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Inter-basin dynamics on multidimensional potential surfaces

Kinetic traps

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Abstract. A statistically based characterization of the topography of a standard potential surface (PS) may allow its reconstruction in basins containing monotonic sequences of local minima and saddles. Starting with this partition of the PS, one can explore kinetic properties of those basins and provide a reliable dynamical diagnosis. We found that certain topographical patterns of the standard PS underly kinetic properties which may lead the probability density to concentrate in basins of high energy, in which "wrong" structures are kinetically favored, rather than in the basin of the global minimum. We examined also considerations that link properties of the contact between the reaction coordinate and thermal bath with the efficiency of relaxation on the PS.

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Potential surfaces (PS) hold the key to understanding a wide range of molecular phenomena. The problems of how a denatured protein re-folds to its active state, what governs a system's "structure-seeking" or "glass-former" characteristics, or similarly, the "strong" and "fragile" classification of liquids and glasses have largely been addressed in terms of the underlying energy landscapes [1,2]. In order to characterize a PS it is necessary to select and then survey its important features: minima, transition states and pathways. Since the number of such features increases at least exponentially with the number of the system's constituents (atoms, ions or molecules), it is impractical and undesirable to catalogue them all for large systems. Thus, it seems more convenient, at a given total energy of the system, to focus on those minima of the PS which can be grouped into disjoint sets, called basins. Recently, we developed the inter-basin motion (IBM) approach, which recasts the dynamics on a multidimensional PS from state-to-state to basin-to-basin transitions [3]. The leading assumption is that the intra- and inter-basin dynamics are of different scales. The IBM approach uses a general prescription to compute, directly, the escape rate of the system from each basin of the characteristic PS with full consideration of the topographical fingerprint of that basin. The theoretical foundation is provided by a non-Markovian treatment of the system's behavior inside the basin. In addition, the approach allows one to study the relation between the dynamics and the coupling with the thermal bath.

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Here, we briefly review the basic concepts of the IBM approach. To illustrate the utility of these concepts we use the IBM approach to diagnose dynamics on various PSs. We show that certain topographical patterns of complex PSs underlie kinetic properties that may lead the probability density to concentrate in basins of high energy, in which "wrong" structures [2] are kinetically favored, rather than in the basin of lowest energy, often assumed to be the native structure in the case of proteins. Based on this information, we are able to conclude that kinetic traps of "wrong" structures are distinctive topographical patterns that may induce kinetic properties similar to those of the basin containing the global minimum, but lie in other basins. We examine also properties that link the contact between a reaction coordinate and thermal bath with the efficiency of relaxation on the PS. This strategy seems very informative in the study of dynamics of conformationally constrained systems, where the constriction in the conformation space may frequently culminate with splitting the energy landscape in multiple competing basins [4]. It may also help to improve the optimization method for controlling the structures of clusters and nanoscale particles during their preparation and to the modeling of real materials [5,6].

The IBM approach assumes that the basin dynamics is governed by energy accumulation and relaxation processes among the local wells (individual minima composing a basin). The change of curvature of the effective potential between the bottom and the top of each local well can bring the typical rate of energy exchange between the

reaction mode and other modes to a value comparable with that of the characteristic vibrational period of the thermal bath. In this case, the system's motion inside the basin is non-Markovian. This behavior is characterized by a time-dependent friction kernel $Z = Z(t)$ at the contact between the system and the thermal bath, which usually is assumed to have a Gaussian form

$$Z(t) = \frac{\gamma}{t_c\sqrt{\pi}} \exp\left(-\frac{t^2}{4t_c^2}\right). \tag{1}$$

Here, $Z(t)$ expresses the time correlation function of the random force $F(t)$ exerted by the thermal bath on the reactive mode and is associated with the correlation time t_c and the Markovian friction γ; t_c is a measure of the extent or rate of equipartition of the reaction mode ω with the thermal bath. The random force $F(t)$ exerted by the thermal bath on the reaction coordinate is also Gaussian and satisfies the second fluctuation dissipation theorem $\langle F(t)F(0)\rangle = Mk_BTZ(t)$ [7]. Here k_BT $(= 1/\beta)$ has the usual meaning and M stands for the mass of the system. The above statement enables a formulation of a stochastic, one-degree-of-freedom process for the energy E in the unstable mode $\omega(E)$

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial E}\left[\mu(E)\left(\frac{\partial}{\partial E} + \frac{1}{k_BT}\right)\omega(E)\,p\right]; \tag{2}$$

