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Stretched Exponential Kinetics of the Pressure Induced Hydration of Model Lipid Membranes. A Possible Scenario

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Abstract. — The kinetics of the pressure induced hydration of model lipid membranes is studied in terms of the Avrami-Kolmogorov model and the fractal-like chemical reaction kinetics concept. As a general result, the stretched exponential relaxation function of the process is obtained and applied to an experimental case of the dioleoylphosphatidylethanolamine (DOPE)-bilayer hydration, understood as a cooperative process in which, both, the structural lipid changes and hydration are coupled in a complex way with each other, and hypothesized in terms of the anomalous random walk. The trends of both theory and experiment are in agreement.

1. Introduction

Amphiphilic assemblies, such as lipids and surfactants dispersed in water or other (*e.g.* organic) solvents can aggregate into a variety of morphological forms among which biomembranes encompass some well-defined structured systems. Under certain external-field (mostly pressure or temperature) conditions they may undergo the phase transformations, *e.g.* from the gel to the liquid crystalline state; some physico-chemical processes occurring within such systems may even strongly be influenced by the solution conditions *e.g.* the pH-characteristics, the electrolyte concentration or some thermodynamic quantities like chemical potential of the water molecules dispersed in there [1].

Such systems can also exhibit a very rich structural behaviour concerning the liquid crystalline (or noncrystalline) phases with many topological arrangements of components from which they are prepared. Under certain physico-chemical circumstances biomembranes are observed to constitute regular (periodic) lattices in one-, two- or even three-dimensional spaces [2]. The structures formed usually resemble the smectic liquid crystals (it is frequently the case of lecithines) because of existence of stacks of amphiphilic layers, mostly separated by water. Some lamellar as well as nonlamellar (like inverted hexagonal or cubic) phases, or even the intermediates called mesophases, can also emerge which is of relevance when investigating some biological processes like ion transport through membrane channels, phase separations, material flexibility, *etc.* [1,3]. There is also a possibility of forming some more irregular mostly

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self-similar complexes (reminiscent of the percolation lattice) when some defects or structural imperfections (anaesthetics, impurities, some interstitially located molecules or thermal fluctuations of the membrane material) are detected in the system [4]. The last case becomes certainly a case that is more realistic and is easily observed in real biosystems, where biomembranes represent the main structural constituent for their complex architecture [5].

It is often argued that the rationale for studying some dynamic or kinetic features usually assigned to model biomembranes, like hydration dynamics or some phase transformations, appears to be one of the most interesting and not completely solved problems in this area of research.

In order to understand the dynamic (or kinetic) aspects of the phenomena mentioned above, one requires not only a proper understanding of the thermodynamics of self-association in the lipid dispersions, but also the temporal rules of how the new phase, whatever it is, may emerge from the old one. An important problem is usually related to the general feature (possibility) of how the interaction forces between amphiphiles within aggregates are affected by certain solution conditions, and how to incorporate it into a rather phenomenological kinetic description [6, 7].

In the paper, we wish to study the pressure induced hydration kinetics of biomembranes. Let us suppose, that a dioleoylphosphatidylethanolamine (DOPE) model membrane, composed of nonlamellar (precisely: inverted hexagonal) lipid phase, is prepared by mechanical mixing to be fully hydrated [8]. In consequence, the membrane (bilayer) is considered to be under a rather homogeneous swelling. It also implies that the macromolecules comprising the bilayer get elongated (or stretched) because of entering the small water molecules or agglomerates of them, throughout pre-existing pores (or free spaces among lipid molecules which are of orders of nanometers) rather than by transient fluctuations in the bilayer structure until an equilibrium state is achieved. Note also that, as ever in the hydration process, the water molecules penetrate the system and eventually get aggregated on the lipid molecules or even on (within) some ensembles or clusters of them, and the effect is of the electrostatic nature, being commonly called the solvation effect [8, 9]. After applying the hydrostatic pressure, *e.g.* taken from the range 0.1-2 kbars, on the system under study, one may notice at least two categories of phenomena which we consider to be of prior importance when studying the hydration phenomenon.

