

Oscillations in p -adic diffusion processes and simulation of the conformational dynamics of protein

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Abstract

Logarithmic oscillations superimposed on a power-law trend appear in the behavior of various complex hierarchical systems. In this paper, we study the logarithmic oscillations of relaxation curves in p -adic diffusion models that are used to describe the conformational dynamics of protein. We consider the case of a purely p -adic diffusion, as well as the case of p -adic diffusion with a reaction sink. We show that, relaxation curves for large times in these two cases are described by a power law on which logarithmic oscillations are superimposed whose period and amplitude are determined by the parameters of the model. We also provide a physical explanation of the emergence of oscillations in relaxation curves and discuss the relation of the results to the experiments on relaxation dynamics of protein.

Keywords: p -adic mathematical physics, p -adic diffusion, p -adic models of conformational dynamics, logarithmic oscillations

1 Introduction

If a dynamical variable $x(t)$ of a physical system behaves as

$$x(t) = At^{-\beta} f(\log t) \quad (1)$$

in some time domain, where $A, \beta \in \mathbb{R}$ and $f(y)$ is a periodic function, then it is said that logarithmic oscillations superimposed on a power-law trend occur in the system. In the early 1990s a number of authors (see, for example, [1, 2, 3, 4]) found that the time variation of the dynamical variables of some physical, chemical, and biological systems is described by a law similar to (1). In a series of papers devoted to the study of the dynamics of financial markets (see, for example, [5, 6, 7, 8] and references therein), the authors also found through the analysis of empirical data that the behavior of the logarithms of prices in financial markets before crashes also resembles a power law multiplied by a sum of log-periodic harmonics, where the presence of logarithmic oscillations is associated with the discrete scale invariance of the system [9, 10]. In the simplest case, this connection can be traced as follows. Consider a real function $x(t)$ of time t that describes a dynamical variable of the system. The discrete scale invariance of the function $x(t)$ implies that there exists a $\theta \in \mathbb{R}_+$ such that the following relation holds for some $\beta \in \mathbb{R}$:

$$x(t) = \theta^\beta x(\theta t). \quad (2)$$

The general solution of equation (2) is given by (1), where $f(y)$ is a periodic function with period $\log \theta$. If relation (2) holds asymptotically as $t \rightarrow \infty$ rather than exactly, then the law (1) also holds asymptotically.

The discrete scale invariance of a dynamical variable of a system implies a self-similar dynamics of the system at different time scales. Such a scenario can be realized for a hierarchical self-similar organization of the state space of the system. These systems include, in particular, systems whose state space is ultrametric. In [11] the authors argued that the relaxation of a system in the ultrametric space described by the boundary of a Bethe tree should lead to the dynamics of observables that can be represented as a sum of exponential functions of time t and this sum can be represented as the product of a power function of t multiplied by a periodic function of $\log t$.

In physics, the models of real systems in ultrametric spaces have first been considered in the 1970s in relation to the study of disordered spin systems (spin glasses) [12, 13, 14, 15]. Almost simultaneously with the appearance of ultrametric models of spin glasses, it was suggested that the space of conformational states of a protein molecule is ultrametric [16, 17]. A significant contribution to the development of ultrametric (and the related p -adic) description of complex systems of different nature, including protein, has been made in the last 30 years (for a review, see [18, 19, 20]). A detailed validation of the ultrametric approach to the simulation of the conformational dynamics of protein is given in a series of papers of the present authors [21, 22, 23, 24, 25, 26, 27, 28, 29, 30] and can be briefly summarized as follows (see [30] for more details). At a given temperature of the medium, protein executes thermal motion, which represents a random walk on the configuration space of the degrees of freedom of a macromolecule. To describe this random walk of protein within the Langevin or the Fokker–Planck approach, one should precisely define all degrees of freedom and the potential energy of protein, which is hardly possible. Therefore, one applies the following approximation to describe the conformational

dynamics of protein. The configuration space of protein is divided into subsets – elementary basins (attraction basins). Each such elementary basin is associated with a local minimum of the potential energy of protein and is defined as an open subset of points from which one can reach the local minimum by gradient descent (see [31, 32, 33] for details). On the set of elementary basins, one can introduce a distance function (a metric), which is defined for any two elementary basins in terms of the minimum potential barrier over all paths connecting the configuration minima of these basins. One can show that this metric is an ultrametric, and thus the set of elementary basins is an ultrametric space [34]. Elementary basins can be combined into sets, which are ultrametric balls, and these sets are also called basins. The conformational state of protein corresponding to a certain basin is a quasi-equilibrium macrostate in which a random walk of protein on a given basin with a distribution function close to the equilibrium distribution function in this basin is implemented. Thus, the set of conformational states associated with elementary basins is also an ultrametric space. One of simplifying assumptions is that this ultrametric space is homogeneous. This allows one to perform a p -adic parameterization of the space of conformational states of protein, i.e., to map this space to the field of p -adic numbers \mathbb{Q}_p (see [35] for the introduction to p -adic analysis). Namely, the set of all possible conformational states of protein corresponding to all possible basins is parameterized by a set of p -adic balls of radius greater than or equal to 1. In this case, 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 $\xi(t, \omega) : \mathbb{R} \times \Omega \rightarrow \mathbb{Q}_p$. The density of the distribution function $f(x, t)$ of such a process is assumed to be a locally constant function with radius of local constancy equal to one (i.e., for any x and x' , $|x'|_p \leq 1$, the equality $f(x) = f(x + x')$ holds, and this function is a solution of the equation of p -adic random walk (the Kolmogorov–Feller equation in the field of p -adic numbers),

$$\frac{\partial f(x, t)}{\partial t} = \int_{\mathbb{Q}_p} W(|x - y|_p) (f(y, t) - f(x, t)) dy, \quad (3)$$

in which the kernel $W(|x - y|_p)$ of the integral operator depends only on the ultrametric distance $|x - y|_p$ between points x and y . Equation (3) is assumed to be covariant under the scale transformations $x \rightarrow x' = \lambda x$ and $t \rightarrow t' = |\lambda|_p^\alpha t$, where $\lambda \in \mathbb{Q}_p$ is the transformation parameter and $\alpha \in \mathbb{R}_+$. The last assumption imposes a strong constraint on the choice of the kernel $W(|x - y|_p)$ of the integral operator in equation (3). Namely, under this condition, the kernel of the operator coincides up to a factor with the kernel of the Vladimirov operator [35]:

$$W(|x - y|_p) \sim \frac{1}{|x - y|_p^{\alpha+1}}. \quad (4)$$

In this case, equation (3) is conventionally called a p -adic diffusion equation, since the integral operator on its right-hand side is the operator of p -adic fractional differentiation of order α . The parameter α can be assigned a physical meaning if one sets $\alpha = \frac{E_0}{kT}$ and writes $\frac{1}{|x - y|_p^\alpha} = \exp\left(-\frac{E_0 \log(|x - y|_p)}{kT}\right)$, where T is temperature, k is the Boltzmann constant, and E_0 is a parameter with the dimension of energy. The last expression is interpreted as a Boltzmann

factor defining the probability that the system overcomes the potential barrier

$$E(x, y) = E_0 \log |x - y|_p \quad (5)$$

between two conformations containing the points x and y , respectively. In this case, the additional factor $\frac{1}{|x - y|_p}$ in (4) is inversely proportional to the combinatorial factor equal to the number of conformations separated by the potential barrier (5) from the conformation containing the point x .

