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Inter–Intra Molecular Dynamics as an Iterated Function System

Kunihiko KANEKO

Department of Basic Science, University of Tokyo and ERATO Complex Systems Biology, JST
Komaba, Meguro-ku, Tokyo 153-8902

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Several extensions of an iterated function system (IFS) are discussed as possible applications to abstract dynamics of units (molecules) with slowly relaxing internal states under frequent collisional interactions. It is found that an increase in the collision frequency leads to successive discrete states that can be analyzed as partial steps to form a Cantor set. By considering the interactions among the units, a self-consistent IFS is derived, which leads to the formation and stabilization of multiple such discrete states. The proposed mechanism, if it exists in a complex polymer under a crowded condition, allows for the kinetically induced formation of multiple states.

KEYWORDS: iterated function system, Cantor set, inter–intra molecular dynamics
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Biological units have internal dynamics which are often in the same order of magnitude as those caused by interactions between different units. Furthermore, the internal relaxation times can be rather long in general. This is true also in complex biomolecules, as, for example, was shown in recent experiments on Ribozymes and some proteins.[1–4] Besides this slowness in relaxation, the molecules also take multiple conformations dynamically.

On the other hand, molecules in a cell are in a very crowded situation, as, for example, was beautifully illustrated by Goodsell,[5] leading to relatively frequent collisional interactions. Then, in contrast to the standard situation, the time scale of the internal relaxation is in the same order of magnitude or even slower than that of the interaction as has also been discussed by Mikhailov and Hess.[6] In this case, if the magnitude of the forces for the two are of the same order, the interaction cannot be treated as perturbation, and such "inter–intra dynamics"[7] may lead to novel behaviors unexpected from internal dynamics. Here we discuss the possibility that molecules with slow relaxation time scales, when put in crowded conditions, may exhibit novel dynamical states that are not expected when considering only single molecular dynamics (see also ref. 8.) To be specific, we consider the situation that the internal dynamics have just a single stable state, and seek the possibility that only random collisional interaction with other molecules induce multiple stable states, by assuming that memory on the internal state is not completely lost through the collisional interaction.

Instead of studying a realistic molecular process, we choose a rather abstract model to propose a novel 'crowdedness-effect' and to describe it in simple dynamical systems. We will show that iterated function systems (IFSs),[9,10] originally studied in the mathematics of fractals, can be relevant for studying such inter-intra molecular dynamics, by making several extensions.

Here, we explain what we mean by "collision" (or collisional interaction) in the present letter. A biomolecule often has some binding sites. When a specific molecule binds to such a site, conformational change in the molecule often occurs before it is released. We call such a process a 'collision' in this letter, i.e., the process of binding of a specific molecule leading to a specific conformational change and its release [see Fig. 1(a)]. By this collision, the molecules are excited so that in this crowded condition with frequent collision, they are assumed to be in a nonequilibrium state.

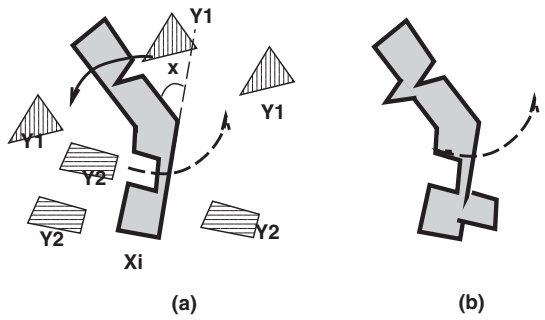

Fig. 1. A toy molecule, that may illustrate the internal variable x. It has two binding sites, and when the "triangle" molecule Y_1 collides (binds) to the corresponding site, a conformational change to a positive angle direction occurs, while the "square" molecule leads to a different conformational change. In (b), multiple units of a single type of molecule collide with each other. When $x < 0$, the "triangle" part is at the outside so that it can bind to the triangle hole of another molecule more easily, and vice versa.