First, the chemical potential of the water present in the mixture is changed which, in consequence, leads to some migration of the molecules throughout the spatially fluctuating membrane (being, in fact, an elastic "porous medium"). The resulting spatial reorganization of water complexes and the unavoidable association of water to lipid domains provides a specific coupling of the hydration process with the lipid structural changes, where none of the processes mentioned stands for the kinetic limitation of the phenomenon in question. Many bimolecular chemical reactions can occur, where the reactants are confined randomly to some compartments (domains) separated from each other due to the previous pressure action, and certain connections and disconnections of lipid domains resembling a phase separation may be observed [10]. Since, generally speaking, such a process is reminiscent of a random walk process on a percolation lattice [11, 12] (there is something like a "moving front" of the hydrated phase propagated through the bilayer), some terminology characteristic of it will be used in our further study. Also, one can see some phase transformation in the system. Namely, before applying the hydrostatic pressure the system and its parts (*e.g.*, lipid macromolecules or domains) are stretched or elongated because of swelling (one can name this phase as a parent phase). After the pressure comes into action a release of water molecules is observed, the swelling conditions are changed, the hydration is still taking place, and the system with its parts is supposed to be not longer in an elongated state, but arrives at a new state that,

in comparison to the old (parent) one, can be termed as the non-elongated (squeezed or compressed, or sometimes “normal”) state (this phase is said to be the children phase). Note here that the children phase still remains hydrated.

Second, from the physical point of view, it is allowed that the pressure will cause some detectable changes in hydration because it induces changes in ionization of surface charges due to either electrostriction or changes in charge repulsion since an effective surface area expansion may occur (*cf.* [13] and Refs. therein). This fact, however, will not be seriously taken into account in the present study. But one has to realize that it supports in a subtle way the whole scenario sketched here.

Thus, establishing on the former, we have proposed a modification of the phenomenological Avrami-Kolmogorov equation [14,15] due to incorporation of the above mentioned fractal-like kinetics [12] and by realizing that the hydration may be coupled in a complex way with the lipid structural changes which is equivalent to hypothesize an existence of the anomalous random walk process on the structure (it is much more than considering the whole lipid structure as a statistical fractal, and, in general, the fractality of the structure is not the necessary feature to establish such a random walk process! note also that, for sure, before applying the pressure the whole structure is a non-fractal [8]). As a result, we have obtained the temporal (kinetic) behaviour of the system in question which, in general, is a stretched exponential (*i.e.*, the non-Debye relaxation kinetics takes place). By applying it to an experimental situation, fully described in [8], we have reached a promising tendency in elucidating the experimental data reported (a rescaled relaxation function of the system under study is a power law of time with an exponent lying between ca. 0.66 and 0.99 [8] which we are able to reproduce by means of our modelling with quite well accuracy). It will be demonstrated in the subsequent chapters.

The paper is organised as follows. After some introductory remarks given in Section 1, we shortly sketch the model that can describe the pressure induced hydration kinetics in lipid bilayers, and next, we modify this model in order to adapt it for a phenomenological description of the anomalous random walk process on the “soft matter” system [8,15] that we investigate (see Sect. 2). In Section 3, some results are revealed and a discussion of them is carried out. The last Section 4 serves for the concluding remarks.

2. Description of Kinetics of the Pressure Induced Hydration of Lipid Bilayers

The well-known Avrami-Kolmogorov kinetic theory of the temporal behaviour of the system has been reviewed and summarized, *e.g.* in [7] and briefly presented in [16]. We do not wish to do the same in this work. One may also consult the original papers [14]. Thus, let us start directly from the simple modified equation of Avrami-Kolmogorov-type that we propose to be

$$\frac{d}{dt} f_h(t) = Nk(t)[1 - f_h(t)] \frac{dV_n}{dt} \quad (1)$$

(in this work, it is taken always with the initial condition $f_h(t_0) = 0$ for $t_0 > 0$), where N is a constant number of randomly distributed nuclei per unit volume each of which will grow to a volume $V_n(t)$ at time t , and $f_h(t)$ is a time-dependent fractional completion of a sample transformed to a new phase [14,16]. Let us notice that a stationary state, $\frac{df_h(t)}{dt} = 0$, is reached for $f_h(t_{st}) = 1$ (*i.e.* in practice, after some large time period t_{st} being passed).

