# Accelerate Sampling in Atomistic Energy Landscapes Using Topology-Based Coarse-Grained Models

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S Supporting Information

ABSTRACT: We describe a multiscale enhanced sampling (MSES) method where efficient topology-based coarse-grained models are coupled with all-atom ones to enhance the sampling of atomistic protein energy landscape. The bias from the coupling is removed by Hamiltonian replica exchange, thus allowing one to benefit simultaneously from faster transitions of coarse-grained modeling and accuracy of atomistic force fields. The method is demonstrated by calculating the conformational equilibria of several small but nontrivial β-hairpins with varied stabilities.
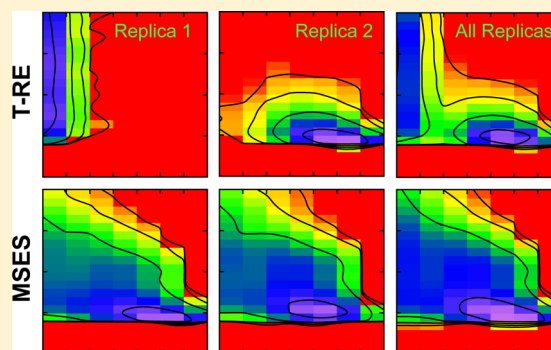
Generating statistically representative conformational ensembles remains a major challenge in atomistic simulation of biomolecules.[1] This is not only due to the large and complex conformational space, but also because of significant energy barriers that frequently separate different subspaces. Temperature replica exchange (T-RE)[2−4] is now widely accepted as a relatively straightforward yet powerful technique for enhanced sampling. Multiple replicas of the system are simulated independently at different temperatures and periodically attempt to exchange simulation temperatures according to a Metropolis criterion that preserves the detailed balance. The resulting random walk in the temperature space helps each replica to escape local energy minima and thus facilitate conformational sampling. Extensive theoretical and simulation studies have confirmed that T-RE enhances sampling compared to constant temperature simulations as long as the activation enthalpies of conformational transitions are positive.[5−9] Nonetheless, the efficiency of T-RE can be severely limited by the presence of sharp cooperative conformational transitions such as protein folding.[10,11] Importantly, this limitation cannot be overcome by various T-RE variants designed to accelerate either exchanges or diffusion in temperature space.[12] In practice, virtually all T-RE protein simulations involve exchange attempt frequencies ($\sim ps^{-1}$) that are several orders of magnitude faster than the slowest protein motions (folding; μs^{-1} or slower[13]). As such, the efficiency of T-RE sampling of large-scale conformational transitions is rarely limited by diffusion in temperature space, but mainly by the inherent rates of spontaneous processes.

Fundamentally, the limited efficiency of T-RE in sampling cooperative transitions such as protein folding can be attributed to large entropic components in the free energy barriers.[14,15] The folding rate only depends weakly on temperature and often displays anti-Arrhenius behaviors,[5,16] such that tempering is

ineffective in driving transitions. Instead, coarse-grained (CG) models[17] are often utilized to significantly reduce the conformational space and allow faster reversible transitions, but this is achieved at the expense of reduced detail and accuracy. An ideal approach could involve CG modeling to overcome major entropic barriers and at the same time seamlessly propagates the transitions to atomistic simulations for detailed sampling of different conformational subspaces. A key requirement is that one must be able to recover canonical ensembles at the atomistic level. The promise of such multiscale enhanced sampling (MSES) has been well recognized, and several clever ideas have been proposed toward this goal.[18−23] The resolution exchange approach is particularly interesting.[19] It involves independent simulations of the system at two or more resolutions and attempts to directly swap shared coordinates of low- and high-resolution models according to Metropolis criteria. Resolution exchange in principle allows the possibility of injecting high-resolution simulation into novel conformational subspaces sampled at low resolution. A key limitation is that conformations sampled at different resolutions must be similar to be exchangeable for large biomolecules, as excessive bad contacts would effectively prohibit successful exchange. A smart resolution replica exchange was proposed to improve exchange acceptance, where a ladder of mixed atomistic and CG potentials are used and CG-sampled configurations are relaxed prior to exchange attempt.[24] However, the detailed balance is broken due to relaxation, and only canonical sampling is achieved. More importantly, the aggressive approach of direct coordinate swap in resolution exchange, with or without relaxation, requires configurations

sampled at different resolutions to closely track each other, which counteracts the purpose of rapid hopping among drastically different conformational subspaces sampled at the CG level.

