 3$, are independent of $r$ and $k$, and their explicit form is unimportant for us.

**Appendix C: Asymptotic estimate of the series**

\[
S(t) = \sum_{n=0}^{\infty} a^{-n} \exp (-b^{-n}t) \quad \text{and} \quad S(t, r) = \sum_{n=0}^{\infty} a^{-n} \exp [-b^{-n}t]
\]

**Theorem 1.** Suppose a given series

\[
S(t) = \sum_{n=0}^{\infty} a^{-n} \exp (-b^{-n}t)
\]

with $a > 1$ and $b > 1$. Then, for any $0 < M < 1$, there exists a $T > 0$ such that the following inequalities hold for $t > T$:

\[
a^{-1} \frac{t^{-z}}{\ln b} \left( \Gamma (z) - (bt)^{z-1} \exp (-bt) \right) <
\]

\[
S(t) < a^{-1} \frac{t^{-z}}{\ln b} \left( \Gamma (z) - M t^{z-1} \exp (-t) \right),
\]  \hspace{1cm} (C1)

where $z = \frac{\log a}{\log b}$.

**Proof.** Since $a^{-x}$ is a monotonically decreasing function and $\exp (-b^{-x}t)$ is a monotonically increasing function, it follows that the following inequality holds for $x \in [n, n+1]$: 

\[
a^{-x} \exp \left[-b^{-x}t\right] \leq a^{-n} \exp \left[-b^{-n}t\right]
\]

\[
\leq a^{-\left(x-1\right)} \exp \left[-b^{-x}t\right].
\]  \hspace{1cm} (C2)

Integrating this inequality over the interval $[n, n+1]$ with respect to $x$ and then summing over $n$ from 0 to $\infty$, we obtain

\[
a^{-1} \int_{0}^{\infty} a^{-\left(x-1\right)} \exp \left[-b^{-x}t\right] \, dx \leq S(t)
\]
\[ \leq a \int_0^\infty a^{-x} \exp \left[ -b^{-x} t \right] dx. \quad \text{(C3)} \]

In the left and right integrals in (C3), we make the changes \( x \to y = b^{-(x-1)} t \) and \( x \to y = b^{-x} t \), respectively. Then we obtain

\[ \frac{a^{-1}}{\ln b} t^{-z} \gamma(z, bt) \leq S(t) \leq \frac{a}{\ln b} t^{-z} \gamma(z, t), \quad \text{(C4)} \]

where \( \gamma(z, x) = \int_0^x y^{z-1} \exp(-y) dy \) is the incomplete gamma function.

Using the asymptotic expansion of \( \gamma(z, t) \) as \( t \to \infty \),

\[ \gamma(z, t) = \Gamma(z) - t^{z-1} \exp(-t) \]

\[ - t^{z-1} \exp(-t) \left\{ \sum_{n=1}^{m-1} (-1)^n \frac{\Gamma(1 - z + n)}{t^n} \Gamma(1 - z) + O(t^{-m}) \right\}, \quad \text{(C5)} \]

We can write

\[ \gamma(z, t) = \Gamma(z) - Mt^{z-1} \exp(-t) - t^{z-1} \exp(-t) \left\{ \sum_{n=1}^{m-1} (-1)^n \frac{\Gamma(1 - z + n)}{t^n} \Gamma(1 - z) + O(t^{-m}) \right\}, \]

where \( 0 < M < 1 \) is an arbitrary number. For sufficiently large \( T \), the expression in the curly brackets \{ \cdots \} is positive for \( t > T \), and we can write

\[ \gamma(z, t) < \Gamma(z) - Mt^{z-1} \exp(-t). \quad \text{(C6)} \]

Completely analogously we can obtain

\[ \gamma(z, bt) > \Gamma(z) - t^{z-1} b^{z-1} \exp(-bt). \quad \text{(C7)} \]

\[ \frac{a^{-1}}{\ln b} t^{-z} \left( \Gamma(z) - \left( bt \right)^{z-1} \exp(-bt) - \left( b^{-r} t \right)^{\frac{1}{z}} \right) \leq S(t, r) \leq \frac{a}{\ln b} t^{-z} \left( \Gamma(z) - Mt^{z-1} \exp(-t) - N \left( b^{-r} t \right)^{\frac{b^{-z}}{b}} \right). \quad \text{(C8)} \]

**Proof.** Integrating inequality (C2) over the interval \([n, n+1]\) with respect to \( x \) and then summing over \( n \) from 0 to \( r \), we obtain

\[ a^{-1} \int_0^r a^{-(x-1)} \exp \left[ -b^{-(x-1)} t \right] dx \leq S(t, r) \leq a \int_0^r a^{-x} \exp \left[ -b^{-x} t \right] dx. \quad \text{(C9)} \]