Two things in the aforementioned equation will be novel when comparing to the classical description. The first one is related to the chemical reaction rate coefficient, represented in equation (1) by $k(t)$ and being assumed as a power function of time of the form [12]:

$$k(t) = k_0 t^{-h} \quad (2)$$

(k_0 is the “equilibrium” chemical reaction rate constant which is, according to the Arrhenius law, temperature-dependent; let us note that for $h = 0$ one gets $k(t) = k_0 > 0$; let us also preserve that, for long times, $k(t)$ exists and is finite), and the h -exponent (being a broken number always placed between 0 and 1) is related to the spectral dimension of the system which, in turn, is possible to get when one can specify how the probability of the system return to its initial state changes in time [11,12]. One is also able to evaluate the quantity utilizing the Alexander-Orbach conjecture [11,12]. Most probable values of h are around 0.33 because the most probable value of the spectral dimension d_s is found to be 1.33 (usually, the quantity exhibits a “connectivity” of the system, *i.e.* how likely a random walker can travel on the whole structure or how easily can the chemical reaction proceed. *etc.*).

The physical motivation of incorporating $k(t)$ into equation (1) may come from the following general picture. Namely, in biosystems or in “soft matter” systems like biomembranes or polymers, the cooperative structural changes in lipid bilayer membranes can be associated to either the growth of lipid domains or with some kind of disruption (lysis, phase separation, rupture, segregation, *etc.*) of the membrane material (or a part of it) caused by certain species like proteins, anaesthetics, impurities or by some external fields like pressure or temperature, or the gradients (changes) of them [4,17]. The phenomena are closely related to the strength of interactions in the system which are in general the lipid-protein (or lipid-solvent) interactions [4,6]. Furthermore, if the biological process involves migration of some agents like water molecules within the lipid matrix and the process of water penetration proceeds in one lipid domain in a quite different time regime than in another one, then the size of the domain, its microscopic structure as well as life-time (and many other factors like chemical affinity to the traveling walker) may be crucial. It can lead to the fractal-like reaction kinetics of the process and for sure cannot be understood in classical reaction-kinetic terms [1,11,12,18]. To be more specific, one could also recall here, *e.g.* the gel-to-liquid crystalline phase transformation of some multilamellar lipid bilayers, where still some discrepancies in the values of fractional dimensionalities characterizing the system kinetics exist (some values of approximately 2 have been reported [16]).

The second thing ($V_n(t)$), in turn, possesses a clear and unique meaning in the Avrami-Kolmogorov description. It has the form [16]

$$V_n(t) = gu^p R^3(t), \quad (3)$$

where g is a geometrical factor (“shape” factor), *e.g.* for spheres of 1.33π , and u is a radial growth rate (known in some typical cases like growth of sphere-like or other symmetric objects). The exponent p takes a value which comes from the $R(t)$ *vs.* t dependence ($R(t)$ is the radius of a single swollen and hydrated round domain taken at time t).

In the case studied it can be represented by a scaling formula of the form [19]

$$R(t) = st^q, \quad s, q > 0. \quad (4)$$

The question arises: what are the values of the quantities s and q ? The proper answer depends probably on whether we consider the behaviour of the system on a molecular (concerning a single lipid chain) level or that we attempt to describe the kinetics of the hydration on the supramolecular (concerning an individual domain or cluster) stage of structural organization of the membrane. In the former, for the lipid macromolecule squeezed by the external pressure applied the pre-factor s depends directly on the ratio of both the second and third virial coefficients, respectively, and if the lipid chain reflects the Gaussian (normal) properties the quantity s becomes just the length of the monomeric unit of the chain (see [19] pp. 90-92, for having more details). Note also that both these virial coefficients are temperature-dependent.

In the latter, one would postulate a phase separation process (*cf.* [20] and Refs. therein) in which the parent (elongated) phase is readily separated from the children (squeezed or normal) one by means of the same “external cause” frequently mentioned above. In this case the proportionality factor s may depend upon the volume fraction of a new phase as well as upon the correlation length of the pressure flow [20]. In both cases mentioned, the values of the exponent q are equal to either 0.33 (the squeezed or compressed state) or 0.5 (the Gaussian or normal state), independent of whether we deal with the system kinetics on molecular or on supramolecular level [19,20].