Despite the apparent simplicity, the p -adic model of conformational dynamics of protein provided a relevant description of two main experiments on the relaxation dynamics of protein. Namely, in [25, 29, 36] we showed that the relaxation curves of spectral diffusion experiments [37, 38, 39] can be described within the p -adic diffusion model. In [22], we showed that the relaxation curves of experiments on the kinetics of CO binding to myoglobin [40, 41] at high temperatures can be described by the model of p -adic diffusion with a reaction sink. Later, in [28, 29, 30], we obtained these results for the entire temperature range.

A characteristic feature of relaxation curves in p -adic models of conformational dynamics of protein is the fact that, at large times, they can take the form of a power law on which oscillations are superimposed. Numerical investigations of the solutions of the p -adic diffusion equation on compact subsets of the set \mathbb{Q}_p have shown that the period of these oscillations increases with time and their amplitude increases with a decrease in temperature (i.e., with an increase in the parameter α). Nevertheless, a detailed analytical investigation of these oscillations in the models of p -adic diffusion has not been carried out yet. In the present paper, we eliminate this gap. Namely, we analyze in detail these oscillations in two cases: in the case of purely p -adic diffusion and in the case of p -adic diffusion with a reaction sink. We show that, in these cases, the relaxation curves at large times are described by a power law on which logarithmic oscillations are superimposed whose period and amplitude are determined by the parameters p and α .

The paper is organized as follows. In Section 2 we study the oscillations of the probability measure of the support of the initial distribution of the solution to the Cauchy problem for a p -adic diffusion equation with the initial condition on a compact set. In Section 3 we analyze the oscillations of the probability measure of the whole \mathbb{Q}_p for the solution of the Cauchy problem for the equation of p -adic diffusion with a reaction sink and with the initial condition on a compact set. In the concluding section we provide a physical explanation for the emergence of oscillations on relaxation curves and discuss the relation of the results obtained to the experiments on the relaxation dynamics of protein. The proofs of a number of propositions necessary for Sections 2 and 3 are given in Appendices 1 – 3.

2 Oscillations in the solution of the p -adic diffusion equation

The p -adic diffusion equation (see [35]) has the form

$$\frac{df(x, t)}{dt} = -\frac{1}{\Gamma_p(-\alpha)} \int_{\mathbb{Q}_p} d_p y \frac{f(y, t) - f(x, t)}{|x - y|_p^{\alpha+1}}. \quad (6)$$

where $\Gamma_p(-\alpha) = \frac{1 - p^{-\alpha-1}}{1 - p^\alpha}$ is the p -adic gamma function. We consider the Cauchy problem for equation (6) with the initial condition on some compact set chosen in the form of a ring of p -adic integers \mathbb{Z}_p :

$$f(x, 0) = \Omega(|x|_p). \quad (7)$$

In physical applications, equation (6) describes a random walk on \mathbb{Q}_p , and $f(x, t)$ is the density of the distribution function of the trajectory at time t . Of special interest is to find the so-called function of survival probability $S_{\mathbb{Z}_p}(t) \equiv \int_{\mathbb{Q}_p} d_p x \Omega(|x|_p) f(x, t)$, which is the probability measure of the support of the initial distribution at time t .

One can analyze the Cauchy problem (6)–(7) numerically by replacing the integration domain \mathbb{Q}_p by a p -adic ball $B_r = \{x : |x|_p \leq p^r\}$. In this case, equation (6) is equivalent to a system of $r + 1$ linear differential equations. Figure 1 demonstrates the graphs of the function $S_{\mathbb{Z}_p}(t)$ in a double logarithmic scale for the following values of the parameters: $p = 2$, $r = 20$, and $\alpha = 3, 5, 10$. One can see that at large times the curves represent a power-law function on which oscillations are superimposed; as α increases, the period and amplitude of the oscillations increase.

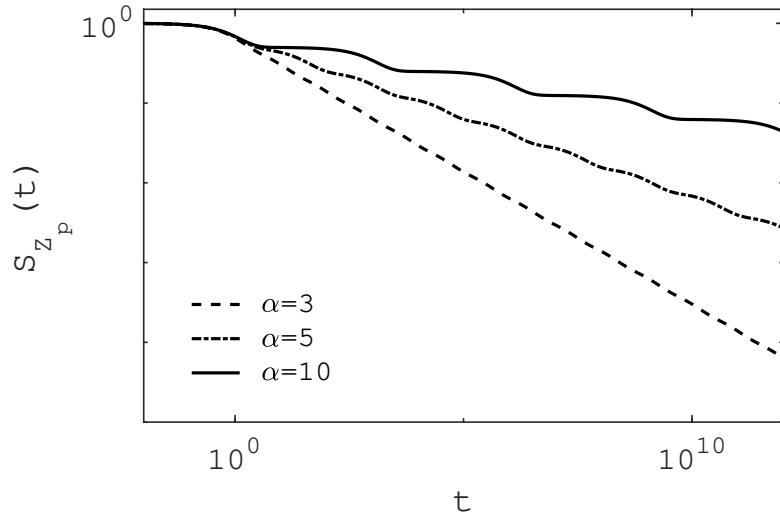


Figure 1: Graph of the survival probability $S_{\mathbb{Z}_p}(t) \equiv \int_{\mathbb{Z}_p} d_p x f(x, t)$, where $f(x, t)$ is the numerical solution of equation (6) on the compact set B_r with the initial condition (7) for $p = 2$ and $r = 20$.

Analytically, the solution of the Cauchy problem (6) – (7) is represented as (see, for example, [22]):

$$f(x, t) = \Omega(|x|_p) (1 - p^{-1}) \sum_{i=0}^{\infty} p^{-i} \exp(-p^{-\alpha i} t) + (1 - \Omega(|x|_p)) |x|_p^{-1} \left((1 - p^{-1}) \sum_{i=0}^{\infty} p^{-i} \exp(-p^{-\alpha i} |x|_p^{-\alpha} t) - \exp(-p^\alpha |x|_p^{-\alpha} t) \right). \quad (8)$$

In this case, the survival probability is

$$S_{\mathbb{Z}_p}(t) = f(x, t)|_{|x|_p \leq 1} = (1 - p^{-1}) \sum_{i=0}^{\infty} p^{-i} \exp(-p^{-\alpha i} t). \quad (9)$$

It follows from the form of the solution (9) that

$$S_{\mathbb{Z}_p}(p^\alpha t) = p^{-1} S_{\mathbb{Z}_p}(t) + (1 - p^{-1}) \exp(-p^\alpha t). \quad (10)$$

Since $\exp(-p^\alpha t)$ decreases as $t \rightarrow \infty$ faster than (9), relation (10) implies the asymptotic discrete scale invariance of the function $S_{\mathbb{Z}_p}(t)$:

$$p S_{\mathbb{Z}_p}(p^\alpha t) = S_{\mathbb{Z}_p}(t) (1 + o(1)),$$

where $o(1)$ is an infinitesimal function as $t \rightarrow \infty$. Hence we can make a conclusion about the general asymptotic behavior of $S(t)$:

$$S_{\mathbb{Z}_p}(t) \sim t^{-\frac{1}{\alpha}} f(\log t) (1 + o(1)), \quad (11)$$

where $f(x)$ is a periodic function with period $\alpha \log p$. The result (11) can be obtained rigorously after determining the explicit form of the function $f(x)$. To this end, we need the following theorem.