μ is the energy diffusion coefficient. This is known as the reduced Fokker-Planck equation which gives the probability distribution $p(E,t)$ for the energy variable E. This equation implies the following expression for the mean first passage time $\tau_{i,\alpha}$ along each "escape channel" that leads the system to reach the top of the basin $\alpha(E_{b\alpha})$ starting from a specified local well i:

$$\tau_{i,\alpha}(E_{b\alpha}, E_s) = \int_{E_s}^{E_{b\alpha}} \mathrm{d}E \frac{\exp(\beta E)}{\mu_{i,\alpha}(E)} \int_0^E \mathrm{d}E' \frac{\exp(-\beta E')}{\omega_{i,\alpha}(E')}. \tag{3}$$

We now define an effective value of the mean first passage time $\tau_\alpha(E_{b\alpha}, E_s)$, which is the summation over independent contributions $\tau_{i,\alpha}(E_{b\alpha}, E_s)$ of all the individual states $w_{i,\alpha}$ $(i = \overline{0, N_\alpha})$ of the basin α

$$\frac{1}{\tau_\alpha(E_{b\alpha}, E_s)} = \sum_{i=0}^{N_\alpha} \frac{f_{i,\alpha}(E_i, E_{bi})}{\tau_{i,\alpha}(E_{b\alpha}, E_s)}. \tag{4}$$

Here, $\tau_\alpha(E_{b\alpha}, E_s)$ is the average time in which the system escapes from the basin α; N_α is the number of conformation states in the basin α and accounts for the geometric entropy dimension of that basin; f is the weight of each individual contribution to the average (4) given by

$$f_{i,\alpha}(E_i, E_{bi}) = \vartheta(E_{bi} - E_s)\,\vartheta(E_s - E_i), \tag{5}$$

where ϑ is the unit-step function. Also E_i and E_{bi} are the positions on the energy spectrum of the minimum $w_{i,\alpha}$ and the saddle between the minima $w_{i,\alpha}$ and $w_{i+1,\alpha}$, uphill. We then use the following expression for computing the escape rate coefficient from the basin α

$$k_\alpha = \int_0^{E_{b\alpha}} \mathrm{d}E_s p_{ss,\alpha}(E_s) \left(\sum_{i=0}^{N_\alpha} \frac{f_{i,\alpha}(E_i, E_{bi})}{\tau_{i,\alpha}(E_{b\alpha}, E_s)}\right), \tag{6}$$

which is the average of the effective value of the mean first passage time τ_α over the steady state distribution $p_{ss}(E_s)$. We assume that the system rapidly achieves thermal equilibrium in the well of the starting point E_s, so that the steady state distribution of probability p_{ss} is of a Boltzmann form

$$p_{ss,\alpha}(E) \simeq \frac{\mathrm{e}^{-\beta E}}{\beta(1 - \mathrm{e}^{-\beta E_{b\alpha}})}. \tag{7}$$

In order to compute the escape rate coefficient k_α (Eq. (6)) corresponding to the basin α, we have first to account for the average value of $\tau_\alpha(E_{b\alpha}, E_s)$. According to equation (4), this quantity can be obtained if one knows the contributions $\tau_{i,\alpha}$ of the individual minima. The independent contributions $\tau_{i,\alpha}$ (Eq. (3)) to the average value of the mean first passage time τ_α depend on both vibrational frequency function $\omega_{i,\alpha}(E)$ and corresponding energy diffusion coefficient $\mu_{i,\alpha}(E)$. The key frequency is derived from the specific form of the potential V_{eff} in the region of the interbasin saddle or divide. Here, this is approximated by a harmonic oscillator of frequency $\omega_\alpha^{(0)}$. Accordingly, the corresponding energy diffusion coefficient is [3]

$$\mu_\alpha(E) = \frac{E\gamma}{\beta\omega_\alpha^{(0)}} \exp\left(-\rho_\alpha^2\right), \tag{8}$$

where $\rho_\alpha = \omega_\alpha^{(0)} t_c$ determines the memory friction parameter. If the system is embedded in a solvent, the friction constant γ (the damping rate) depends on the viscosity of the environment and on the characteristic geometry of the system inside the particular basin α [4]. What we obtain here is the connection between the thermal bath properties and the ability of the system to relax on a complex PS. Generally, this information is of great utility in controlled optimization of the structures of clusters and nanoscale particles during their preparation and in the modeling of real materials.