The efficacy of an MSES scheme, regardless of how sampling at different resolutions is coupled, depends critically on the ability of CG simulations to generate transitions that are consistent with inherent conformational dynamics of the atomistic model. Otherwise, CG simulations would attempt to engage the atomistic model along unfavorable pathways and become ineffective in accelerating atomistic transitions. For proteins, topology-based CG modeling has been highly successful and demonstrated impressive correspondence between experiment and theory for folding mechanisms.[25] This approach is based on the minimal frustration theory of protein folding,[26] which argues that native interactions dictate the protein free energy landscape and that stabilization due to non-native contacts ("frustration") should be minimal. Accordingly, the true protein energy landscape can be approximated by effective energy functions that only include native interactions. These effective energy functions, commonly referred to as Gō or Gō-like models, are highly efficient and yet powerful enough to generate realistic reversible folding pathways. As such, they should be ideally suitable for driving conformational sampling on atomistic protein energy landscapes. Here, we describe an MSES approach that utilizes the efficient sequence-flavored Gō-like model[27] to accelerate the sampling of atomistic protein conformational equilibria and demonstrate its efficiency using a series of small but nontrivial β-hairpins with varied stabilities.

Our approach is inspired by Moritsugu et al.'s multiscale essential sampling method,[20] where both the CG and atomistic representations of the protein are simulated simultaneously in a hybrid system. The atomistic and CG copies do not interact and are only coupled through restraint potentials designed to restrict the divergence between CG and atomistic configurations. The overall potential function of the hybrid system is

$$U_{mix}(r_{AT}, r_{CG}, \lambda) = U_{AT}(r_{AT}) + U_{CG}(r_{CG}) + \lambda U_{MSES}(r_{AT}, r_{CG}) \tag{1}$$

where U_{AT} and U_{CG} are the atomistic and CG potential functions, respectively. Only the coupling potential U_{MSES} depends on both atomistic (r_{AT}) and CG (r_{CG}) coordinates. Given a proper coupling potential, the atomistic and CG copies can be restrained to track one another when the overall coupling scaling factor $\lambda = 1$. Hamiltonian RE can be performed to communicate coupled conformational dynamics to the limit of $\lambda = 0$, where the CG and atomistic copies are fully independent and proper canonical ensembles are generated simultaneously at both resolutions. Our MSES approach incorporates both Hamiltonian and temperature RE to further accelerate conformational sampling. Specifically, N replicas of the hybrid system are simulated independently with increasing couple scaling factors and temperatures, $\{\lambda_i, T_i\}$, $i = 1, 2, ..., N$; $\lambda_1 = 0$ and $\lambda_N = 1$. Replicas periodically attempt to exchange simulation conditions according to

$$P_{m \leftrightarrow n} = \min(1, e^{\Delta_{mn}}) \tag{2}$$

where $\Delta_{mn} = \beta_m[U_{mix}(r_{AT,m}, r_{CG,m}, \lambda_m) - U_{mix}(r_{AT,n}, r_{CG,n}, \lambda_m)] + \beta_n[U_{mix}(r_{AT,n}, r_{CG,n}, \lambda_n) - U_{mix}(r_{AT,m}, r_{CG,m}, \lambda_n)]$, and $\beta = 1/k_BT$ (k_B is the Boltzmann constant). When the same temperature is used for all replicas, the exchange probability is determined by

the coupling term only, allowing excellent scalability to large systems.[20]

Coupling the CG and atomistic models using restraint potentials is a significant advantage compared to direct coordinate swapping in resolution exchange. It allows one to control the impacts of large divergences between CG and atomistic configurations on the total energy, which dramatically improves exchange efficiency and provides superior scalability to large systems. Motivated by the notion that native contacts dictate protein folding transitions,[26] the CG and atomistic copies are coupled by penalty functions that depend on the differences in Cα–Cα distances of residues involved in all native contacts:

$$U_{MSES} = \sum E_i(\Delta d_i) = \sum \frac{1}{2}k_i(d_i^{AT} - d_i^{CG})^2 \tag{3}$$