Theorem 1. Suppose that the series

$$S(\tau) = \sum_{i=0}^{\infty} c_i e^{-d_i \tau},$$

where $c_i \geq 0$ and $d_i \geq 0$, $i = 0, 1, 2, \dots$, converges uniformly in τ and that there exist $a > 0$, $b > 0$, $\gamma > 0$, and $\delta > 0$ such that

$$\lim_{i \rightarrow \infty} \frac{c_i}{a^{-i}} = \gamma, \quad \lim_{i \rightarrow \infty} \frac{d_i}{b^{-i}} = \delta,$$

Then

$$S(\tau) = \frac{\gamma}{\log b} (\delta \tau)^{-\frac{\log a}{\log b}} \left(\Gamma \left(\frac{\log a}{\log b} \right) + u(\log(\delta \tau)) \right) (1 + o(1))$$

as $\tau \rightarrow \infty$, where

$$u(x) = 2\text{Re} \sum_{k=1}^{+\infty} \exp \left(-i \frac{2\pi k}{\log b} x \right) \Gamma \left(\frac{\log a - 2\pi i k}{\log b} \right) \quad (12)$$

is a periodic function with period $\log b$ and $o(1)$ is an infinitesimal function as $\tau \rightarrow \infty$.

The proof of Theorem 1 is given in Appendix 1.

The upper bound of the function (12) is determined by the following theorem.

Theorem 2. When $a > 1$, $b > 1$, and $a < b^2$, the following inequality holds for all $x \in \mathbb{R}$:

$$|u(x)| \leq 4\pi \exp \left(-\frac{\log a}{\log b} \right) \left(\frac{\log a}{\log b} \right)^{\frac{\log a}{\log b} - \frac{1}{2}} \exp \left(\frac{\log b}{4 \log a} \left(1 + \frac{4\pi^2}{\log^2 a} \right)^{-\frac{1}{2}} \right)$$

$$\times \left(1 + \frac{4\pi^2}{\log^2 a}\right)^{\frac{\log a}{2\log b} - \frac{1}{4}} \frac{\exp\left(-\frac{2\pi}{\log b} \arctan \frac{2\pi}{\log a}\right)}{1 - \exp\left(-\frac{2\pi}{\log b} \arctan \frac{2\pi}{\log a}\right)}. \quad (13)$$

The proof of Theorem 2 is given in Appendix 2.

Applying Theorem 1 to series (9) and setting $c_i = a^i = p^{-i}$, $d_i = b^{-i} = p^{-\alpha i}$, $\gamma = 1$, $\delta = 1$, and $\tau = t$, we obtain

$$S_{\mathbb{Z}_p}(t) = \frac{(1 - p^{-1})}{\alpha \log p} \tau^{-\frac{1}{\alpha}} \left(\Gamma\left(\frac{1}{\alpha}\right) + u(\log t) \right) (1 + o(1)),$$

where

$$u(\log t) = 2\operatorname{Re} \sum_{k=1}^{+\infty} \exp\left(-\frac{2\pi i k}{\alpha \log p} (\log t)\right) \Gamma\left(\frac{1}{\alpha} - \frac{2\pi i k}{\alpha \log p}\right). \quad (14)$$

It is clear from the explicit expression for (14) that this function oscillates with period $\alpha \log p$ in $\log t$ about the mean value $f = 0$. Similarly, from (8) for $f(x, t)$ with $|x|_p = p^\gamma$, $\gamma > 0$, we have

$$f(x, t) = \frac{(1 - p^{-1})}{\alpha \log p} \tau^{-\frac{1}{\alpha}} \left(\Gamma\left(\frac{1}{\alpha}\right) + u(\log t - \alpha \gamma \log p) \right) (1 + o(1)).$$

Using Theorem 2, we can obtain the following upper bound for the function (14) for $\alpha > \frac{1}{2}$:

$$|u(\log t)| \leq A_{\text{up}}(\alpha),$$

where

$$A_{\text{up}}(\alpha) = 4\pi \alpha^{-\frac{1}{\alpha} + \frac{1}{2}} e^{-\frac{1}{\alpha}} \left(1 + \frac{4\pi^2}{\log^2 p}\right)^{\frac{1}{2\alpha} - \frac{1}{4}} \\ \times \exp\left(\frac{\alpha}{4} \left(1 + \frac{4\pi^2}{\log^2 p}\right)^{-\frac{1}{2}}\right) \frac{\exp\left(-\frac{2\pi}{\alpha \log p} \arctan \frac{2\pi}{\log p}\right)}{1 - \exp\left(-\frac{2\pi}{\alpha \log p} \arctan \frac{2\pi}{\log p}\right)}.$$

This formula shows that an increase in α leads to an exponential growth in the upper bound of the amplitude $|u(\log t)|$, as illustrated by the graph of the function $A_{\text{up}}(\alpha)$ for $p = 2$ and $p = 3$ in Fig. 2.

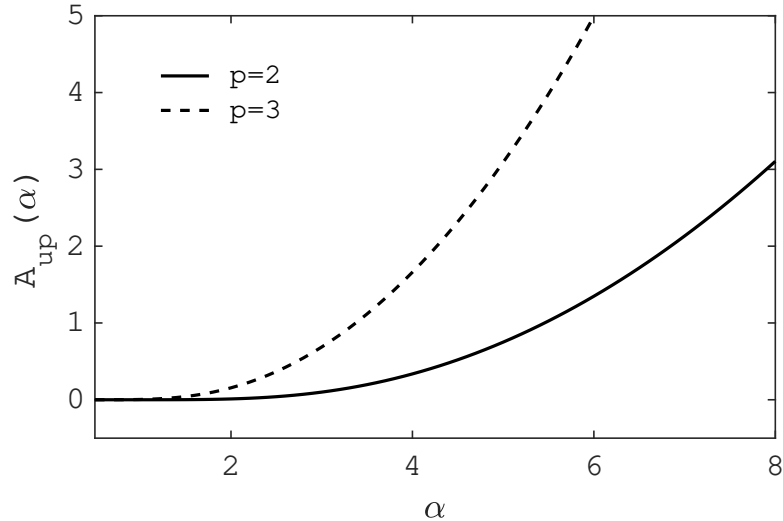


Figure 2: Graph of $A_{\text{up}}(\alpha)$ for $p = 2$ and $p = 3$.

3 Oscillations in the solution of the p -adic diffusion equation with a reaction sink

The solution of the equation of ultrametric diffusion with a reaction sink with different initial conditions on a compact set was studied in a number of works in relation to the description of the kinetics of binding a CO molecule to myoglobin [22, 29, 30]. Here we consider the simplest version of this problem in the case when both the sink and the initial condition are homogeneous and their support is \mathbb{Z}_p . Thus, we consider the Cauchy problem of the form

$$\frac{df(x, t)}{dt} = -\frac{1}{\Gamma_p(-\alpha)} \int_{\mathbb{Q}_p} d_p y \frac{f(y, t) - f(x, t)}{|x - y|_p^{\alpha+1}} - \sigma \Omega(|x|_p) f(x, t) \quad (15)$$

with the initial condition (7), where $\sigma > 0$ is the reaction constant.