The above approach makes it possible to study the relation between topography and kinetics on those complex potential surfaces that are reasonably described by samples of their basin patterns. Thus, equation (6) contains all the requisite information about the main properties of the topographical pattern, particularly the relative positions of minima and saddles along the monotonic sequences. (These are sequences of stationary points whose successive minima have energies that increase monotonically from the basin bottom [5].) Moreover, general properties of the thermal bath also intervene in system's dynamics. The set of equations (3–8) is used to compute escape rates from corresponding steep basins on a particular sample of the PS. Those rates are incorporated into a master equation

$$\frac{\partial P_\alpha}{\partial t} = \sum_\lambda \left(k_{\lambda\alpha} P_\lambda - k_{\alpha\lambda} P_\alpha\right). \tag{9}$$

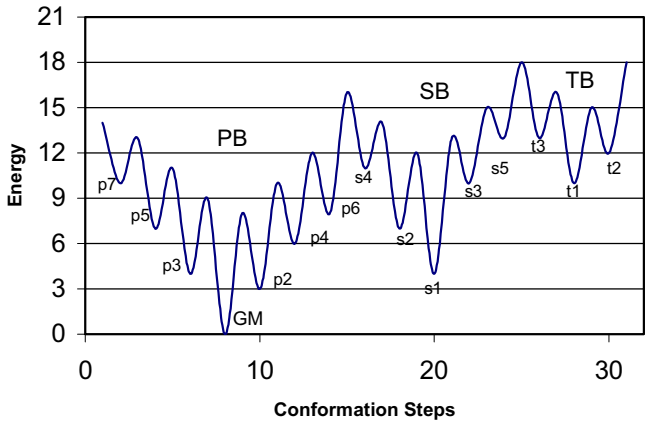

Fig. 1. The archetype of potential surface (PS) yielding the kinetic trap in the secondary basin (SB). In this figure, PB stands for the primary basin, TB denotes the tertiary basin and p_i, s_i and t_i define the individual minima composing these basins.

The description of flow of a distribution on the surface is then extracted by analyzing the eigenvectors (P_α) of the master equation in terms of the pattern of the topography of that PS. The $k_{\alpha\lambda}$ is the transition probability from basin α to basin λ [5].

Based on our previous results [3], we are able to design the topography of a PS that may afford kinetic traps. For instance, we can select arbitrarily a sample of PS, proceed further with partitioning the basins and compute the escape rates from those basins. Then, we smoothly modify the topographical pattern of a certain basin, say the secondary basin (SB) of the PS depicted in Figure 1, to make its kinetic properties the same as those of the primary basin (PB). Afterwards, we examine the probability flow on this new PS sample and show that, at long times, the system explores equally both primary and secondary basins. Obviously, the system remains in the SB for very long times before achieving equilibrium if the topography of the SB is designed to yield even a lower rate of escape.

With all the assumptions of the model and its mathematical output now presented, we are in the position to compute the escape rate k_α for each of these three basins. All topographical information about the PS required in our computation is contained in Figure 1. The energy is displayed in k_BT units. The numerical value of the dimensionless parameter ρ is 1.5, which is in the domain of weak coupling of the reaction coordinate with the thermal bath. The output of the above theory for the escape rate of the system from the PB to SB is $k_{PS} = 0.0280$ in units of γ ($\sim 10^{13}$ s^{-1}). (All the numerical results of the escape rates are given in units of the damping rate γ.) The value of the escape rate from the PB to the TB is $k_{PT} = 0.0275$ and that corresponding to the transition from the high-energy basin TB is $k_T = 0.321$. All these three escape rates are kept constant in the following. The original topographical pattern of the SB, which was slightly different from that displayed in Figure 1, yielded $k_{SP} = 0.0314$ for the transition from SB to PB and $k_{ST} = 0.0309$ for the transition from SB to TB, respectively. Figure 2a depicts the