where $\Delta d_i = d_i^{AT} - d_i^{CG}$ and d_i^{AT} and d_i^{CG} are the Cα–Cα distances of the ith native contact in atomistic and CG copies, respectively. The force constant, k_i, can be different for various subsets of native contacts, for example, to emphasize the relative importance of tertiary contacts vs local secondary ones. For large proteins with hundreds of native contacts, the simple harmonic potential of eq 3 can lead to large penalty energies and result in severe exchange bottlenecks, particularly between the uncoupled ($\lambda_1 = 0$) and coupled ($\lambda > 0$) conditions. For this, a restraint potential with a soft asymptote is used at large Δd_i:

$$E_i(\Delta d_i) = A + \frac{B}{(\Delta d_i)^s} + f_{max}\Delta d_i, \text{ if } \Delta d_i > d_s \tag{4}$$

In eq 4, d_s is the distance threshold where the penalty function $E_i(\Delta d_i)$ switches from the harmonic form (eq 3) to the soft asymptote. The switching exponent s controls how quickly the limiting slope, f_{max}, is approached at large Δd_i. The parameters A and B are identified by requiring both $E_i(\Delta d_i)$ and its first derivative to be continuous at the switching distance ($\Delta d_i = d_s$). We note that similar penalty functions with soft asymptotes are widely employed in NMR structure calculations.[28] The purpose is to avoid premature structural collapse due to a few large distance restraint violations and thus allow better conformational sampling to generate structures that are maximally consistent with all structural restraints. The simulations in the current work only involve exchanging a ladder of models with different λ_i. More sophisticated Hamiltonian RE schemes can be devised that involve additional parameters of the restraint potentials, particularly k_i, d_s, and f_{max}, to more carefully control how conformational transitions are communicated between CG and atomistic copies for larger proteins.

The MSES method has been implemented in CHARMM[29] and MMTSB.[30] Its efficacy is examined here using a series of β-hairpins derived from the protein G B1 domain, including GB1p (GEWTYD <u>DATK</u> TFTVTE), GB1m1 (GEWTYD <u>DATK</u> T**A**TVTE), and GB1m3 (KKWTYN <u>**P**ATG</u> KFTVQE) (loop regions underlined and key mutations highlighted in bold fonts). The wild-type GB1p is ∼42% folded at 278 K based on NMR chemical shift analysis.[31] The Phe to Ala mutation in GB1m1 reduces the hairpin stability to ∼6% folded, and the more rigid proline-containing loop increases the stability of GB1m3 to ∼86% folded.[31] These β-hairpins, albeit small, resemble larger proteins in many essential aspects including cooperative folding transitions and microsecond folding time scales. The optimized generalized Born with smooth switching

(GBSW) atomistic implicit solvent force field appears to recapitulate both the structures and stabilities of these β-hairpins.[32] However, the previous T-RE simulations failed to generate converged conformational ensembles for GB1p.[32] In fact, no reversible folding/unfolding transition was sampled by T-RE for any of these β-hairpins, and the apparent convergence for GB1m1 and GB1m3 ensembles was mainly due to mixing of conformational states sampled at different temperatures.

A sequence-flavored Gō-like model was first generated by the MMTSB Gō-Model Builder[27] and then used in simulations of all three hairpins. The model represents each residue using a single Cα bead and adopts the Miyazawa−Jernigan (MJ) statistical potential[33] for residue-specific native interactions. The Gō-like model was coupled to the GBSW atomistic implicit solvent model (Figure 1a), by imposing the restraint
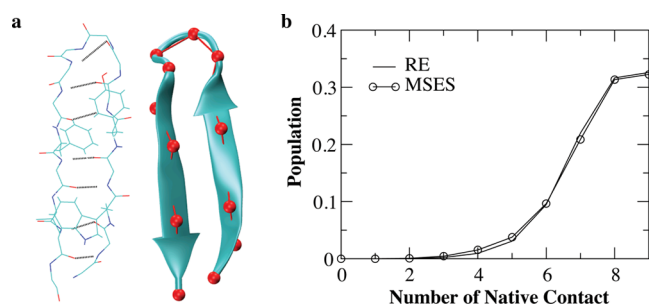

