Selecting fast folding proteins by their rate of convergence.

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Abstract

We propose a general method for predicting potentially good folders from a given number of
amino acid sequences. Our approach is based on the calculation of the rate of convergence of each
amino acid chain towards the native structure using only the very initial parts of the dynamical
trajectories. It does not require any preliminary knowledge of the native state and can be applied
to different kinds of models, including atomistic descriptions. We tested the method within both
the lattice and off-lattice model frameworks and obtained several so far unknown good folders. The
unbiased algorithm also allows to determine the optimal folding temperature and takes at least
3–4 orders of magnitude less time steps than those needed to compute folding times.
It is well-known, that most proteins fold rapidly and reliably to a unique native state from any of a vast number of unfolded conformations \[1, 2\]. One of the main problems in protein folding is described by the so-called Levinthal paradox, which states that if the folding pathway of a protein in the phase space would be governed by a random search the time needed to locate the native state among all configurations would exceed the age of the universe. Nowadays, the consent answer to this paradox is found in the designed energy landscape of a foldable protein, which resembles a many-dimensional funnel, where moving along the free-energy gradient narrows the accessible configuration space and guides to the unique native structure, which lies at the bottom of the funnel \[3–5\]. The funnel is also rough, giving rise to local minima, which can act as traps during folding. In contrast to a designed protein, a random amino acid chain will not fold to its global free-energy minimum in times less than that needed to explore the configuration space completely, the times, which are astronomically large \[3\].

In this paper we call good folders those amino acid sequences, which exhibit a protein-like behavior, \textit{i.e.} those that fold into the unique native state within a reasonable time. To find a way of characterizing good folders, like typical motifs in the amino acid sequence or specific properties of the energy landscape is of vital importance. A widely used criterion to characterize a good folder is a pronounced energy gap between its global energy minimum and the energies of configurations, which are structurally dissimilar to the configuration of the global minimum (the native state) \[4, 6, 7\]. This energy gap ensures the “thermodynamic stability” and one finds a correlation between the energy gap and the ability to fold into the global minimum within a reasonable time. Yet, without knowing the native state, there is still no good way to check whether a given amino acid sequence is a good folder other than letting it dynamically evolve from various initial conformations and checking if it does actually fold into a unique native state. Due to an unknown folding time it may take very long before one could identify some amino acid chain as a bad folder.

Many studies have been devoted to the search of determinants of a protein-like system. Apart from the energy gap, one could mention the relation between the folding and glass transition temperatures, see f. e. \[8\], the collapse cooperativity \[9\], etc. In this respect it is important to understand how these features, which are characteristic to foldable proteins, could help distinguish a good folder from a bad folder. Not always a clear determinant of a good folder can serve as a criterion for selection of protein-like aminoacid sequences. It turns
out that in order to do a fast selection in most cases one needs to know the global minimum (native state) from the beginning. The energy gap clearly assumes the knowledge of the energy in the native state. In [10], the authors use the microcanonical ensemble to distinguish good folders from bad folders but the efficient procedure also requires the knowledge of the global energy minimum. In simple Go–like models [11], where similar problems have been posed (c.f. [12–14]), the model space as a whole is biased by the predetermined native state.

In [15], the authors propose an interesting idea to study the fluctuations of the energy landscape curvature (this requires a smooth energy surface). This idea was tested on the off-lattice model with three amino acids; the description of the model and some of the good folders can be found in [16]. It turns out that the averaged curvature of potential energy $K_R := \nabla^2 U$ of a foldable protein suffers a dramatic enhancement of the fluctuations in the vicinity of the folding temperature $T = T_f$. This direction of research was further pursued in [13, 17]. Thereby, the preliminary knowledge of the native state is not necessary. Successful selection of good folders in [15, 17] was done from only 6 sequences, which is too little to make a comparative analysis and to judge on the effectiveness of the method. It is also important to note that the curvature is averaged almost along the whole folding pathway, i.e. over the whole folding time (the folding time can be found in [16]). Sometimes the energy landscape is funneled towards several deep minima, and since the approach in [15, 17] is purely local, it is unclear how one can distinguish good folders from bad folders in this case. Presumably, this method works well when one compares a funneled and a totally frustrated energy landscape, which was indeed the case in [15, 17].