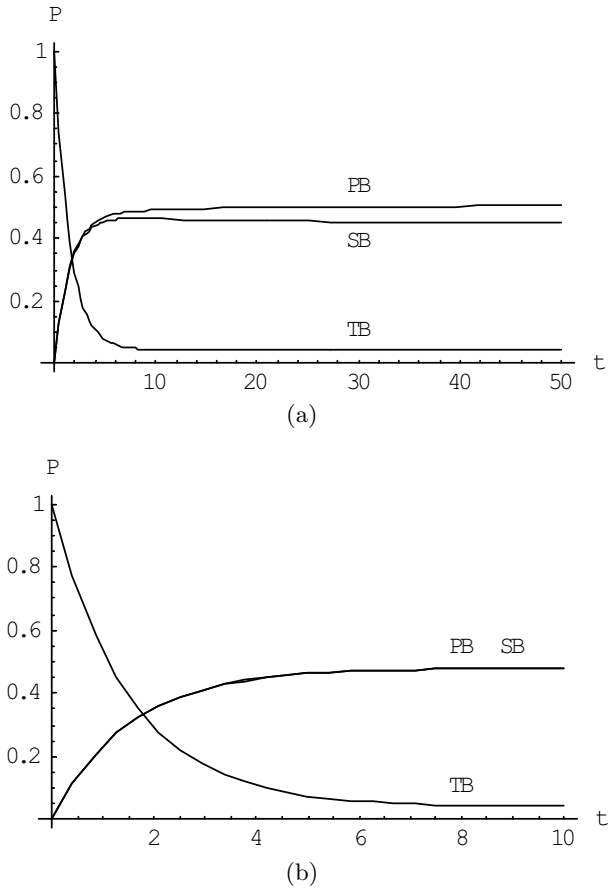

Fig. 2. (a) Time evolution (in units of $1/\gamma$, $\gamma \sim 10^{12}$ s^{-1}) of probability density distributions in primary basin (PB), secondary basin (SB) and tertiary basin (TB) corresponding to the original potential surface (PS). Populations are well defined on the same time scale. (b) Time evolution (in units of $1/\gamma$, $\gamma \sim 10^{12}$ s^{-1}) of probability density distributions in basins of the PS displayed in Figure 1. This PS was modified in order to produce a kinetic trap in the SB.

time evolution of the probability density distributions corresponding to the escape rates given above. (We assumed that at the initial moment ($t = 0$) the system is in the TB with the probability $P_T(t = 0) = 1$.) One can observe that all three basins have well defined population distributions on the characteristic time-scale. The increase in the population of the PB is sharp (see the curve labeled PB) and the probability reaches a plateau, which is higher than that corresponding to the SB (see SB in Fig. 2a).

By varying the positions on the energy axis of the minima (or saddles) corresponding to the SB, we are able to control the value of the escape rate from that basin. For the topographical fingerprint displayed in Figure 1, the IBM approach produces similar numerical values for the forward and backward escape rates between PB and SB, $k_{PS} \equiv k_{SP} = 0.0280$. This is the condition for the occurrence of the kinetic trap. As can be seen in Figure 2b, the equilibrium population of the SB is attained on the same time scale and evenly balances that corresponding to the PB. Consequently the system is found, at long times,

with the same probability in the PB of the global minimum or is trapped in the SB of "wrong structures". The balance may decisively be turned around if the escape from the SB is tuned to a low rate. This circumstance is attained, for example, by decreasing the weight with which the low energy minimum $s2$ (see, Fig. 1) contributes to the average value of the mean first passage time τ_α, *e.g.*, by moving its position up on the energy scale. The system will now stack in the SB. Indeed, the energies corresponding to the stationary points in the SB can be changed systematically to induce the asymptotic probability of the SB above, or below, that of the PB.

The main inference from above is that the relative positions of the stationary points in the monotonic sequences with respect to the lowest minimum are important in setting the efficiency of passage into or out of a steep basin. There is yet an other important observation to be made. This comes out by comparing the escape rate from the SB with that corresponding to the escape from a smooth potential well of the same depth as above ($12k_BT$), with no other secondary minima. The smooth potential well provides the lower bound of the escape rate, that is $k_0 = 0.6 \times 10^{-4}$. The rate coefficient k_0 is about three orders of magnitude smaller than k_{SP}. Therefore we can say that generally the presence of secondary minima on the wall of the basin assists the rate of passage. These two consequences allow us to conclude that the number of local minima in the monotonic sequences and the distribution on the energy scale of both minima and saddles have significant effects on the escape rate of the system from that basin. The former aspect is an entropic manifestation of the structural variety of the system while the latter relates to the topographical fingerprint of that basin.

Finally, to bring our question to a larger perspective, we recall that the topology of the PS plays also an important role in the occurrence of kinetic traps. The way in which different regions of the PS are inter-connected may facilitate trapping in "wrong" structures. Especially, the multiplicity of the pathways from high-energy states towards regions of the PS other than the region containing the global minimum can be decisive [1]. As in the solid-liquid transition for which densities of locally stable states control the balance, in complex systems, entropy may win over energy in transition processes, if the number of high-energy pathways more than compensates for the energetic advantage of the lowest-energy path. Moreover, for those PSs characterized by basin regions with similar kinetic connectivities and/or energies, there is a fragile balance between trapping and focusing to the native structure or to one of a few, closely related structures. The conditions that are thermodynamically most favorable for focusing to the global minimum for the standard PS also most favor trapping in "wrong" structures.

We conclude that for polyatomic molecules, clusters, proteins and other nanoscale particles, it is beginning to seem feasible to infer from topographical and thermodynamical properties of the PS the extent to which a system is either trapped in basins of "wrong structures" or "focusing", in the sense of going to a single structure or a small set of related structures. Work in progress is exploring tests of the reliability of statistical samples, and of the influence of the density of saddles, the distribution of saddle heights along monotonic sequences of minima and the distribution of monotonic sequences among the basins on the trapping or focusing character of the surface.

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