Making the changes \( x \to y = b^{-(x-1)} t \) and \( x \to y = b^{-x} t \), respectively, in the left and right integrals in (C9)

\[ \frac{a^{-1}}{\ln b} t^{-z} \gamma(z, b^{-r} t, bt) \leq S(t, r) \leq \frac{a}{\ln b} t^{-z} \gamma(z, b^{-r-1} t, t), \quad \text{(C10)} \]

and denoting \( z = \frac{\log a}{\log b} \), we obtain

\[ \frac{a^{-1}}{\ln b} t^{-z} \gamma(z, b^{-r} t, bt) \leq S(t, r) \leq \frac{a}{\ln b} t^{-z} \gamma(z, b^{-r-1} t, t), \quad \text{(C10)} \]
where \( \gamma(z, x_1, x_2) = \int_{x_1}^{x_2} y^{z-1} \exp(-y) \, dy = \gamma(z, x_2) - \gamma(z, x_1) \).

Consider

\[
\gamma(z, b^{r-1}t, t) = \gamma(z, t) - \gamma(z, b^{r-1}t). \tag{C11}
\]

It follows from (C6) and (C12) that

\[
\gamma(z, b^{r-1}t) \geq N \frac{b^z}{z} \left( \frac{t}{b^z} \right)^z. \tag{C12}
\]

Similarly we can prove that

\[
\gamma(z, b^{r-1}t, bt) \geq \Gamma(z) - \frac{n b^z}{z} \left( \frac{t}{b^z} \right)^z - \sum_{n=1}^{\infty} \frac{(1-N) b^z}{z+n} \left( \frac{t}{b^z} \right)^{z+n}.
\]

Inequalities (C13), (C14), and (C10) imply the assertion of Theorem 2.
Sherrington, D., 1997. Landscape paradigms in physics and biology: Introduction and overview. Physica D 107, 117-121. https://doi.org/10.1016/S0167-2789(97)00076-6.

Stillinger, F.H., Weber, T.A., 1982. Dynamics of structural transitions in liquids. Phys. Rev. A 25, 978-989. https://doi.org/10.1103/PhysRevA.25.978.

Stillinger, F.H., Weber, T.A., 1982. Hidden structure in liquids. Phys. Rev. A 25, 978-989. https://doi.org/10.1103/PhysRevA.25.978.

Stillinger, F.H., Weber, T.A., 1984. Packing structures and transitions in liquids. Phys. Rev. A 25, 2408-2416. https://doi.org/10.1103/PhysRevA.25.2408.

Stilinger, F.H., Weber, T.A., 1984. Packing structures and transitions in liquids and solids. Science 225, 983-989. https://doi.org/10.1126/science.225.4666.983.

Becker, O.M., Karplus, M., 1997. The topology of multidimensional protein energy surfaces: Theory and application peptide structure and kinetics. J. Chem. Phys. 106, 1495-1517. https://doi.org/10.1063/1.473299.

Dragovich, B., Kuremarkov, A.Yu., Kozyrev, S.V., Volovich, I.V., 2009. On p-adic mathematical physics, p-Adic Numbers, Ultrametric Analysis and Applications 1(1), 1-17. https://doi.org/10.1134/S2070046609010014.

Vladimirov, V.S., Volovich, I.V., Zelenov, E.I., 1994. p-Adic analysis and mathematical physics. World Sci. Publishing, Singapore.

Kochubei, A.N., 2001. Pseudodifferential equations and stochastics over non-Archimedean fields. New York: Marcel Dekker.

Schikhof, W.H., 1984. Ultrametric calculus. An Introduction to p-adic Analysis. Cambridge Studies in Advanced Mathematics. Cambridge University Press, Cambridge.

Avtiev, V.A., Bikulov, A.Kh., Kozyrev, S.V., 1999. Application of p-adic analysis to models of spontaneous breaking of replica symmetry. Journal of Physics A: Mathematical and General 32(50), 8785-8791. https://doi.org/10.1088/0305-4470/32/50/301.

Avtiev, V.A., Bikulov, A.Kh., Kozyrev, S.V., Osipov, V.A., 2002. p-Adic Models of ultrametric diffusion constrained by hierarchical energy landscapes. Journal of Physics A: Mathematical and General 35(2), 177-189. https://doi.org/10.1088/0305-4470/35/2/301.

Avtiev, V.A., Bikulov, A.Kh., Osipov, V.A., 2003. p-Adic description of characteristic relaxation in complex systems. Journal of Physics A: Mathematical and General 36(15), 4239-4246. https://doi.org/10.1088/0305-4470/36/15/301.