In this paper using lattice and off–lattice models we investigate to which extent the convergence of dynamical trajectories in configuration space on early stages could serve a distinguishing criterion for a good folder. We emphasize that the knowledge of the native state is not required! One can illustrate the idea using a suitable analogy to convergence criteria for a sequence of real numbers. On one hand, by definition, a sequence $A_n \in \mathbb{R}$ for $n = 1, 2, \ldots$ converges if there exists $A_0 \in \mathbb{R}$ such that for all $\varepsilon > 0$ one can find $N$, which guarantees that $|A_n - A_0| < \varepsilon$ holds for $n \geq N$. Equivalently, on the other hand, the sequence $A_n$ converges if for all $\varepsilon > 0$ one can find $N$ so that $|A_n - A_m| < \varepsilon$ holds for $n, m \geq N$. In the first case one needs to know the exact limit of a sequence (read native state). In the second case one does not have to know the limit of a sequence, and similarly, it is not necessary to know the native state in our approach.
There are various ways to describe the dynamics of an amino acid chain in the solvent (Langevin dynamics for atomistic models \cite{18}, Monte Carlo (MC) dynamics for lattice models \cite{7,19}, etc.). Generally, the time development of the configuration can be written as \( C(t) = g^t C(0) \), where \( C(0) \) is the initial configuration and \( g^t \) denotes the dynamical transformation, which depends on temperature and has a probabilistic nature if it simulates how water molecules affect the amino acid chain.

The effect of the folding funnel could also be expressed in terms of the dynamical transformation, saying that if the dynamical transformation acts on two arbitrary points in the configuration space then the “distance” between them becomes contracted \( d(C_1(t), C_2(t)) < d(C_1(0), C_2(0)) \), where \( d \) stands for “distance” between configurations. The time \( t \) should surpass the minimal time required for overcoming typical local traps in the folding funnel. This expresses the idea that if one considers a good folder in two randomly chosen initial configurations and lets it dynamically propagate over a proper time, then there should emerge structural similarities between two propagated yet initially unrelated configurations.

Now imagine the following problem being posed: out of \( K \) amino acid sequences one has to sort out the best candidates for folding in some reasonable time. The brute force solution to this problem would be to let each amino acid sequence evolve according to the dynamics starting from various random initial configurations and to check whether the dynamical trajectories reach the same native conformation. This may be, however, extremely time consuming (especially in the case of molecular dynamics simulations with water molecules included). In addition, it is \textit{a priori} unclear how long the dynamical simulation must be run because the folding time is initially unknown. Moreover, the native contacts must not be necessarily known for an arbitrary sequence, which prevents the application of go-type models. In this paper we propose an alternative solution to this problem based on comparing amino acid sequences through their \textit{rate of convergence}. To define the rate of convergence for a given amino acid sequence \( S \) we proceed as follows.

Suppose, the pairwise interaction between two monomers is \( V_{ij}(r_{ij}) \), where \( r_{ij} \) is a relative coordinate between two monomers. Let us extract the negative part of the potential function setting \( W_{ij}(r) := \max[0, -V_{ij}(r)] \) and define the magnitude of a contact between amino acids \( i \) and \( j \) as

\[
\mathcal{V}_{ij}(r) := \frac{W_{ij}(r)}{\max_{r}[W_{ij}(r)]} \quad \text{(for } j \neq i - 1, i, i + 1),
\]  

(1)
and $V_{ij}(r) := 0$ for $j = i - 1, i, i + 1$ (in the expression for $V_{ij}(r)$ we exclude the bulk contributions from neighboring monomers). Clearly, $0 \leq V_{ij}(r) \leq 1$. Let $r_{ij}^{(1)}$ and $r_{ij}^{(2)}$ denote $r_{ij}$ in the configurations $C_1$ and $C_2$ respectively. Then the overlap between two configurations $C_1$ and $C_2$ is defined as

$$O(C_1, C_2) = \sum_{i,j=1}^{N} V_{ij}(r_{ij}^{(1)})V_{ij}(r_{ij}^{(2)}),$$

where $N$ is the number of aminoacid molecules in the protein. The overlap introduces the topology in the space of configurations. Note that the more compact and structurally similar two configurations are the larger is the overlap between them. Eqs. (1) and (2) are quite general and can be applied to any force field. As a particular case, for lattice models $V(r_{ij}) = 1$ if the monomers are “in contact” in the given configuration and zero otherwise. For various definitions of contact see, for example [20, 21].