Figure 1. Folded structure and simulated ensembles of GB1p. (a) Left: Atomistic structure of GB1p. Dashed lines indicate all seven native hydrogen bonds. Right: Hybrid model containing atomistic (cyan cartoon) and Cα-only CG (red beads) copies. (b) Probability distributions of the number of native contacts for CG ensembles derived from a reference T-RE simulation of the Gō model alone (solid line) and the MSES control simulation of GB1p (solid line with circles).

potentials on all nine native contacts (see eqs 3 and 4). All MSES simulations were performed using eight replicas with $\{\lambda_i, T_i\}$ = {0, 270}, {0.05, 290}, {0.1, 312}, {0.25, 336}, {0.4, 361}, {0.6, 388}, {0.8, 418}, and {1.0, 450}. These conditions were assigned by having roughly exponential distributions for both λ and T. The exchange acceptance rates were uniform and ~25% for all MSES simulations. Other parameters of the MSES restraint potential were k = 1.0 kcal/mol/Å^2, s = 1, d_s = 2.0 Å, and f_{max} = 0.1 kcal/mol/Å. We note that the soft asymptote has minimal impacts on the exchange and sampling efficiencies for these small hairpins. Langevin simulations were performed with a friction coefficient of 0.1 ps^{-1}, and exchanges were attempted every 2 ps. For each peptide, two independent simulations were performed, starting from the folded (control) and fully extended (folding) structures, respectively. The length of all MSES simulations was 100 ns per replica. Control and folding T-RE simulations were also performed for GB1p as a reference. These simulations are summarized in Table 1.

We first validate if MSES can indeed recover the correct canonical ensembles at the uncoupled condition. Reliable reference atomistic ensembles are not available for these hairpins due to the apparent difficulty in achieving convergence using T-RE simulations.[32] Therefore, we compare the CG ensembles derived from MSES simulations to a reference ensemble obtained from a 4-μs T-RE simulation of the Gō-like model alone. Over 1300 reversible folding transitions were sampled in the T-RE simulation, and the resulting reference CG ensemble at 270 K is fully converged. As illustrated in

Table 1. Summary of T-RE and MSES Simulations of GB1p, GB1m1, and GB1m3[a]

sequence	protocol	run	N_{TS}	k_{TS} (ns^{-1})
GB1p	T-RE	control	1	0.0013
		folding	0	
GB1p	MSES	control	43	0.054
		folding	33	0.041
GB1m1	MSES	control	32	0.040
		folding	20	0.025
GB1m3	MSES	control	34	0.043
		folding	26	0.033

[a]All simulations involve eight replicas and last 100 ns. N_{TS} is the number of reversible folding transitions sampled by all replicas during the entire course of the simulation. The effective reversible transition rate k_{TS} is calculated as N_{TS} divided by total simulation time (800 ns in all cases).

Figure 1b, MSES simulations generated CG ensembles virtually identical to the reference. That is, bias due to coupling between atomistic and CG models is completely removed via Hamiltonian RE as expected. The coevolution of the CG and atomistic copies during MSES simulations is illustrated in Figure S1. As designed, the CG and atomistic conformations can diverge at low temperature/weak coupling conditions but strongly track one another at high temperature/strong coupling conditions.

The efficacy of MSES in accelerating large-scale atomistic conformational transitions is first evaluated by calculating the number of reversible transitions between the folded (≥ 5 native hydrogen bonds) and unfolded (no hydrogen bond) states at the atomistic level. Summarized in Table 1, the results show that T-RE simulations rarely sampled reversible folding transitions, with only one such event observed in the control and folding runs of GB1p. In contrast, many reversible transitions (~31 on average) were sampled in MSES simulations of all β-hairpins, reflecting almost 2 orders of magnitude enhancement in the efficiency of sampling atomistic transitions. Figure 2 depicts the evolution of the number of
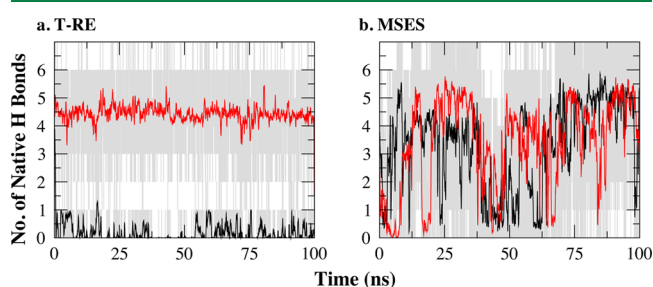