An analytical treatment of the Cauchy problem (15) – (7) is described in detail in [42]. Here we only consider the case of $\alpha > 1$, since it is this range of values of α that corresponds to the physical values of temperature when simulating the relaxation dynamics of protein [29, 30]. The quantity of physical interest is $S(t) \equiv \int_{\mathbb{Q}_p} d_p x f(x, t)$, which represents the probability measure of \mathbb{Q}_p . It follows from (15) that the function $S(t)$ is related to the survival probability $S_{\mathbb{Z}_p}(t) \equiv \int_{\mathbb{Z}_p} d_p x f(x, t)$ by the formula

$$\frac{dS(t)}{dt} = -\sigma S_{\mathbb{Z}_p}(t). \quad (16)$$

Just as in the no-sink case, the Cauchy problem (15) with the initial condition (7) admits a numerical analysis when the integration domain \mathbb{Q}_p is replaced by a p -adic ball $B_r = \{x : |x|_p \leq p^r\}$. For the parameters $p = 2$, $\sigma = 0.1$, and $r = 20$, the graphs of the function

$S(t)$ corresponding to the values of $\alpha = 3, 5, 10$ are demonstrated in Fig. 3 in a double logarithmic scale. We can see that the graphs show oscillations characterized by an increase in the amplitude and period with increasing α .

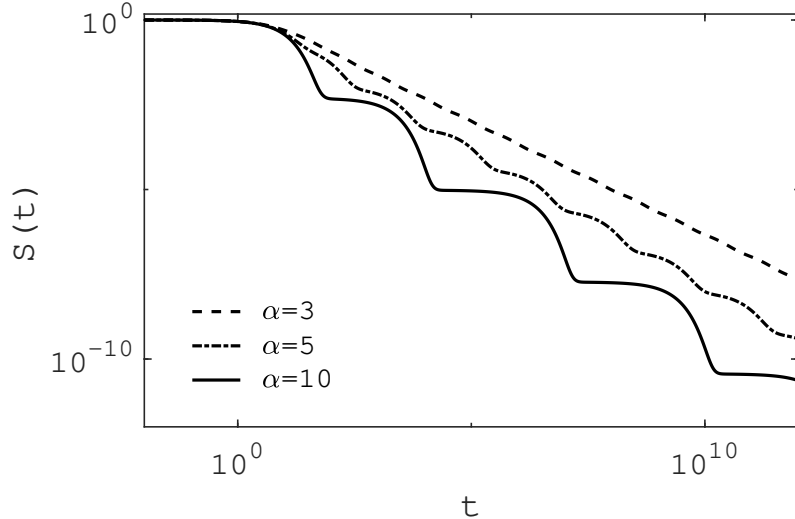


Figure 3: Graph of $S(t) \equiv \int_{\mathbb{Q}_p} d_p x f(x, t)$, where $f(x, t)$ is the numerical solution of equation (15) on the compact set B_r with the initial condition (7) for $p = 2$, $\sigma = 0.1$, and $r = 20$.

In [42], the first author showed that the function $S_{Z_p}(t)$ can be represented as an infinite series

$$S_{Z_p}(t) = \sum_{k=-1}^{\infty} b_k \exp(-\lambda_k t), \quad (17)$$

where the values of λ_k and b_k , $k = -1, 0, 1, 2, \dots$, are determined from the equations

$$1 + \sigma J(s)|_{s=-\lambda_k} = 0, \quad (18)$$

$$b_k = \frac{1}{\sigma^2 |J'(-\lambda_k)|}, \quad (19)$$

and the function $J(s)$ is given by

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

Using (16) and (17), we can show (see also [30]) that

$$S(t) = \sigma \sum_{k=-1}^{\infty} c_k \exp(-\lambda_k t), \quad (20)$$

where $c_k = \frac{b_k}{\lambda_k}$.

Next, we need the following theorem.

Theorem 3. There exist $\gamma > 0$ and $\delta > 0$ such that

$$\lim_{k \rightarrow \infty} \frac{c_k}{p^{-(\alpha-1)k}} = \gamma, \quad \lim_{i \rightarrow \infty} \frac{\lambda_k}{p^{-\alpha k}} = \delta.$$

The proof of Theorem 3 is given in Appendix 3.

Applying Theorems 1 and 3 to (20) and setting $a = p^{\alpha-1}$, $b = p^\alpha$, and $\tau = t$ in Theorem 1 and $d_k = \lambda_k$ in Theorem 3, we obtain

$$\tilde{S}(t) = \frac{\gamma}{\alpha \log p} (\delta t)^{-\frac{\alpha-1}{\alpha}} \left(\Gamma \left(\frac{\alpha-1}{\alpha} \right) + u(\log(\delta t)) \right) (1 + o(1)),$$

where

$$u(\log(\delta t)) = 2\text{Re} \sum_{k=1}^{+\infty} \exp \left(-i \frac{2\pi k}{\alpha \log p} \log(\delta t) \right) \Gamma \left(\frac{(\alpha-1) \log p - 2\pi i k}{\alpha \log p} \right)$$

is a function periodic in $\log(\delta t)$ with period $\alpha \log p$.

4 Discussion

We have considered the solution of the Cauchy problem with the initial condition on a compact set in two cases: for purely p -adic diffusion and for p -adic diffusion with a reaction sink. We have shown that the large-time solution in these two cases is described by a power law on which logarithmic oscillations are superimposed. We emphasize that the very presence of oscillations in the solution does not mean its periodicity; it only means a periodic deviation of this solution from the main trend described by a decreasing power-law function.

As already mentioned, the presence of oscillations in ultrametric models describing the relaxation dynamics of protein is associated with the hierarchy of the space of conformational states of protein. From physical considerations, the emergence of these oscillations in the hierarchical model of pure random walk of protein on conformations can be explained as follows. Suppose that at the initial time protein is in some basin B_0 of conformational states and that, in the space of all conformational states, one can select basins B_1, B_2, \dots that are hierarchically embedded in each other: $B_0 \subset B_1 \subset B_2 \subset \dots$. Suppose also that the basins B_0, B_1, B_2, \dots are separated from each other by energy barriers E_1, E_2, E_3, \dots and that $E_1 \ll E_2 \ll E_3 \ll \dots$. At the initial time, the support of the distribution function coincides with B_0 , and the probability measure “spreads” over the whole conformation space in the course of time. The average time to overcome the energy barrier E_i separating the i th basin from the basins embedded in it is proportional to the Boltzmann factor $\tau_i \sim \exp(\alpha E_i)$, where $\alpha = \frac{1}{kT}$, k is the Boltzmann constant, and T is temperature; in this case it is obvious that $\tau_1 \ll \tau_2 \ll \tau_3 \ll \dots$.

Consider a basin B_{i-1} and denote by $S_{i-1}(t)$ the probability measure of this basin. Suppose that the function $S_{i-1}(t)$ can be approximated by a simple function $S_{i-1, \text{trend}}(t)$ (for example, by a decreasing power trend) with a sufficiently high degree of accuracy. Consider a time instant t such that $\tau_{i-1} \ll t \ll \tau_i$. Since $t \ll \tau_i$, the probability measure at this time instant t is mainly concentrated in the basin B_{i-1} because the average time to overcome the energy

barrier separating the basin B_{i-1} from the set $B_i \setminus B_{i-1}$ is much greater than t . Moreover, since $t \gg \tau_{i-1}$, we can assume that the distribution in B_{i-1} at these instants of time is close to the quasi-equilibrium distribution because the probability of transition from B_{i-1} to $B_i \setminus B_{i-1}$ is small compared to the transitions inside B_{i-1} .