Next, let us fix some time scale $t_0$, which should be larger than the typical time required for the dynamically evolving configurations to overcome local minima on the energy surface. We then let a given amino acid chain dynamically propagate over the time $t_0$ starting from two randomly chosen initial configurations (self–avoiding random walks on the lattice) $C_1$ and $C_2$. The overlap between the resulting configurations $g^{t_0}C_1$ and $g^{t_0}C_2$ is then $O(g^{t_0}C_1, g^{t_0}C_2)$. Sampling over randomly chosen initial configurations $C_1$ and $C_2$ we calculate the arithmetic mean of the overlaps, which we denote as $R(t_0, T)$ and call the rate of convergence of the given amino acid sequence. Here $T$ denotes the temperature (the dependence on $T$ is hidden in the dynamical transformation). Below we would show that the rate of convergence $R(t_0, T)$ can be used to select and design good folders. (In order to give a proper dimension to the rate one could divide $R(t_0, T)$ by $t_0$; we do not do this because this rescaling does not affect the results). Let us remark that since the proteins coil into the native state from any initial configuration, we impose no restrictions on the domain of initial configurations.

Now we take the next step and construct the normalized rate of convergence. For this purpose we first generate a large number of random amino acid sequences and calculate $R(t_0, T)$ for each sequence, where $t_0$ and $T$ are fixed time of evolution and temperature respectively. The arithmetic mean of these values we denote as $R_{\text{random}}(t_0, T)$. This quantity is the expectation value of the rate of convergence of a random sequence depending on temperature and on the time scale $t_0$. The normalized rate of convergence $R_N(t_0, T)$ of an
amino acid sequence $S$ is then defined as

$$R_N(t_0, T) = R(t_0, T)/R_{random}(t_0, T).$$

(3)

Let us remark that the values of $R_{random}(t_0, T)$ can be tabulated so that $R_N(t_0, T)$ can be determined with the same computational effort as $R(t_0, T)$.

If an amino acid sequence has $R_N(t_0, T) > 1$ then its rate of convergence is larger than that of a random sequence; the converse is also true. The normalized rate of convergence can be assigned to any amino acid sequence and the larger $R_N(t_0, T)$ the better are the chances for this sequence to be a good folder. Therefore, the best candidates for being a good folder from a number of given amino acid sequences can be found through sorting the sequences by their normalized rate of convergence. The degree to which this sorting algorithm is effective depends on how $t_0$, which is sufficient for proper sorting, relates to the mean folding time. In the following we demonstrate that the selection and design of good folders using the rate of convergence works for both a standard lattice and an off-lattice models of proteins [4, 6, 22].

Although geometrically poor, the lattice model is protein-like in the sense that lattice proteins fold to a unique native structure from an astronomically large number of possible initial conformations and do so rapidly and reproducibly. A random configuration is then a self avoiding random walk on the cubic lattice. The sequences are composed of 20 amino acids. Two monomers are "in contact" if they occupy neighboring positions on the lattice but are not sequence neighbors. The energy of two monomers in contact is calculated using the $20 \times 20$ Miyazawa-Jernigan matrix (Table VI in [23]). The dynamic transformation $g^t$ is implemented through the Monte Carlo dynamics [22] with move set including end moves, corner flips, and crankshaft moves.

We have chosen a designed sequence [24] of 36 monomers $S_0 = \text{SQKWLERGATRI-ADGDLPVNGTYFSCKIMENVHPLA}$. The native state of $S_0$ has the energy $E_{\text{Stat}} = -16.5$ in dimensionless $k_B T_{\text{room}}$ units, where $T_{\text{room}}$ stands for the room temperature [23]. At the folding temperature $T_f = 0.25$ (in Miyazawa-Jernigan dimensionless units) the configuration $S_0$ always reaches its native state starting from any conformation and the mean folding time (obtained by sampling $10^3$ self-avoiding random walks in initial configurations) is $t_f = 1.5 \times 10^6$ steps.

In our calculations we have generated 800 sequences with a random amino acid decomposition and the designed sequence $S_0$ was hidden among random sequences as "a needle in a
For each amino acid sequence we calculated the normalized rate of convergence and then sorted all sequences by the corresponding value in descending order. We computed $R_N(t_0, T_f)$, where $T_f = 0.25$ is the folding temperature of $S_0$, over 500 randomly chosen pairs of positions (conformations), starting with $t_0 = 50$ and repeated the procedure incrementing each time $t_0$ by 50. The initial conformations are generated as self-avoiding random walks in the lattice. We stress that for each new time period the 800 random sequences were generated anew. We have observed that further increase of the number of random sequences changes the value of $R_{\text{random}}(t_0, T)$ by $\pm 1\%$ in the considered range of $t_0, T$. Recall that these values can be obtained once with a high accuracy and then tabulated for various values of $t_0, T, N$, where $N$ is the number of monomers.