Applying equations (3) and (4) one gets at once

$$V_n(t) = gu^p s^3 t^{3q} \quad (5)$$

which means that $V_n(t)$ increases powerly with t (for $q = 1/3$, it increases linearly with t). Notice here that the value of the exponent into which t is raised (*i.e.*, $3q$) ranges between 1 and 1.5. It is in a qualitative agreement with the values measured in [16]. The difference, however, would be that the authors of [16] obtained the fractional dimensionality around 2, but for some phosphatidylcholine systems composed of multilamellar vesicles, whereas our system is mostly comprised of a non-lamellar (inverted hexagonal) DOPE-phase [8]; in general, some values of the exponent presented in [16] are greater than 1 and less than 2.

Let us mention that equation (1) is reminiscent of a typical chemical reaction kinetic equation of the first order with respect to f_h (*cf.* [12] and Refs. therein). If the hydration were slow when compared with lipid material structural changes then the first order kinetics with k being time-independent would be the case; in the opposite situation the hydration had to follow exactly the kinetics assigned to the structural lipid changes. Also, the case studied here is more complex, indeed. Moreover, notice that the f_h -variable is of the form of $f_h = \frac{V_h}{V}$, where V_h represents a volume of the swollen phase and V is the total volume of the system in question (note that f_h looks simply like the concentration of the reacting species or their molar ratio).

3. Results and Discussion

The solution of the problem represented by equations (1-5) reads

$$f_h(t) = 1 - A \exp \left(- \left(\frac{t}{t_r} \right)^{3q-h} \right) \quad (6)$$

i.e., for $0 < 3q < h + 1$, it is a stretched exponential (for $3q = h + 1$, it looks like a Debye relaxation function; otherwise, *i.e.* for $3q > h + 1$, the physical meaning of function (6) is unclear) [21]. The quantities A and t_r are of the form

$$A = \exp \left(\frac{w_1}{1 + w_2} t_0^{1+w_2} \right) \quad (7)$$

and

$$t_r = \left(\frac{1 + w_2}{w_1} \right)^{1/(1+w_2)} \quad (8)$$

where w_1 and w_2 are represented by

$$w_1 = 3Nk_0 q g u s^3 ; \quad w_2 = 3q - h - 1 \quad (9)$$

(Note that we have put here $p = 1$, for simplicity.) Throughout the rest of the paper, without loosing of generality, one may assume that $A = 1$ which holds for some t_r large compared to t_0 (it is a rather usual case observed in many biophysical systems [3, 8, 17]; *cf.* Eqs. (7–9)).

Now, the solution (6) can be rewritten as

$$f_h(t) = 1 - \exp\left(-\left(\frac{t}{t_r}\right)^{3q-h}\right), \quad (10)$$

and in the case of $h = 0$ and $q = 1/3$ or $h = 1/2$ and $q = 1/2$, this is the classical Debye relaxation function of the exponential form. Otherwise, it is always a stretched exponential with a critical exponent h_1 , where $h_1 = 3q - h$, ranging most probably between 0 and 1, but never reaching $h_1 = 0$ (discarding, however, the unphysical case mentioned above). Typically, h_1 is placed between 0.5 and 1 (see [11, 12, 19, 20] for details). Because of assuming above (see Introduction) the hydration process (represented by the exponent h) to be coupled in a complex (random walk) way with the lipid structural changes (represented here by the exponent q), we are aware that the result (10) can be restricted to h_1 ranging from 0 to 1 (this is the case of the classical stretched exponential relaxation kinetics [21]). Therefore, because of the limits of the h -range [11, 12], the most probable value of q is $1/3$ which physically means that the squeezed but hydrated state will dominate after the phase transformation, and some Gaussian chains or domains will be met rarely in the system after the pressure is applied. For this reason the most probable value of h_1 would be $2/3$. Note that, because of our assumption $A = 1$ which holds for the relaxation times big enough, one can approximate equation (10) by

$$f_h(t) = \left(\frac{t}{t_r}\right)^{h_1} \quad (11)$$

expanding solution (10) around its argument into the Taylor series and finishing this expansion on the linear first order term, and neglecting the higher terms because of being small.