Further, as time proceeds from τ_i to τ_{i+1} , the region in which the the main part of the probability measure is concentrated increases, and, due to the conservation of probability measure in the whole space of conformational states, the distribution function increases in the set $B_i \setminus B_{i-1}$ and decreases in B_{i-1} . Then at times t such that $\tau_i \ll t \ll \tau_{i+1}$, the probability measure is mainly concentrated in the basin B_i , and this distribution in B_i is also close to the quasi-equilibrium distribution. Since the variation rate of the distribution function decreases as it approaches the equilibrium state, it is natural to assume that, for all $j > i$ at time instants t such that $\tau_{j-1} \ll t \ll \tau_j$, the decrease rate of the function $S_{i-1}(t)$ with respect to the decrease rate of the trend $S_{i-1,\text{trend}}(t)$ should be less than its decrease rate with respect to the decrease rate of the trend at time instants t satisfying the conditions $\tau_{j-1} < t \ll \tau_j$ or $\tau_{j-1} \ll t < \tau_j$. It is this change in the decrease rate of the function $S_{i-1}(t)$ with respect to the function $S_{i-1,\text{trend}}(t)$ that manifests itself as a superimposition of oscillations on the trend $S_{i-1,\text{trend}}(t)$. It is obvious that the period $\tau_i - \tau_{i-1}$ of these oscillations increases with time. In the general case of arbitrary relation between the times τ_i (which corresponds to an arbitrary relation between the energy barriers E_i), these oscillations are aperiodic. Nevertheless, if the times τ_i are related by $\tau_i = \tau_0 \theta^i$, where τ_0 and θ are some parameters, then the period $\lambda_i - \lambda_{i-1} = \log \theta$ as a function of the variable $\lambda = \log t$ does not depend on time. This means that the decrease rate of the distribution function oscillates with a period, which increases in time by a logarithmic law. Hence we can also conclude that, as temperature decreases, the logarithmic oscillations become more pronounced. Indeed, as temperature decreases, the ratio $\frac{E_i}{E_{i-1}}$, and hence also $\frac{\tau_i}{\tau_{i-1}}$ increase. Hence, the lower the temperature, the closer to equilibrium the state of protein is in the region B_{i-1} at time instants from the interval close to τ_i (τ_{i-1}, τ_i). However, the closer the state of protein to equilibrium, the lower the decrease rate of the distribution function in any region contained in the basin B_{i-1} . Thus, at sufficiently low temperatures, one should observe regions of decreasing relaxation curves, which are close to horizontal lines in the logarithmic scale (see, for example, the curves in Figs. 1 and 3 corresponding to $\alpha = 10$).

Naturally, the observation of logarithmic oscillations on experimental relaxation curves can provide a convincing support for the assumption of ultrametricity of the space of conformational states of protein and the adequacy of p -adic models for the description of relaxation dynamics of protein. In this context we emphasize once again that the p -adic diffusion equation (6) is fundamental for the description of the conformational dynamics of protein and underlies the description of experiments on spectral diffusion [25, 29, 36], while the p -adic diffusion equation with a reaction sink (15) underlies the description of experiments on the kinetics of CO binding to myoglobin [22, 28, 29, 30]. Hence, the presence of logarithmic oscillations in the solutions of these equations should also manifest itself to some extent in the relaxation curves of experiments that can be described within the models of p -adic diffusion.

An analysis of experimental studies on the conformational dynamics of protein shows that there seem to be no experiments directly aimed at finding the oscillations of relaxation curves. The study of the graphs presented in a number of experimental works in principle allows one to carry out an approximate analysis of the presence of oscillations within the available accuracy.

As pointed out in [11], it is convenient to consider instead of the relaxation function $S(t)$ the logarithmic derivative of its logarithm, i.e., the function $\frac{d \log S(t)}{d \log t}$, which should demonstrate purely logarithmic oscillations in the neighborhood of its mean value. Nevertheless, a similar analysis on the detection of logarithmic oscillations in the behavior of relaxation curves with a power-law trend presents a problem, first, due to the small amplitude of these oscillations and, second, due to the presence of rather large errors in the location of experimental points. As an example, below we present an attempt to detect logarithmic oscillations in some experimental relaxation curves obtained in [43, 44, 46, 47].

In [43, 44], the authors investigated the evolution of the absorption spectrum of the heme group of myoglobin (Mb) in the tertiary structure at room temperature after photodissociation $\text{MbCO} \rightarrow \text{Mb} + \text{CO}$. The observations were made on the so-called band III, which is responsible for the porphyrin- $\pi \rightarrow$ iron-d charge-transfer transition with a frequency of about 13110 cm^{-1} (763 nm). The variation of conformational states was identified with the variation $\Delta\nu$ in the position of band III relative to its position in the equilibrium state Mb. In [43, 44], the authors presented experimental graphs of the function $\Delta\nu(t)$ for different lengths of the laser pulse and in different observation time windows. In [45], using the data for $\Delta\nu(t)$ obtained in [44], the authors illustrated the presence of oscillations in the function $\frac{d \log \Delta\nu(t)}{d \log t}$, which, according to the authors, indicate the hierarchy of protein relaxation. Here we present a similar analysis carried out for the experimental data obtained in [43]. Figure 4 (top) shows the graph of the experimentally measured dependence of the variation $\Delta\nu$ in the position of band III on time, which was presented in [44]. Figure 4 (bottom) demonstrates the function $\frac{d \log \Delta\nu(t)}{d \log t}$, which exhibits an oscillation-like behavior.