Concretely, we consider situations where the average time between molecular collisions t_c is less than or in the same order of magnitude as the internal relaxation time of each molecule t_r. As we have mentioned, the major assumption we made here is that the memory of the internal variable is not completely lost by the collision: for some variable characterizing the internal state, the value after the collision depends on that before the collision to some degree, even though large fluctuations exist around the mean value. Although the existence of such memory has not been directly been proved experimentally, it is interesting to consider such a theoretical possibility, as motivated by recent discoveries on long-term dynamics in proteins.[1–4]

Instead of attempting to simulate realistic dynamics of complex biomolecules, we consider an abstract model here in order to obtain insights into possible novel features in systems with slow internal relaxation and frequent interaction, as a first step to understanding interacting biomolecule dynamics. We take a simple internal state of a "molecule" X that is represented by a scalar variable x.

For example, one can consider a toy molecule with an internal angular variable x, as schematically shown in Fig. 1(a). As a starting point, we take the simplest form of relaxation of this internal state towards $x = 0$,

$$dx/dt = -\gamma x + \sqrt{\gamma T}\eta(t), \tag{1}$$

with white Gaussian noise $\eta(t)$, $\gamma = 1/t_r$, and T the temperature. Hence the distribution of x approaches Gaussian around $x = 0$ as the collision frequency decreases. In the toy molecule of Fig. 1(a) the energy is at a minimum when the molecule is straight.

In general, collisions with other molecules induce changes in the internal states such that $x \to x'$, which are assumed to occur randomly at the rate $r_c = 1/t_c$. If the memory on the state before collision is lost completely, x' is just $x^* + \xi$, with x^* as the target value after collision and ξ a random variable, both of which are independent of x (before the collision). Instead, we have assumed here that some memory is retained, meaning that x' approaches x^* but still retains some memory on x. As a simple idealization, let us represent this change as the map $x \to x' = f(x)$, which will depend on the species of the colliding molecules. Here, $f(x)$ is a function contracting to the target value x^* but preserving some memory on x, the value before the collision. As an abstract example, let us consider the case where there are other molecule species $Y_1, Y_2, \ldots, Y_k$ ($k > 1$), and the target value depends on the type of collided molecule. Upon collision, the state of molecule X changes as $x \to f_j(x)$ ($j = 1, \ldots, k$).[11] As mapping has the target value x_j^*, and retains some memory on x, a simple illustration will be $f_j(x) = a_j(x - x_j^*) + x_j^*$. In other words, the state x of molecule X moves towards x_j^*, depending on which molecule type Y_j it collides with, while retaining some memory of the original state value x before the collision, to the degree of a_j ($j = 1, 2$). Thus x takes a value between x and x_j^* with the weight $a_j : 1$. Representation of the change in the internal state upon collision as a map is a drastic simplification. Still, by assuming that some memory is retained, existence of such variable x may not be so absurd. (Note the use of the above one-dimensional map merely represents memory for some variable on the previous value of x, while one can add a large noise term to it, as will be discussed.)

Now we study an ensemble of "molecules" X, to see how the distribution of the states x depends on $r = r_c/\gamma$. Note that in the limit of $\gamma \to 0$ (i.e., $r \to \infty$), this problem is reduced to an IFS (with noise). Iterated function systems have been studied extensively[9,10] in fractal geometry and dynamical systems theory[12–14] as well as in the context of image data compression. It was shown, for example, that the stationary distribution of the states x obtained through random iterations of functions with these contracting mappings can take an infinite number of peaks on a Cantor set. On the other hand, in the limit of $r \to 0$, the distribution of internal state x approaches the normal distribution given by Langevin equation (1). For a finite value of r, and under finite temperature T, it is then expected that the complete Cantor set by the original IFS is destroyed. Still, more than single states may remain, which will be interesting since the molecule in a less crowded condition (with small r) takes only a single state. If so, the formation of these multiple states are a salient feature of "crowdedness". Hence, we first discuss how the behavior in the original IFS is altered for a finite value of r and finite temperature T.