The power function of t , represented by equation (11) and being a relaxation function of the system studied, is a particular result of this work. In fact, this result reflects a nonexponential relaxation kinetics of the system that we study. It will be used for a comparison with an empirical relation got from the fitting of data in the experiment [8]. The data show how does the lattice spacing in the DOPE-membrane relax in the course of time measured which is equivalent to the increase of the average number of water molecules per lipid molecule with time (designated by $n_w(t)$) after applying a hydrostatic pressure. (The relative lattice spacing, in turn, is a decreasing function of time; the temperature is kept constant during the whole measurements.) The authors of [8] got, finally, the empirical form of the following relaxation function, $F_h(t)$, namely

$$F_h(t) = \frac{n_w(t) - n_w(T)}{n_w(t_0) - n_w(T)}, \quad (12)$$

where T is the final time of the experiment. being distinctly larger than the relaxation time, and the function relaxes from 1 to 0 (*cf.* [8] for details). They fitted the function (12) by [8]

$$F_h(t) = \left(\frac{t_r}{t + t_r}\right)^{h_2} \quad (13)$$

which is also a power function of time (here, h_2 ranges from *ca.* 0.66 to 0.99). Note, however, that in [8], the current times of the experiment (say t_n) are measured as the multiples of the relaxation times t_r , *i.e.*

$$t_n = nt_r. \quad (14)$$

(Note that t_n are equivalent to the *discrete observation* times and n stands here for an averaged number of the measurement points in the time domain, *i.e.* $n = 1, 2, 3, \dots$).

In the case that we have developed theoretically (*cf.* Eq. (11) for comparison) times t_n , by construction of our model, are exclusively some fractions of the relaxation time, namely

$$t_n = \frac{1}{n+1} t_r. \quad (15)$$

It is so, because the relaxation time was assumed to be practically the largest time of the time domain taken into account (see discussion at the beginning of this chapter). Replacing formally t by t_n and inserting (14) into (13) and (15) into (11), one gets perfectly the same sequences of broken numbers. The only necessary condition for saying it would be

$$|h_1 - h_2| \rightarrow 0. \quad (16)$$

It would be so indeed, because the ranges of values of the both afore presented exponents are very close to each other or even the same. The most probable case that we opt for would be when $q = 1/3$. It means, that for satisfying equation (16), one has to have h between *ca.* 0 and 0.33 (notice, once again, that $h_1 = 3q - h$). Thus, it implies that, both, the theoretical as well as the experimental cases are, at least, of the same quality. Some quantitative agreement between them can also be anticipated (see above). Note formally, that one gets equation (13) by applying equation (11) and some “group properties” (or rescaling) like $t \rightarrow t_r$ and $t_r \rightarrow t + t_r$ as well (obviously, Eq. (16) has also to be considered in this case).

Such rather small values of the h -exponents are observed in the case when the random walk process (hydration coupled with structural lipid changes) is proceeds anomalously, *i.e.* when the structure has many kinetic *obstacles* like *e.g.* a change of the tilt angle under pressure even under equilibrium conditions [22] or some steric hindrances or structural traps and cavities [4,23]; also, one has to take into account a strong tendency towards hydrogen bond formation, the presence of polar head groups (there is no simple correlation between the number of polar head groups and solubility; note also that the polar groups of the lipid will tend to react with water on the surfaces of lipid domains) or even accessibility of polar groups and, also, relative strength of the water-water *versus* water-polymer bonds [2,4,6,11,12,24] (*cf.* [25] for a general information as well). The situation can generally be called a case in which the reactants are compartmentalized or confined well enough to the interior or, perhaps, to a vicinity of the lipid domain chosen [10,18,24]. Moreover, some defects may be contained in the system; for instance, one knows that a lecithin in the process of swelling is a smectic with some dislocations or focal conics [1-7]. This is also a general motivation why one may try to use the fractal-like chemical reaction kinetics in this context (*cf.* Eq. (2)).

Obviously, the agreement between theory and experiment presented in these considerations has not been obtained in a very formal way. The formal agreement would demand some very carefully developed theory, where “such useful but a bid protetic tools”, like equations (14) and (15) are not necessary at all. But this work is rather addressed to some experimentalists which like mostly certain simple arguments. To be in very agreement in this study, one should also have available some measured values of the exponents h and q which are quite well-known for some model systems [11,12,18-20]. Therefore, the modelling served shows rather some promising trends (note, for example, that f_h and F_h are not the same functions, but they may certainly be related to each other) between the theory and experiment than it gives someone satisfaction from the formal point of view. It has, in consequence, some hypothetical character, though, it was readily motivated by the experimental study [8].