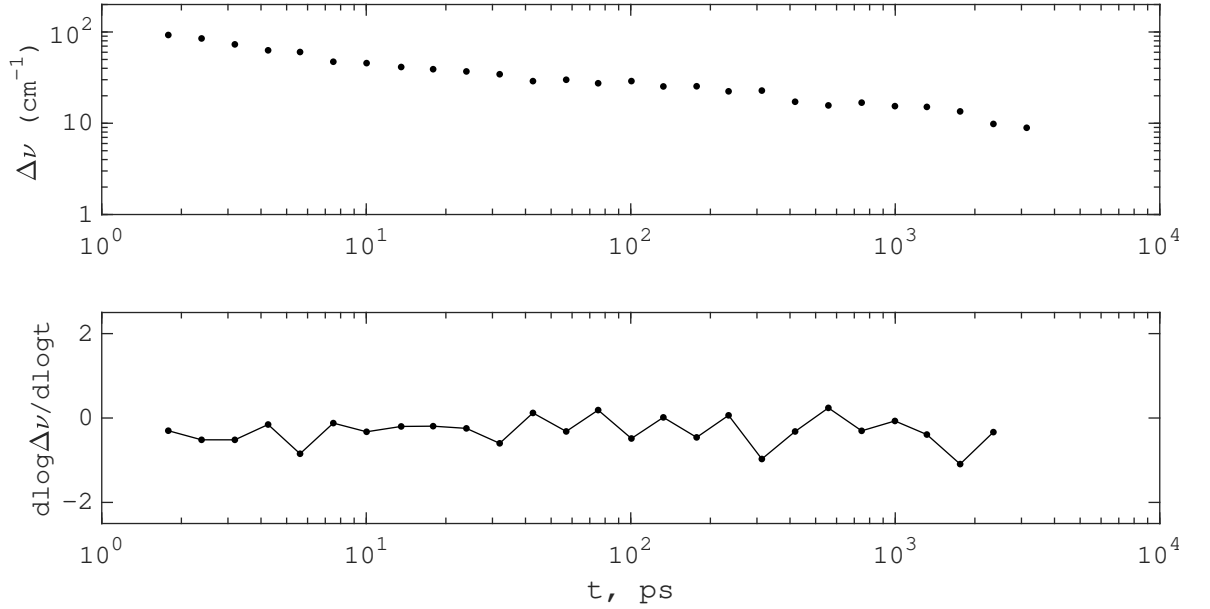


Figure 4: Top: experimental dependence of the variation $\Delta\nu(t)$ in the position of band III after photodissociation MbCO, shown in Fig. 3 in [43]; bottom: the function $\frac{d \log \Delta\nu(t)}{d \log t}$ constructed using the function $\Delta\nu(t)$.

The emergence of logarithmic oscillations was also mentioned in [46, 47], where the authors presented the results of experiments on the folding kinetics of phosphoglycerate kinase protein (PGK). In these experiments, a protein sample was subjected to cold denaturation in supercooled aqueous buffer at temperature T_1 . Then the aqueous buffer was rapidly heated by an infrared pulse to temperature T_2 , after which the protein in the heated buffer started to fold. During folding in the time window $t \in (0, 1000 \mu s)$ in the experiment, in each time interval $\tau = 14 \text{ ns}$ protein was irradiated by a nanosecond laser pulse, which led to the fluorescence of protein. The time profile of this fluorescence was described by a function $f(t')$, which rapidly decreased in time $t' \in (0, \tau)$. The state of the protein at time t was determined by the function $f(t, t')$, which was approximated as $f(t, t') = C_1(t) f_1(t') + C_2(t) f_2(t')$, where $t' \in (0, \tau)$; the function $f_1(t)$ described the fluorescence profile in the initial (denaturated) state, and $f_2(t)$, in the final (folded) state. The observable parameter χ_1 shown in the graphs in these studies represented the ratio $\chi_1(t) = \frac{C_1(t)}{C_1(t) + C_2(t)}$. Figure 5 (top) shows the graph of of the normalized quantity $\chi_1(t)$ ($\max \chi_1 = 1$), which is plotted using the data presented in Fig. 6 in [47] for hisPGK protein. Figure 5 (bottom) presents the function $\frac{d \log \chi_1(t)}{d \log t}$, which also exhibits an oscillation-like behavior.

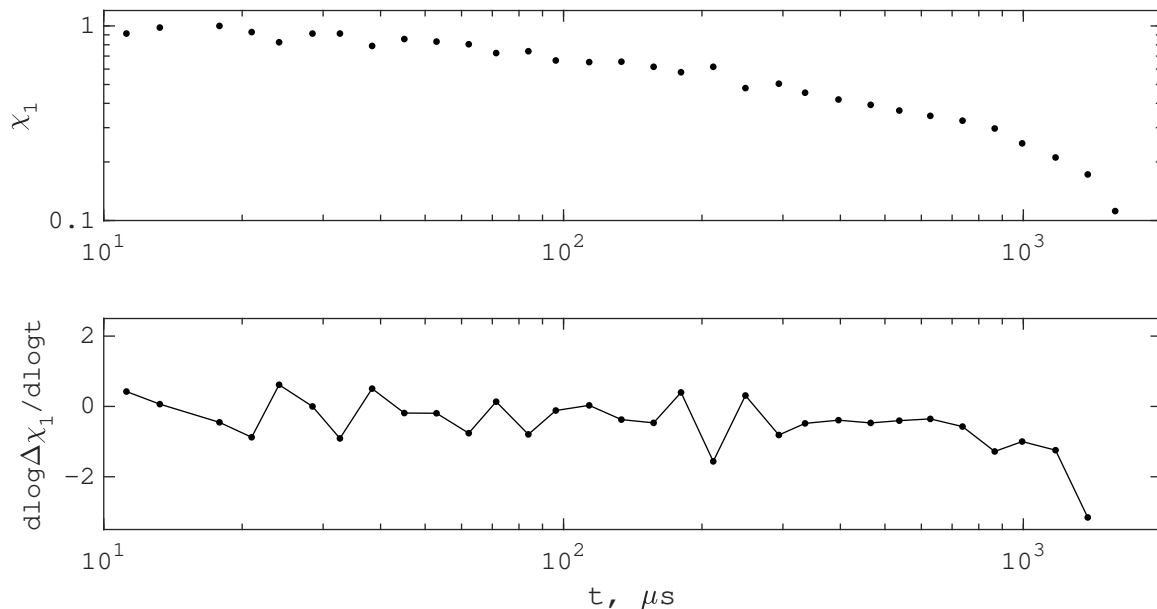


Figure 5: Top: experimental function $\chi_1(t)$ for hisPGK protein, presented in Fig. 6 in [47] for $T_1 = -12^\circ\text{C}$ and $T_2 = +3^\circ\text{C}$; bottom: the function $\frac{d \log \chi_1(t)}{d \log t}$ constructed using the function $\chi_1(t)$.

Naturally, the analysis carried out above of relaxation curves in two different experiments can in no way serve as a proof of the presence of logarithmic oscillations in these processes. First of all, note that the experimental data presented by dots in the graphs have a large dispersion due to experimental errors. For example, one should note the local growth of relaxation curves in separate regions in the upper graphs. Obviously, this is an artifact of the measurement process and should not occur in reality. Therefore, the oscillations shown in the lower graphs in Figs. 4 and 5 are strongly distorted, even if they have to do with real oscillations.

Summarizing, we can state that the currently available experimental data on the relaxation dynamics of protein do not allow one to make an unambiguous conclusion about the presence of logarithmic oscillations in the behavior of relaxation curves. Thus, the problem of experimental verification of the presence (or absence) of oscillations in the evolution of conformational rearrangements of a protein molecule still remains topical, since its solution would provide a deeper insight into the applicability of the ultrametric concept to the description of the conformational dynamics of protein.