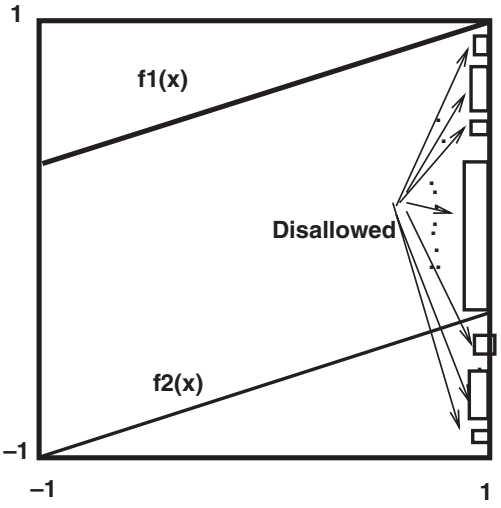

Fig. 2. One-dimensional map of eq. (2), with $a_1 = a_2 = 1/3$. The values of x which belong to the invariant measure of the IFS consisting of these two maps can simply be obtained by successively removing the preimages $f^{-j}(X_k)$, starting from the interval $X_0 = [2a_2 - 1, 1 - 2a_1]$, which leads to a standard Cantor set that is constructed by removing the middle one-third segments successively.

As a simple example, we consider the case $k = 2$ with

$$f_1(x) = a_1(x - 1) + 1; \quad f_2(x) = a_2(x + 1) - 1, \tag{2}$$

as illustrated in Fig. 2, where state x of molecule X moves towards $+1$ or -1, depending on which molecule type Y_j ($j = 1, 2$) it collides with. The molecule state x is shifted to either $+1$ or -1, retaining some memory of the original state value x before the collision, to the degree of a_j ($j = 1, 2$). For example, in the toy model described in Fig. 1, there are two types of colliding molecules: triangles and squares. Depending on the type, the binding site on X where a molecule attaches is different, so that the direction of the angle change is opposite.

Let us consider the distribution of state values x when the collision process is repeated. In the limit of $r \to \infty$ the distribution of state values x is shown to form a Cantor set if $a_1 + a_2 < 1$, i.e., if there is a gap between maps f_1 and f_2, as displayed in Fig. 2. [This is easily understood by considering the distribution function to be invariant in time, as constructed by the inverse of map (2).] This invariant measure on the Cantor set does not rely on the specific linear form of eq. (2), but is general as long as there are (at least) two stable fixed points around which the map is contracting sufficiently, corresponding to the condition $\sum_j a_j < 1$.

For finite r and finite temperature T, we numerically studied our model by colliding two types of equally distributed molecules at a rate r_c. We obtain the stationary distribution of x by taking a large number of molecules, or by sampling the values of x of a single molecule over time. (The results of the two methods agree, as expected from ergodicity.) As shown in Fig. 3(a), several peaks are observed in the distribution with the increase of $r > 1$. Even though the whole Cantor set structure is not observed for finite r, multiple peaks are clearly discernible for $r > 1$. Several discrete states of x are formed through the molecular

collisions, even if the original relaxation dynamics has just a single stable state. The peaks successively split as r increases, so that many discrete states are formed. Figure 4 shows that the number of peaks in the distribution versus r displays a power-law increase with an exponent that is consistent with that for the increase of the peaks against the precision in the Cantor-set construction, $-\log 2/\log a$ (for the present example with $a_1 = a_2 = a$). In other words, an increase of the collision frequency corresponds to an increase of the precision in the Cantor set construction. This power law is not altered much by changing γ or T, while for large T (i.e., larger noise), the increase is suppressed. Also, even if the condition for the Cantor set $\sum a_j < 1$ is not satisfied, the multiple broad peaks appear, as shown in Fig. 3(b).

So far we have discussed the case where molecule X collides with only a finite number of other molecule species, $Y_1, \ldots, Y_k$. Now, we consider the case where there is only a single type of colliding molecule, but it has a continuous state so that the change of molecule X by it depends on the state of the Y molecule whose internal state is represented by the variable y. (Or one can consider the case that the change of x upon collision depends on how it collides, *e.g.*, the angle of collision, which corresponds to y.) In other words, the state change of x is given by a family of functions $g(x, y)$ parametrized by continuous y, instead of $f_j(x)$, for discrete j. Here the distribution of y is given by some distribution function $\rho(y)$. The question now is whether the discretization of states appears even for this continuous case. (As a dynamical system, this provides a novel class of problem, i.e., a continuous IFS.) As a specific example, we investigate