Figure 2. Numbers of native hydrogen bonds as a function of time for representative replicas from (a) T-RE and (b) MSES control simulations of GB1p. Gray lines depict the raw data, and black and red lines show the 50-ps running averages.

native hydrogen bonds from representative T-RE and MSES replicas. The T-RE replicas remain at either the folded or unfolded states throughout the simulation (Figure 2a), whereas all MSES replicas undergo rapid reversible transitions between the folded and unfolded states (Figure 2b), apparently driven by coupling to the efficient Gō-like model. To further evaluate the effects of MSES coupling on folding kinetics and efficiency, we performed multiple sets of folding simulations of GB1p at 270 K using the GBSW, Gō-like, and hybrid potentials (eq 1).
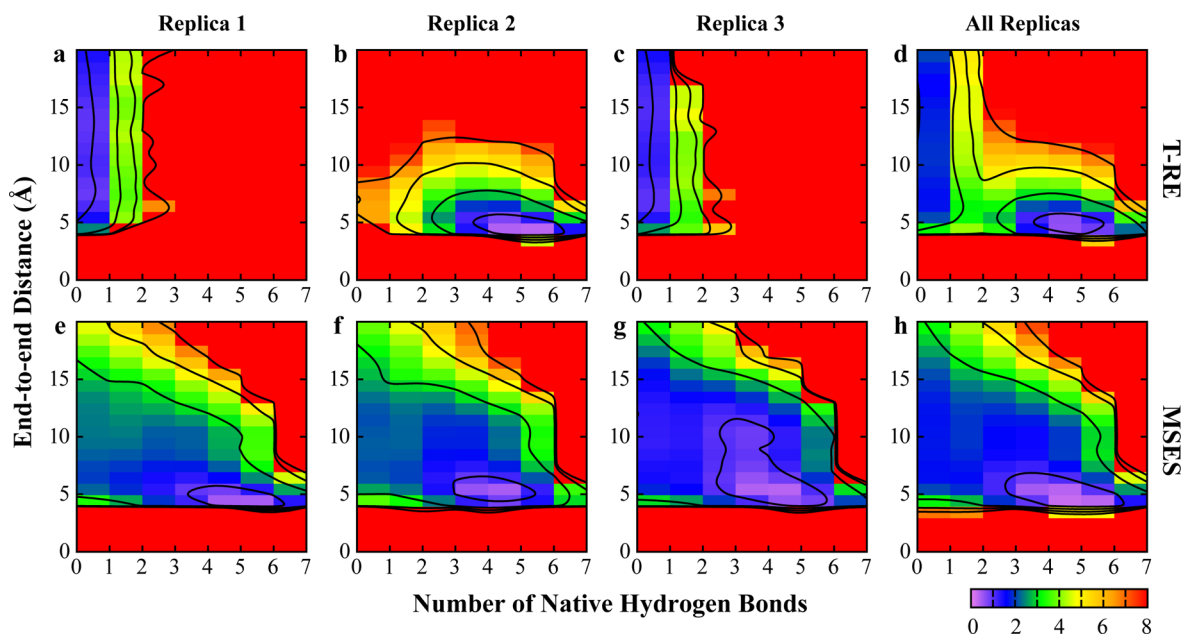
Figure 3. Conformational space sampled by individual replicas in the T-RE (a−c) and MSES (e−g) control simulations of GB1p. Panels d and h were calculated by including all replicas. All atomistic conformations sampled during the last 80 ns of these simulations, regardless of the temperature or coupling scaling factor, were included to compute the pseudo-free energy surfaces, which are plotted in the units of kT. Contours are shown at 1, 3, 5, and 7 kT levels.

A total of 100 50-ns simulations were initiated from unfolded atomistic and CG structures randomly selected from pregenerated equilibrium ensembles (see Table S1 and Figure S2). The results show that coupling with the CG model allowed the atomistic model to reach the folded state in 34% of the trajectories within <18 ns on average, while all simulations in GBSW alone were trapped in various compact states and failed to fold within 50 ns. The dramatic improvement in atomistic folding efficiency was achieved with only a moderate 50% increase in the average folding time of the CG model (from 0.83 to 1.19 ns). Curiously, we observed that the CG model actually also underwent faster reversible folding transitions in MSES simulations, with an average rate of $k_{TS} \sim 0.084$ ns^{-1} compared to $k_{TS} \sim 0.041$ ns^{-1} in the T-RE simulation of the Gō-like model alone. This is likely because that coupling with the atomistic model accelerates unfolding transitions at the CG level.