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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 1

In this appendix, we present the proof of Theorem 1. Consider the series

$$F(\tau) = \gamma \sum_{i=0}^{\infty} a^{-i} e^{-\delta b^{-i} \tau}, \quad (21)$$

which obviously converges uniformly in τ . Then $\sum_{i=0}^{\infty} (a^{-i} e^{-b^{-i} \tau} - c_i e^{-d_i \tau})$ also converges uniformly in τ and

$$\lim_{\tau \rightarrow \infty} (F(\tau) - S(\tau)) = \sum_{i=0}^{\infty} \lim_{\tau \rightarrow \infty} (\gamma a^{-i} e^{-\delta b^{-i} \tau} - c_i e^{-d_i \tau}) = 0;$$

hence it follows that

$$S(\tau) = F(\tau) (1 + o(1)) \quad (22)$$

as $\tau \rightarrow \infty$, where $o(1)$ is an infinitesimal function as $\tau \rightarrow \infty$. Rewriting (21) as $F(\tau) = \sum_{m=0}^{\infty} g(m)$, where $g(m) = \gamma a^{-m} e^{-\delta b^{-m} \tau}$, we apply the well-known Poisson summation formula

$$\sum_{m=0}^{\infty} g(m) = \sum_{k=-\infty}^{+\infty} \int_0^{\infty} g(x) \exp(2\pi i k x) dx.$$

Then

$$F(\tau) = \gamma \sum_{k=-\infty}^{+\infty} \int_0^{\infty} a^{-x} \exp(-\delta b^{-x} \tau + 2\pi i k x) dx. \quad (23)$$

Let us change the variable $y = \delta b^{-x} \tau$ in the integral in (23). After straightforward transformations we arrive at the expression

$$F(\tau) = \frac{\gamma}{\log b} \tau^{-\frac{\log a}{\log b}} \sum_{k=-\infty}^{+\infty} (\delta \tau)^{\frac{-2\pi i k}{\log b}} \gamma \left(\frac{\log a - 2\pi i k}{\log b}, \delta \tau \right), \quad (24)$$

where $\gamma(z, t) = \int_0^t y^{z-1} e^{-y} dy$ is the incomplete gamma function. As $\tau \rightarrow \infty$,

$$\gamma \left(\frac{\log a - 2\pi i k}{\log b}, \delta \tau \right) = \Gamma \left(\frac{\log a - 2\pi i k}{\log b} \right) (1 + o(1)),$$

where $\Gamma(z) = \int_0^{\infty} t^{z-1} e^{-t} dt$ is the gamma function, and we have

$$F(\tau) = \frac{\gamma}{\log b} (\delta \tau)^{-\frac{\log a}{\log b}} \left(\Gamma \left(\frac{\log a}{\log b} \right) + 2\text{Re} \sum_{k=1}^{+\infty} (\delta \tau)^{\frac{-2\pi i k}{\log b}} \Gamma \left(\frac{\log a - 2\pi i k}{\log b} \right) \right) (1 + o(1)), \quad (25)$$

which, combined with (22), proves the theorem.

Appendix 2

In this appendix, we present the proof of Theorem 2. It follows from the explicit form of the function (12)

$$u(x) = 2\operatorname{Re} \sum_{k=1}^{+\infty} \exp\left(-i\frac{2\pi k}{\log b}x\right) \Gamma\left(\frac{\log a - 2\pi ik}{\log b}\right)$$

that

$$|u(x)| \leq 2 \sum_{k=1}^{+\infty} |\Gamma(z)|, \quad (26)$$

where $z = \frac{\log a}{\log b} - \frac{2\pi ik}{\log b}$; in this case, $\arg z = -\arctan \frac{2\pi k}{\log a}$, $-\frac{\pi}{2} < \arg z < 0$, and $|z| = \frac{\log a}{\log b} \left(1 + \frac{4\pi^2 k^2}{\log^2 a}\right)^{\frac{1}{2}}$. Let us apply Stirling's formula

$$\Gamma(z) = 2\pi z^{z-\frac{1}{2}} e^{-z} \exp(\mu(z)) \text{ for } |\arg z| < \pi, \quad (27)$$

where $\mu(z)$ has the Stieltjes representation

$$\mu(z) = \int_0^{\infty} \frac{Q(t)}{(z+t)^2} dt, \quad Q(t) = \frac{1}{2} (t - [t] - (t - [t])^2),$$

and $[t]$ denotes the greatest integer $< t$ (see, for example, [48]). Taking into account the inequality $0 \leq Q(t) \leq \frac{1}{8}$, we can obtain the following upper bound for the function

$$|\exp(\mu(z))| = \exp\left(\int_0^{\infty} \frac{Q(t)}{|z+t|^2} dt\right) \leq \exp\left(\frac{1}{8} \int_0^{\infty} \frac{dt}{|z+t|^2}\right).$$

Since

$$\begin{aligned} |z+t|^2 &= |z|^2 + 2|z|\cos(\arg z)t + t^2 = \\ &= (|z|+t)^2 - 4|z|t\left(1 - \cos^2\left(\frac{\arg z}{2}\right)\right) \end{aligned}$$

and since $(|z|+t)^2 \geq 4|z|t$, it follows that

$$|z+t|^2 \geq (|z|+t)^2 \cos^2\left(\frac{\arg z}{2}\right).$$

Then

$$|\exp(\mu(z))| \leq \exp\left(\frac{1}{8 \cos^2\left(\frac{\arg z}{2}\right)} \int_0^{\infty} \frac{dt}{(|z|+t)^2}\right) = \exp\left(\frac{1}{8|z| \cos^2\left(\frac{\arg z}{2}\right)}\right).$$

Since $\cos \arg z > 0$, it follows that $\cos^2 \left(\frac{\arg z}{2} \right) = \frac{1}{2} + \frac{1}{2} \cos \arg z \geq \frac{1}{2}$ and we have

$$|\exp(\mu(z))| \leq \exp\left(\frac{1}{4|z|}\right) = \exp\left(\frac{\log b}{8 \log a} g_k^{-\frac{1}{2}}\right), \quad (28)$$

where $g_k = 1 + \frac{4\pi^2 k^2}{\log^2 a}$. In view of (27),

$$\begin{aligned} |\Gamma(z)| &= 2\pi |e^{z \log z}| |z|^{-\frac{1}{2}} |e^{-z}| |\exp(\mu(z))| \leq \\ &\leq 2\pi \left| \exp\left(\left(\frac{\log a}{\log b} - \frac{2\pi i k}{\log b}\right) \left(\log\left(\frac{\log a}{\log b} g_k^{\frac{1}{2}}\right) - i \arctan \frac{2\pi k}{\log a}\right)\right) \right| \\ &\quad \times \left(\frac{\log b}{\log a}\right)^{\frac{1}{2}} g_k^{-\frac{1}{4}} \exp\left(-\frac{\log a}{\log b}\right) \exp\left(\frac{\log b}{4 \log a} g_k^{-\frac{1}{2}}\right) \\ &\leq 2\pi \exp\left(-\frac{\log a}{\log b}\right) \left(\frac{\log a}{\log b}\right)^{\frac{\log a}{\log b} - \frac{1}{2}} g_k^{\frac{\log a}{2 \log b} - \frac{1}{4}} \exp(-h_k) \exp\left(\frac{\log b}{4 \log a} g_k^{-\frac{1}{2}}\right), \end{aligned} \quad (29)$$

where $h_k = \frac{2\pi k}{\log b} \arctan \frac{2\pi k}{\log a}$. Then from (26) we have

$$\begin{aligned} |u(x)| &\leq 4\pi \exp\left(-\frac{\log a}{\log b}\right) \left(\frac{\log a}{\log b}\right)^{\frac{\log a}{\log b} - \frac{1}{2}} \\ &\quad \times \exp\left(\frac{\log b}{4 \log a} g_k^{-\frac{1}{2}}\right) g_k^{\frac{\log a}{2 \log b} - \frac{1}{4}} \sum_{k=1}^{+\infty} \exp\left(-\frac{2\pi k}{\log b} \arctan \frac{2\pi k}{\log a}\right), \end{aligned}$$

which implies the assertion of Theorem 2.