$$g(x; y) = a(x - f(y)) + f(y); f(y) = \tanh(\beta y), \qquad (3)$$

where, for simplicity, we take $\rho(y) =$ constant over $[-1, 1]$. In the limit of $\beta \to \infty$, the model reduces to eq. (2), and here we are interested in how the behavior is altered for finite β. The distribution of $P(x)$ obtained in this case is depicted in Fig. 5(a) which shows the existence of a Cantor-set-type structure as β increases beyond 2. To have these multiple peaks in the distribution, threshold-type dynamics ($\tanh(\beta y)$ with $\beta > 1$) is necessary, a situation which often exists in molecular interactions or in biological systems in general.

Thus far we have discussed the situation where the distribution of $\rho(y)$ is given in advance. There are cases, however, in which the distribution of state x influences the distribution of the state of the colliding molecules. For example, assume that X is an enzyme protein with multiple catalytic activities and the shape of X governs which molecule it can catalyze. We consider a single species of X, but the production rate of molecule species Y_j depends on the internal state x of molecule X, and thus on the distribution of $P(x)$, with the internal variable x being an index of the shape. If this influence of the distribution of x on the distribution of Y molecules is sufficiently fast, the fraction of Y molecules can be regarded to change instantaneously, and is adiabatically eliminated. Then the distribution of y is replaced by the distribution of x, which changes through the collision dynamics. Alternatively, one can simply consider the collision dynamics just among X molecules such that the configuration of the colliding molecule determines what type of collision takes place [for example, consider the modified toy model in Fig. 1(b)].

In these cases, the state change of molecule X (with the state value x) upon collision with another molecule X' of the same species (with the state value x') is given by the mapping $x \to g(x; x')$. If the distribution of x' were given and fixed, this would be nothing but the IFS discussed above. The distribution of X, however, changes upon collision, because the distributions for x and x' are identical since they are the same molecule species. With this update of the distribution, the problem is represented by a "self-consistent IFS".

As a specific example, consider the case

$$g(x; x') = a(x - y) + y; y = \tanh(-\beta x'). \qquad (4)$$

The result of a numerical simulation of this model[15] is given in Fig. 5(b) where it can be seen that the distribution has again multiple peaks when r is larger than 1, i.e., when the collisions are frequent. With the increase of r, peaks successively split, thus discretizing the states. There are already 4 peaks for $\beta = 2$, and as the threshold function becomes steeper, more peaks are formed, again mirroring a few steps in the construction of a Cantor set. These discrete states corresponding to peaks are stabilized "self-consistently" through interactions with other X molecules and are stable against noise and the influence of the relaxation dynamics.

In summary, we have shown that multiple discrete states can be formed as partial Cantor sets, through collisions of units with internal dynamics, even if the dynamics of each element has just a single stable state. This process is possible when the time scale of the collisional interaction is similar to or faster than the internal relaxation time scale and when there are several types of interactions that cause different conformational changes, and each element has some memory of the previous state through the collision. A novel class of phenomena, i.e., the formation of multiple internal states due to the crowdedness, is observed. The discretization of states becomes clearer as the ratio of collision frequency to internal relaxation time increases.

Note that whether the present phenomena exist under a crowded condition depends on the degree of the memory of conformation through the collisional process. As the collisional process includes high-dimensional dynamics represented as noise, the preservation of very fine structures in the partial Cantor set should be almost impossible. When the memory is totally lost [*e.g.*, for $a_i = 0$ in model eq. (2)], there is only a transition in the distribution from the peak around $x = 0$ to those at $x = \pm 1$ due to the crowdedness. With some memory in the collisional process, however, the formation of intermediate states is possible, despite the presence of internal relaxation and noise, even though finer structures in the distribution may be smeared out by noise. Indeed, we have studied the present model by further adding a Gaussian noise term ξ at every collision event. Even if the standard deviation of this noise is 0.5, 6 peaks are observed for $a_i = 0.3$, while even for $a_i = 0.1$, 4 peaks remain. Thus, the generation of several intermediate states is possible, even if the standard deviation of the noise is much larger than the memory term (of the order of a_i).