Ideally, a fully converged RE simulation should involve all replicas sampling the same entire accessible conformational space. This limit is almost never achieved in atomistic T-RE simulations of nontrivial peptides and proteins, where individual replicas generally sample separate major conformational states throughout the simulations (e.g., see Figure 3a−c). Amazingly, MSES simulations of all three β-hairpins display many characteristics of full convergence, with all replicas sampling similar, complete atomistic conformational spaces (Figure 3e−g and Figure S3). When combining information from all replicas, T-RE and MSES simulations appear to cover similar conformational spaces (Figure 3d and h), even though T-RE undersamples most regions except the major free energy basins. Atomistic conformational ensembles derived from independent control and folding runs were compared to further evaluate the ability of MSES to achieve convergence in key thermodynamic properties. Figure 4 compares the probability distributions of the number of native hydrogen bonds. The results show that MSES does generate largely
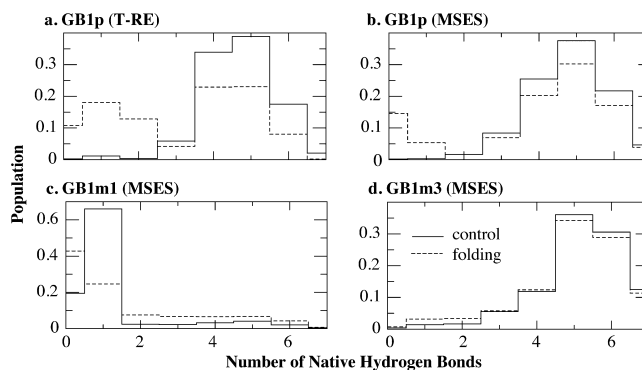

Figure 4. Probability distributions of the number of native hydrogen bonds for GB1p (a,b), GB1m1 (c), and GB1m3 (d). These distributions were calculated from structure ensembles extracted from the last 80 ns of T-RE or MSES simulations at $T = 270$ K and $\lambda = 0$ (see Table 1 for detailed simulation setups).

consistent ensembles from the control and folding runs. Especially for GB1p, large discrepancies that persist between control and folding T-RE runs (Figure 4a) are greatly reduced (Figure 4b). We also note that, although the same Gō-like model was used for all three β-hairpins, the MSES simulations were able to recapitulate varied stabilities of these sequences in the GBSW implicit solvent as expected. Nonetheless, despite impressive conformational space coverage by all replicas in MSES simulations (Figure 3e−g and Figure S3), substantial differences persist in ensembles derived from control and folding MSES runs, except for GB1m3 with a more rigid proline-containing loop. This illustrates the formidable challenges in generating converged equilibrium ensembles even for small but flexible peptides.

In conclusion, we have developed an effective MSES approach that utilizes efficient topology-based CG models to accelerate the sampling of complex and rough atomistic energy landscapes. The CG and atomistic model are coupled using

native contact-based restraint potentials that are motivated by the current understanding of protein folding mechanisms as well as lessons from NMR structure calculations and allow excellent scalability to larger and more complex systems. The flexible and soft nature of the coupling potentials (eqs 3 and 4) also provides robust tolerance of moderate discrepancies in folding pathways at CG and atomistic levels, including potential involvement of non-native interactions. The bias from the coupling potential is removed by performing Hamiltonian/temperature RE, allowing one to benefit simultaneously from faster transitions of the CG model and the accuracy of the atomistic force field. Application to implicit solvent simulations of small but nontrivial GB1p series of β-hairpins demonstrates that MSES dramatically accelerates atomistic folding/unfolding transitions and improves the convergence of various thermodynamic properties of interest. We anticipate MSES to be highly useful whenever generation of well-converged protein conformational ensembles is critical, including intensive current efforts that rely on peptide simulations to optimize implicit and explicit solvent protein force fields.[34,35]

■ ASSOCIATED CONTENT

ⓈSupporting Information

Three figures and a table showing coevolution of CG and atomistic models, conformational coverage, and folding kinetics and efficiency of CG and atomistic models in MSES. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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