In general, for $t_0 \leq 150$ the designed sequence gets lost among other random sequences, indicating that the time $t_0 \leq 150$ is insufficient for overcoming local minima through potential barriers. For $t_0 \geq 200$ the sequence $S_0$ gets into the top ten, which makes us conclude that $t_0 \geq 200$ is sufficient for distinguishing the sequences by their ability to fold. The dependence of normalized rate of convergence on the temperature $T$ for fixed $t_0$ is also a relevant quantity. Remarkably, $R_N(t_0, T)$ of $S_0$ peaks exactly at the folding temperature $T_f$, see Fig. 1.

In order to show that the rate of convergence can also be used to perform sequence design we applied the algorithm to 5000 randomly generated amino acid sequences having 36 monomers. The top 5 sequences turned out to be good folders. We used $t_0 = 200$ and the sampling was done over 300 pairs of initial positions. The temperature was set to the folding temperature of the designed sequence $S_0$, namely $T = T_f$. Interestingly, the sequence $S_0$ occupied only the position 3. The two top folders found correspond to the sequences $S_1 = KWEHEWGKDNLSDLHMEERFAQEQHNRDPQTD$ and $S_2 = NALCDDCSTEWCIPSMCCMFEDFYKKQQWRQM$. The native states of $S_1$ and $S_2$ are shown in Fig. 4. The energies of the native states are $E_{\text{Nat}}(S_1) = -16.88$ and $E_{\text{Nat}}(S_2) = -14.29$ respectively. Note that $E_{\text{Nat}}(S_1)$ is even lower than that of the previously known sequence $S_0$, despite the fact that $S_1$ has the number of native contacts by 6 less than $S_0$ (note that the structure of $S_0$ was specifically designed to maximize the number of native contacts and 40 native contacts is the maximal reachable number for the sequence length of 36 monomers). Fig. 1 shows the normalized rate of convergence for the sequences $S_0$ and $S_1$ as a function of temperature. In the given temperature range the normalized rates of
convergence for $S_1$ is larger than that of $S_0$. The same occurs for $S_2$ (not shown in Fig. 1).

Both newly found sequences $S_{1,2}$ have the folding temperature equal to $T_f$ and their folding time is approximately 50 times longer than the folding time of $S_0$. This is the fact which deserves a discussion: in spite of $S_{1,2}$ having at all temperatures a better normalized rate of convergence compared to $S_0$, their folding time is substantially longer. In [24] one finds the procedure for the sequence design, where one fixes the target conformation and finds the amino acid sequence, which minimizes the energy in this conformation. The target structure then becomes the native state for the obtained good folder. The same design works also in the case of off–lattice models [26]. The sequence design in our approach does not fix the native conformation but rather fixes the target temperature. The obtained good folders have the folding temperature equal to the target temperature!

In addition, we applied our method to other sequences already designed by other authors. For instance, for the sequences in Figs. 1,2 of Ref. [25] the method yields excellent results. In Fig. 1 we also plot the rate of convergence versus temperature for the sequence $S_3 = GYLGEMKWIMWAEEMMKSWMSGWKGEMGEWGLKGIGK$ (Fig. 2 in [25]). The curve peaks exactly at the folding temperature.

As we have mentioned before, the rate of convergence $R(t_0, T)$ of a given sequence is calculated by sampling over randomly chosen pairs of initial conformations. If one consider 100 pairs of random initial conformations then the distribution of the overlaps for $t_0 = 300$ and $T = T_f$ is almost Gaussian (as it should be in the perfect case according to the central limit theorem).

We now demonstrate that the method proposed here is also able to characterize and design good folders in the more sophisticated off-lattice model of proteins proposed by Clementi et al. in [26]. In this force field the interaction between amino acids $i$ and $j$ is given by [27],

$$V_{ij} = \delta_{i,j+1} a (r_{ij} - r_0)^2 + (1 - \delta_{i,j+1}) 4 \epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right],$$

(4)

where $a = 50 \text{ Å}^{-2}$ and $r_0 = 3.8 \text{ Å}$. The set of parameters $\epsilon$ and $\sigma$ denote the minimum energy and the equilibrium distance for the Lennard-Jones (LJ) part of the potential. We considered $N_{\text{conf}}$ sequences (with $N_{\text{conf}}=100$) of $N = 30$ monomers. To compute the time evolution $g^t$ of the monomers we used Monte Carlo dynamics. The overlap between configurations was computed using Eq. (2) and the rate of convergence was obtained by averaging over
\( N_{\text{conf}} \times N_{\text{conf}}/2 = 4950 \) pairs of randomly chosen conformations, which were determined as follows. First, we have chosen random positions for the monomers in the range \([0:16]\) in units of distance without any bias. Then, the so generated structures were equilibrated during 2000 Monte Carlo steps, thus generating the starting structural configurations.