We have further studied a novel class of IFS by extending it to a continuous family of functions in the IFS, while a

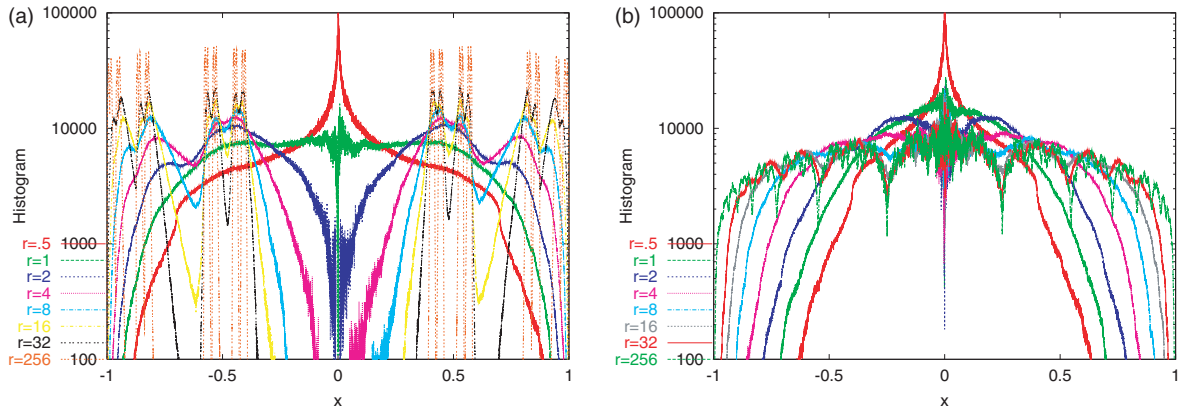

Fig. 3. Histogram $P(x)$ for various values of r and fixed $\epsilon = 0.01$, $\gamma = 0.01$. (a) $a_1 = a_2 = 0.3$, (b) $a_1 = a_2 = 0.6$. The histogram is obtained with 5×10^8 iteration steps after discarding the initial transients, and sampled with bin size 0.001. $T = 0.01$.

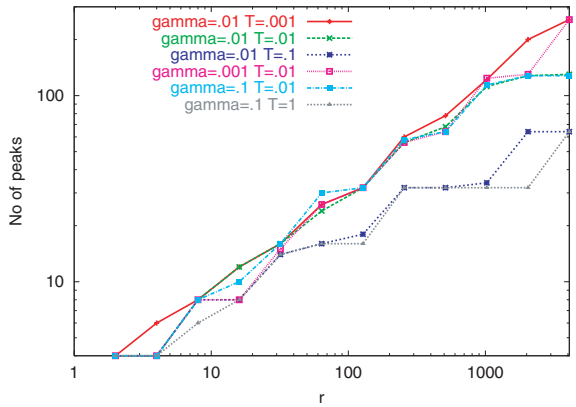

Fig. 4. The number of peaks in $P(x)$ plotted as a function of r. $a_1 = a_2 = 0.3$. The distribution $P(x)$ is obtained in the same way as in Fig. 3. Results from several values of γ and T varied over 0.001, 0.01 and 0.1, as displayed in the figure, are overlaid.

novel class of statistical dynamics is introduced that could be termed a self-consistent IFS (SIFS), by including a feedback to the distribution of the internal states from the distribution of the colliding units. Note that in the limit of $r \to \infty$, the SIFS is nothing but a random-update version[16] of a globally coupled map,[17] where the distribution of states x can show collective motion. By taking, for example, a non-monotone map of $g(x, x')$ for x, there are cases that the distribution function changes in time.