4. Concluding Remarks

Let us first summarize the results obtained in the paper. Namely, in Section 2 we have presented the description of the pressure induced hydration in terms of the Avrami-Kolmogorov [14,16] and fractal-like chemical reaction kinetics concept [11,12] combined together. In Section 3 we have revealed some results of that modelling, mostly by stating explicitly and applying the relaxation function $f_h(t)$ of the system studied. We have also obtained quite promising trends concerning the agreement with the experimental measurements reported in [8] and represented by the relaxation function $F_h(t)$ (see all the equations presented in the preceding section).

Here, we wish to list a few possible advantages and drawbacks of our modelling. In our opinion, to the first group belong:

- (i) some well-established “physical structure” of the relaxation time (*cf.* Eqs. (8) and (9)), being essentially of the Vogel-Fulcher form [21];
- (ii) quite physical picture of the situation modelled: domain-growth like in [14,16,18,20], swelling proceeded in a homogeneous way, and fractal-like reaction concept utilized which is, however, not exclusively applicable to the geometric fractals [12]; also, the hydration process coupled in a complex way with the lipid structural changes (h would be a characteristics of this complexity);
- (iii) very good tendency towards agreement with the experimental data reported in [8].

The second group can contain some doubts like:

- (i) for which time regime the application of that modelling is firm?
- (ii) how to apply in a precise and not so phenomenological way the spectral dimension or anomalous random walk concept and what should the experimentalists do under such circumstances?
- (iii) is the scaling for a squeezed lipid macromolecule with the exponent 0.33 (see Eq. (4)) really the case?
- (iv) is the description presented not too oversimplified because at the nanometric size scales the quantum effects [26] may enter and because it requires to estimate only two parameters h and q (from the practical point of view, note that if one will apply the Alexander-Orbach conjecture only [12], it will need to determine two parameters of the system: by, *e.g.*, small-angle X-ray or light scattering experiments [17], the fractal dimension of the membrane that will typically be an Euclidean object or, perhaps, a percolation cluster, and the fractal dimension of the random walk of a water-lipid complex that can be obtained from the fluorescence photobleaching recovery experiments or in single-particle tracking measurements; *cf.* [27] and Refs. therein)?

One can see, at least, two other ways that lead to justify the reasoning presented in this study and to get the solution to the problem of the forms of equations (10) and (11). The first one is more or less equivalent to the modelling shown here. The only difference is that the kinetics of the process would be postulated to be of the broken order, denoted usually by x (*cf.* [11,12] for details), like that $x = 1 + \frac{1}{1-h}$, but with the chemical reaction rate coefficient being constant. The second one, in turn, would explore, in a more formal way, the same concept like this studied here (also, one would be pleased to start from the Eq. (1) with the same “additional assumptions” represented by Eqs. (2–5)). A technical difference when comparing with our modelling would be that, firstly, a formal substitution of $Nk(t)$ by $N(t)$ (one can read it as a time dependent number of swollen “nuclei”) is required, and then, a

change of variables during the integration process is to be done, that physically would mean that there exist a constant density of hydrated domains (“nuclei”) in the system in question. This would be, however, an interesting case for subsequent study [28].

A question concerning the role of the fluctuations in the system seems to be worth stating. Namely, after the pressure being applied and when the swelling effect still influences the whole behaviour of the system, the “invasion” of water molecules and/or water agglomerates proceeds rather throughout transient fluctuations in the bilayer structure. Because it may cause, due to the elastic free energy change, some effect on the membrane channel lifetime as well as on membrane curvature elasticity [29], it may also influence the permeation through the membrane channels [30]. Under such circumstances, the mechanism proposed can fail, and *e.g.* the anequilibrium phase transitions theory, where the first order time derivatives can be replaced by some derivatives of a broken order (these phase transitions are of the order of less than unity) might be of help; such a formalism is very suitable for dealing with the phase transitions in highly fluctuating inhomogeneous systems like glassy polymers [31].

Last but not least, it is hoped that the problem will attract an undivided attention because of possible vast applications mentioned. *e.g.* in [2,8,15,26,32]. A need for some new experiments, mostly leading to determination of *h*-exponent seems to be worth suggesting as well.

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