We analyzed 6 sequences (see Table I) belonging to 3 different polymer types according to the classification in [27]. We considered 3 sequences of heteropolymer character (DHTP), labeled as SEQ1, SEQ2 and SEQ3, 2 sequences of random heteropolymers (RHTP) (SEQ4 and SEQ5) and the homopolymer (SEQ6). In general, heteropolymers designed following the procedure introduced in [27] have good chances to be protein-like, whereas for random heteropolymers and for homopolymers one expects a rugged energy landscape and consequently a bad folding behavior.

Note that SEQ1 has been shown to be a good folder, whereas SEQ4 and SEQ6 have been previously characterized as bad folders [27]. The sequences SEQ2, SEQ3 and SEQ5 generated by us in this work were not considered so far in the literature.

The rate of convergence clearly allows one to separate good folders from bad ones already at almost any step of the dynamical simulation. Fig. 2 shows the rate of convergence as a function of time for the 6 studied sequences at fixed temperature. From the inset of Fig. 2 one can see that good folders can be identified already after less than \(10^4\) time steps, i.e., at an early stage of the dynamical transformation \(g^t\). At folding temperature our method allows for a selection of good folders by computing trajectories at least 3 to 4 orders of magnitude smaller than those needed to compute the folding time.

In Fig. 3 we show the temperature dependence of the normalized rate of convergence \(R_N(t_0, T)\) for the 6 sequences studied. The values of \(R_{\text{random}}(t_0, T)\) were computed using 100 random sequences; further increase of the number of random sequences changes the value of \(R_{\text{random}}(t_0, T)\) by \(\pm 2.5\%\) in the considered range of \(t_0, T\). Let us stress that one can get a better accuracy for \(R_{\text{random}}(t_0, T)\) using a larger number of random sequences; this does not affect the effectiveness of the method since for all models the values \(R_{\text{random}}(t_0, T)\) can be tabulated after being calculated once.

The normalized rate of convergence was computed over 100 random sequences SEQ1, SEQ2,..., SEQ100, from which SEQ1, SEQ2 and SEQ3 belonged to the DHTP model, SEQ6 was a HMP and the rest of the sequences were random heteropolymers (RHTPs). The different functional dependence of good and bad folders is very clear. For good folders
$R_N(t_0, T)$ is larger than 1 at all temperatures and exhibits a well defined maximum, whereas for bad folders $R_N(t_0, T) \simeq 1$ and practically does not depend on temperature.

In order to investigate whether the temperature dependence of $R_N(t_0, T)$ is also physically relevant as in the case of the lattice model, we performed Wang-Landau Monte Carlo simulations to calculate the specific heat curves of the three good folders. Results are displayed in the low panel of Fig. 3. The specific heats of SEQ1, SEQ2 and SEQ3 show the typical peaked shape at the folding temperatures $T_f(SEQ_i)$, $i = 1, 2, 3$, characteristic of protein-like sequences. By comparing the upper and lower panels of Fig. 3 one concludes that from the position of the maxima of $R_N(t_0 = 10^7, T)$ one obtains a reasonably good approximation to the folding temperatures. In order to obtain smooth curves of $R_N$ vs $T$ as those shown in Fig. 3 one has to take large values of $t_0$. From Fig. 3 it is clear that for each sequence $R_N(t_0, T)$ exhibits a broad maximum around $T_f$. Again, let us stress that the rate of convergence is not only efficient in distinguishing good and bad folders but also accurately predicts the suitable temperature range for a good folder.