Another extension of the present approach will be an explicit use of the population dynamics of the colliding molecules Y_j, instead of the adiabatic elimination of Y_j molecules as adopted in the SIFS. For example, by assuming that which type of molecule Y_j is synthesized depends on the state x, the production rate of molecules Y_j is proportional to $\int_{x \epsilon I_j} \rho(x,t)\,\mathrm{d}x$, where $\rho(x,t)$ is the density of state x at a given time t, and I_j is the range of x values that catalyzes the synthesis of Y_j. By introducing the population dynamics $\mathrm{d}N_j/\mathrm{d}t = c \int_{x \epsilon I_j} \rho(x)\,\mathrm{d}x - \Gamma N_j$ for molecule species Y_j, and the collision dynamics $x \to f_j(x)$ as in eq. (2), self-consistent dynamics on the distribution $\rho(x,t)$ is derived, that couples with the population dynamics of N_j as above. This model was also studied numerically and it was found that, besides the appearance of multiple peaks in the distribution, the height of the peaks can change over time, suggesting the existence of the collective motion well known to occur in globally coupled maps.

The aim of the present letter is to propose a theoretical framework where (self-consistent) IFS is applied to inter–intra molecular dynamics of an ensemble of units. As an illustration, a very simple model for collision and relaxation

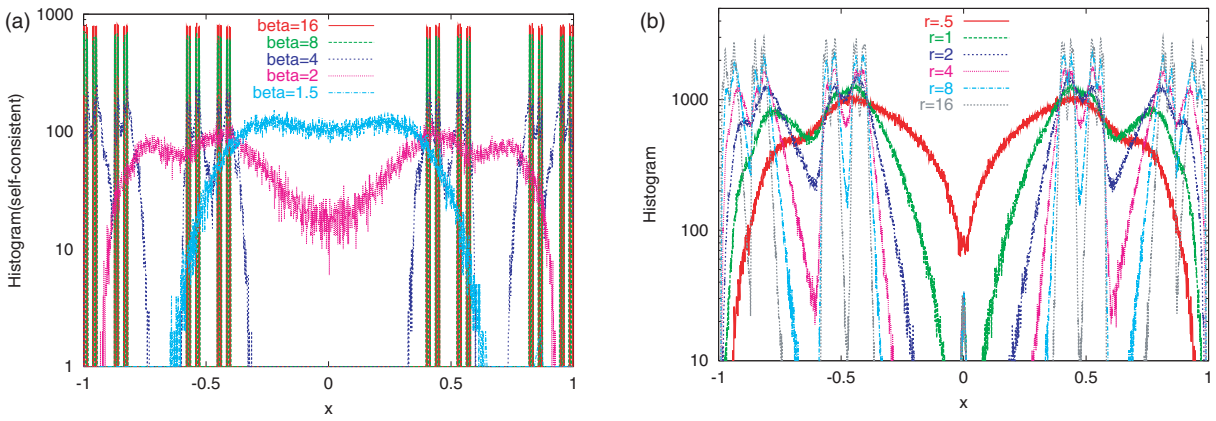

Fig. 5. (a) Distribution $P(x)$ of the states x, for model (3) with $a = 1/3$. For simplicity, the internal relaxation dynamics is excluded here (only for this figure) by taking $\gamma = 0$, while, these discrete states are again stable as long as $r_c/\gamma > 1$, as discussed for Fig. 3. (b) Self-consistent formation of many discrete states. A snapshot distribution $P(x)$ of the states x is plotted for the model (4) by using 10^6 molecules with $a = 0.3$ and $\beta = 8$. $T = 0.01$, and $\gamma = 0.01$.

dynamics was discussed, while a variety of straightforward extensions, such as higher degrees of freedom for internal dynamics, more realistic collision dynamics and feedback with several types of molecules, will be discussed in the future. As cells are very crowded and some proteins such as Ras show multiple conformations with a slow timescale, it would be interesting to pursue the possibility of the present mechanism studied here, which suggests that the conformations of some plastic molecules may depend on the concentrations of the molecules themselves and of the molecules they collide with. If the mechanism exists, we expect to see the stabilization of the discrete states through the interaction with other molecules, as well as switching among these states.

Finally, the present discretization of states by IFS can also be applied to systems with internal dynamics and 'kicking' interactions in general.[18] The dynamics of coupled neurons can also be discussed along these lines, while the relevance of Cantor sets in neural information processing has been pointed out by Tsuda.[19] Several extensions of IFS, as proposed here, will provide novel theoretical schemes for analyzing biological systems that exhibit the formation of stable, discrete states through synergies between interaction and internal dynamics.

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