Appendix 3

In this appendix, we present the proof of Theorem 3.

Taking into account that $\lim_{\sigma \rightarrow 0} \lambda_k = p^{-\alpha(k+1)}$ (see the solution of the Cauchy problem (6) – (7) in the absence of a sink), it is convenient to use the following representation for λ_k :

$$\lambda_k = p^{-\alpha k} (p^{-\alpha} + \Delta_k). \quad (30)$$

It can be shown from the graphical analysis of the equation $1 + \sigma J(s) = 0$ that $0 < \Delta_k < 1 - p^{-\alpha}$. Then (30) implies the following estimate for λ_k : $p^{-\alpha k} p^{-\alpha} < \lambda_k < p^{-\alpha k}$. From the equation $1 + \sigma J(-\lambda_k) = 0$ we have

$$\sum_{n=0}^{\infty} \frac{p^{-n}}{p^{-\alpha n} - \lambda_k} = -\frac{p}{p-1} \frac{1}{\sigma}. \quad (31)$$

Singling out the $(k + 1)$ th term in the sum on the left-hand side of equation (31), multiplying it by p^k and dividing by $p^{\alpha k}$, and taking into account (30), we can rewrite (31) as

$$\frac{p^{-1}}{\Delta_k} = \frac{p}{p-1} \frac{p^{-(\alpha-1)k}}{\sigma} + \sum_{i=0}^k \frac{p^i}{p^{\alpha i} - p^{-\alpha} - \Delta_k} - \sum_{j=2}^{\infty} \frac{p^{-j}}{p^{-\alpha} - p^{-\alpha j} + \Delta_k}. \quad (32)$$

For further proof we need the following two lemmas.

Lemma 1.

$$\frac{1 - p^{-\alpha+1}}{1+p} (1 - p^{-\alpha}) < \Delta_k < \frac{1 - p^{-\alpha}}{p}. \quad (33)$$

Proof. The upper bound for Δ_k follows from the inequality

$$\frac{p^{-1}}{\Delta_k} \leq \frac{1}{1 - p^{-\alpha} - \Delta_k} - \frac{p^{-1}}{p-1} \frac{1}{\Delta_k}, \quad (34)$$

which, in turn, follows from (32). The lower bound for Δ_k follows from the inequality

$$\frac{p^{-1}}{\Delta_k} < \frac{p}{p-1} \frac{p^{-(\alpha-1)k}}{\sigma} + \frac{1}{1 - p^{-\alpha} - \Delta_k} \frac{p^{(\alpha-1)}}{p^{(\alpha-1)} - 1}, \quad (35)$$

which also follows from (32). Lemma 1 is proved.

Lemma 2. There exists the limit $\lim_{k \rightarrow \infty} \Delta_k \equiv \Delta > 0$.

Proof. By Lemma 1, a sequence $\frac{p^{-1}}{\Delta_k}$ is defined that is also bounded. Suppose that the limit $\lim_{k \rightarrow \infty} \Delta_k$ does not exist. Then the limit of the sequence $\frac{p^{-1}}{\Delta_k}$ as $k \rightarrow \infty$ also does not exist. In view of the statement logically opposite to the Cauchy criterion, this means that there exists a number $\varepsilon > 0$ such that, for any $K \in \mathbb{Z}_+$, there exist $k, n \in \mathbb{Z}_+$, $k > K$, such that $\left| \frac{p^{-1}}{\Delta_k} - \frac{p^{-1}}{\Delta_{k+n}} \right| > \varepsilon$ (or $|\Delta_{k+n} - \Delta_k| > \varepsilon' = p \frac{(1 - p^{-\alpha+1})^2 (1 - p^{-\alpha})^2}{(1+p)^2} \varepsilon$).

Consider the difference

$$\begin{aligned} \frac{p^{-1}}{\Delta_k} - \frac{p^{-1}}{\Delta_{k+n}} &= \frac{p}{p-1} \frac{p^{-(\alpha-1)k}}{\sigma} (1 - p^{-(\alpha-1)n}) \\ &\quad - \sum_{i=1}^n \frac{p^k p^i}{p^{\alpha k} p^{\alpha i} - p^{-\alpha} - \Delta_{k+n}} \\ &\quad + \sum_{i=0}^k \left(\frac{p^i}{p^{\alpha i} - p^{-\alpha} - \Delta_k} - \frac{p^i}{p^{\alpha i} - p^{-\alpha} - \Delta_{k+n}} \right) \\ &\quad + \sum_{j=2}^{\infty} \left(\frac{p^{-j}}{p^{-\alpha} - p^{-\alpha j} + \Delta_{k+n}} - \frac{p^{-j}}{p^{-\alpha} - p^{-\alpha j} + \Delta_k} \right). \end{aligned} \quad (36)$$

Irrespective of Δ_k and Δ_{k+n} , for sufficiently large K the terms on the right-hand side of equality (36) in the first and second rows can be made arbitrarily small. Conversely, the terms in the

third and fourth rows in (36) depend on the relation between Δ_k and Δ_{k+n} . For $|\Delta_{k+n} - \Delta_k| > \varepsilon'$, the absolute values of these terms cannot be made arbitrarily small for an indefinite increase in K , and they are bounded from below. Moreover, notice that the sign of these terms in the third and fourth rows of expression (36) is opposite to the sign of the difference $\frac{p^{-1}}{\Delta_k} - \frac{p^{-1}}{\Delta_{k+n}}$. This means that, for sufficiently large K , there always exist $k, n \in \mathbb{Z}_+$, $k > K$, such that the right- and left-hand sides of (36) have opposite signs, which leads to a contradiction. This contradiction proves Lemma 2.

It follows from Lemma 2 that there exists the limit

$$\lim_{i \rightarrow \infty} \frac{\lambda_k}{p^{-\alpha k}} = \lim_{i \rightarrow \infty} \frac{p^{-\alpha k} (p^{-\alpha} + \Delta_k)}{p^{-\alpha k}} = p^{-\alpha} + \Delta \equiv \delta.$$

Next, for b_k we can write

$$b_k = \frac{\sigma^{-2}}{P(\lambda_k)},$$

where

$$\begin{aligned} P(\lambda_k, \alpha) &= \frac{dJ(s)}{ds} \Big|_{s=-\lambda_k} = (1 - p^{-1}) \sum_{n=0}^{\infty} \frac{p^{-n}}{(p^{-\alpha n} - \lambda_k)^2} = \\ &= (p - 1) \frac{p^{(2\alpha-1)k}}{\Delta_k^2} (1 + o(1)), \end{aligned}$$

and where $o(1)$ is an infinitesimal sequence as $k \rightarrow \infty$. Hence,

$$\begin{aligned} b_k &= \frac{\sigma^{-2} \Delta_k^2}{p - 1} p^{-(2\alpha-1)k} (1 + o(1)), \\ c_k &= \frac{b_k}{\lambda_k} = \frac{\sigma^{-2} \Delta_k^2}{(p^{-\alpha} + \Delta_k)(p - 1)} p^{-(\alpha-1)k} (1 + o(1)) \end{aligned}$$

and thus

$$\lim_{k \rightarrow \infty} \frac{c_k}{p^{-(\alpha-1)k}} = \frac{\sigma^{-2} \Delta^2}{\delta(p - 1)} \equiv \gamma,$$

which proves Theorem 3.

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