Finally, we demonstrate that the new sequences SEQ2 and SEQ3, designed using the method of the rate of convergence, are indeed foldable. We computed the average root mean square deviation

$$\theta(t) = \frac{1}{N_{conf}} \sum_{\nu=1}^{N_{conf}} \sqrt{\frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j>i}^{N} |\bar{r}_{ij,\nu}^{Nat} - \bar{r}_{ij,\nu}(t)|^2}$$

where $r_{ij}^{Nat}$ refers to the intermonomer distances in the native state and $N_{conf} = 100$ to the number of initial conformations we average over. In Fig. 4 we show the behavior of $\theta$, averaged over 100 independent trajectories, as a function of $\log_{10}(t)$ for sequences SEQ1, SEQ2 and SEQ3. We can define the folding time as the time when $\theta$ approaches a certain threshold value $\theta_{thr}$. We set $\theta_{thr} \sim 3.9$ Å, which allows to estimate the folding times as $t_f(SEQ1) = 4.5 \times 10^6$ time steps, $t_f(SEQ2) = 6.6 \times 10^5$ time steps, and $t_f(SEQ3) = 2.4 \times 10^7$.

The three dimensional structures of some of the sequences designed in this work using the rate of convergence are shown in Fig. 5. Note that the main conclusion of this paper, namely, that the computational time required by the method of the rate of convergence is many orders of magnitude less than the folding time remains valid even taking into account that the definition of $R$ involves sampling over many different initial conditions. Such sampling
TABLE I. The six sequences studied in this paper and their corresponding models. All the sequences have \( N = 30 \) monomers. The numbers in the second column denote the sequence of amino acids in the peptide chain (using the same notation as in Ref. 26.

| Name | Sequence | Model |
|------|----------|-------|
| SEQ1 | 311114442344312212224434333334 | DHTP |
| SEQ2 | 341233331323331112112421234111 | DHTP |
| SEQ3 | 443234232334213211322342343111 | DHTP |
| SEQ4 | 41412432343214324242141441 | RHTP |
| SEQ5 | 44444444444444444444444444444 | RHTP |
| SEQ6 | 321224314333113213344411112243 | HMP |

operations can be run absolutely parallel on as many different nodes as initial conditions one needs. Let us, however, mention that the procedure presented here is, indeed, a good method to identify potentially good folders, but it cannot serve as an ultimate measure of a good folder.

The method of the rate of convergence developed in this paper is applicable in all model frameworks which allow for dynamics, including accurate atomistic descriptions. Note that the rate of convergence \( R \) can also be computed basing on arbitrary definitions of overlap, different from Eqs. (1) and (2). Moreover, it must not be restricted to the coordinate (structural) space. One could, for instance, consider the overlap between strings containing property factors [28] or their Fourier components [29].

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FIG. 1. (Color online). Thick solid line: the normalized rate of convergence versus temperature for the designed sequence $S_0$ for the time period $t_0 = 500$. Dash-dot and thin solid line: the same for the sequences $S_1$ and $S_3$ respectively. Note that the folding temperature of $S_3$ is approximately $1.2T_f \simeq 30$ as can be seen from Figs. 9 (a,b) in [25]. Dashed line: the normalized rate of convergence $S_{bad}$ of a typical bad folder (in this case a homopolymer). The vertical dotted line corresponds to the folding temperature of $S_0$. The temperature is given in dimensionless Miyazawa-Jernigan units multiplied by 100.

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FIG. 2. (Color online). Normalized rate of convergence $R_N(t_0, T)$ vs time step $t_0$ for fixed temperature $T = 0.001987k_B^{-1}$ of the 6 analyzed sequences in the off-lattice model (see the text). For each point, $R_N(t_0, T)$ was calculated averaging over 100 conformation pairs. Inset: first stages of the time development of $R_N(t_0, T)$. The different behavior of good and bad folders is already evident.
FIG. 3. (Color online). Upper panel: temperature dependence of the normalized rate of convergence $R_N(t_0, T)$ for the 6 sequences considered within the off-lattice model. $t_0 = 10^7$ time steps. Lower panel: specific heat curves of the sequences SEQ1, SEQ2 and SEQ3, characterized as good folders by our method.
FIG. 4. (Color online). Time evolution of the root mean square deviation $\theta$ of sequences SEQ1, SEQ2 and SEQ3 (with respect to their global minimum structures). The value of $\theta$ was computed according to $\ref{eq:theta}$. Time axis is plotted in logarithmic scale. $\theta$ decays exponentially in time for the three sequences. Threshold value of $3.9\,\text{Å}$ is denoted by the dotted line. SEQ2 shows the fastest folding Monte Carlo dynamics followed by SEQ1 and SEQ3 (folding times are given in text).
FIG. 5. (Color online). Native state conformations for some of the sequences designed using the rate-of-convergence method developed in this work. Lower panel: $S_2$ (left) and $S_3$ (right) obtained in the framework of the lattice model. Dotted lines connect those monomers that are in contact. Upper panel: SEQ2 and SEQ3, designed within the off-lattice model.