Avtiev, V.A., Bikulov, A.Kh., Osipov, V.A., 2004. p-Adic Models for ultrametric diffusion in conformational dynamics of macromolecules. Tr. Mat. Inst. Steklova 245, 55-64. http://mi.mathnet.ru/eng/tm/v245/p55.

Avtiev, V.A., Bikulov, A.Kh., 2008. Protein ultrametricity and spectral diffusion in deeply frozen proteins. Biophysical Reviews and Letters 3, 387-396. https://doi.org/10.1142/S1793480008000836.

Avtiev, V.A., Bikulov, A.Kh., Zubarev, A.P., 2009. First passage time distribution and number of returns for ultrametric random walk. Journal of Physics A: Mathematical and General 42(8), 85005-85021. https://doi.org/10.1088/1751-8113/42/8/085003.

Avtiev, V.A., Bikulov, A.Kh., Zubarev, A.P., 2011. Mathematical modeling of molecular “nano-machines”. Vestn. Samar. Gos. Tekhn. Univ. Ser. Fiz.-Mat. Nauki 1(22), 9-15. https://doi.org/10.14498/vsgtu906.

Avtiev, V.A., Bikulov, A.Kh., Zubarev, A.P., 2013. Ultrametricity as a basis for organization of protein molecules: CO binding to myoglobin. Vestn. Samar. Gos. Tekhn. Univ. Ser. Fiz.-Mat. Nauki, 1(30), 315-325. https://doi.org/10.14498/vsgtu1137.

Zhikov, A.A., Fisher, S.F., 1996. Scaling law of the non exponential liding of CO in myoglobin. Chem. Phys. Lett. 263, 749-758. https://doi.org/10.1016/0009-2614(96)01275-4.

Krupianskii, Yu.F., Gol’danskiii, V.I., 2002. Dynamical properties and energy landscape of simple globular proteins. Phys. Usp. 45, 1131-1151. https://doi.org/10.1070/PU2002v045n11ABEH001145.

Frauenfelder, H., 1987. The connection between low-temperature kinetics and life. In Protein Structure (pp. 245-261). Springer, New York, NY. https://doi.org/10.1007/978-1-4612-4796-8_15.

Ogelski, A.T., Stein, D.L., 1985. Dynamics on ultrametric spaces. Phys. Rev. Lett. 55(15), 1634-1637. https://doi.org/10.1103/PhysRevLett.55.1634.

Huberman, B.A., Kerszberg, M., 1988. Ultradiffusion: The relaxation of hierarchical systems. Journal of Physics A: Mathematical and General 21(6), L331-L336. https://doi.org/10.1088/0305-4470/18/6/013.

Zumofen, G., Blumen, A., Klafter, J., 1986. Reaction kinetics on ultrametric spaces. The Journal of chemical physics 84(12), 6679-6686. https://doi.org/10.1063/1.450721.

Kohler, G., Blumen, A., 1987. Subordination on ultrametric spaces. Journal of Physics A: Mathematical and General 20(16), 5627-5633. https://doi.org/10.1088/0305-4470/20/16/036.

De Dominicis, C., Schreckenberg, M., 1987. Diffusion in ultrametric spaces. In Heidelberg Colloquium on Glassy Dynamics (pp. 255-274). Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-62572-1.

Hoffmann, K.H., Sibani, P., 1988. Diffusion in hierarchies. Phys. Rev. A 38, 4261-4270. https://doi.org/10.1103/PhysRevA.38.4261.

Wales, D.J., Miller, M.A., Walsh, T.R., 1998. Archetypal energy landscapes. Nature 394, 758-760. https://doi.org/10.1038/29487.

Krivor, S.V., Karplus, M., 2001. Free energy disorder connectivity graphs: Application to peptide models. Journal of Chemical Physics 117, 10894-10903. https://doi.org/10.1070/PU2002v045n11ABEH001145.

Berry, R.S., 1993. Potential Surfaces and Dynamics: What Clusters Tell Us. Chem. Rev. 93, 2379-2394. https://doi.org/10.1021/cr00023a003.

Berry, R.S., Breitengraser-Kunz, R., 1995. Topography and dynamics of multidimensional interatomic potential surfaces. Physical review letters 74(20), 3951-3954. https://doi.org/10.1103/PhysRevLett.74.3951.

Gardiner, C.W., 1996. Handbook of Stochastic Methods: For Physics, Chemistry and the Natural Sciences. New York: Springer.

Kozyrev, S.V., 2011. Methods and applications of ultrametric and p-adic analysis: From wavelet theory to...
