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Review

Conformational sampling for the impatient

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Abstract

Several new methods for sampling conformations of biomolecules have appeared recently. A brief review thereof is presented, with particular emphasis on applications that have been published, and suitability for different kinds of systems. Four methods (namely: RESPA, replica-exchange molecular dynamics, CONCOORD and Gaussian network method) are readily applicable for biomolecular systems.

Keywords: Enhanced sampling; Molecular dynamics; Monte Carlo; Energy landscape; Principal component analysis; Coarse-grain method

1. Introduction

> An intellect which at any given moment knew all the forces that animate nature and the mutual positions of the being that comprise it, if this intellect were vast enough to submit its data to analysis, could condense into a single formula the movement of the greatest bodies of the universe and that of the lightest atom: for such an intellect nothing could be uncertain; and the future just like the past would be present before our eyes [1,2].

After nearly two centuries, this Newtonian–Laplacian statement seems over-optimistic, if valid at all. The collective intellect of the scientific community, even when given the crystallographic positions of atoms in a protein, finds itself scrambling for barely enough computing power to predict the behaviour thereof.

The motivation for this review is to list the new computational methods for conformational sampling, given structural knowledge of only one conformational state of a biomolecule. The community now faces new challenges, such as the need to simulate larger biopolymers and even supramolecular assemblages [3,4], but conventional molecular dynamics (MD) method is showing its limitations [5,6]. Though new methods have indeed sprung up to take on the challenges in their stride, the last reviews covering similar grounds are now a few years old [7–10].

The title of this review may be taken in two ways: First, the impatient researcher, interested in the dynamics and function of a protein [11], may wish to use a new, faster method than conventional MD to sample the conformations of a biomolecular

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system so as to save a few weeks of computing time; second, the reviewer writes with the hope that he may save the researcher a few days of plowing through in the literature looking for the appropriate sampling method.

Before we start, readers new to the metaphor of energy landscapes of biomolecules are encouraged to familiarize themselves using the papers by Frauenfelder et al. [12–14]. Principal component analysis (PCA), also called essential dynamics [15–17], has become a standard analysis tool for MD trajectories. It has been used to demonstrate the capability [18] and expose the inadequacies [19,20] of MD in conformational sampling. Some of the most powerful energy landscape visualization [21] and enhanced sampling (reviewed below) methods are built upon the foundation of PCA. Therefore, a good understanding of PCA is essential. In these matters, several chapters of the book edited by Becker et al. [22] are helpful.

As much as possible, this review aims to include recent application of methods to specific biomolecular systems, with a bent towards the functional dynamics of proteins. Whenever something has not been—but can be—tried, hints are placed to inspire the reader. Methods for determining the reaction path given the initial and final conformations are outside our scope; the reader is directed to two recent reviews [23,24].

2. More of the same, but a bit different

2.1. Multiple timestep methods

The development of multiple timestep MD has been going on for a few years [25], the most popular being the RESPA (reference system propagation algorithm) methods [26–28]. Applications to biological systems have been tested, showing that carefully using an appropriate method with an outer timestep of approximately 5 fs can be safe—that is, giving a stable and useful trajectory–whilst affording a 2–3-fold speed-up [29]. Notably, the tests have included some lipid membrane systems [30,31].

Langevin methods, with fast degrees of freedom being stochastic, claim speed-ups as ambitious as 2 orders of magnitude [32]. Though interesting development are done (for example, constant pH extensions [33]), so far the use of atomic-model Langevin dynamics is limited to small peptides [34], despite well-placed promotion by its proponents [35]. With such ambitious promise of large speed-ups, perhaps researchers interested in the dynamics and function of (medium-sized) proteins should explore this way a bit more.

On a passing note, other attempts to speed up conventional MD have been concentrated at improving the performance of electrostatics (and other long range) calculations. For this, the reader is directed to the review [9] and Part VI of the book [36].

2.2. Feverish: high-temperature molecular dynamics

An old method for sampling more of the conformational space is to raise the temperature in conventional MD to a value higher than the physiological (approx. 300 K). This may be followed by dropping to a lower temperature and continuing the simulation run—in which case it is called simulated annealing. We cite particularly two recent papers, out of many that used this slightly-improved method [37,38].

While it is technically easy to implement, there are several objections usually used to dismiss this method: (a) the MD forcefield usually has not been designed with a temperature much higher than 300 K in mind, so it is doubtful that such MD is actually sampling the 'correct' energy landscape, let alone being physiologically relevant; (b) although accelerated barrier crossing is indeed observed and useful in many cases, algorithmically there is little speed improvement upon conventional MD afforded by running at a higher temperature; (c) the sampling over-estimates the entropic contribution to the free energy [39].

To give a fair assessment, this is a conceptually-easy method to quickly sample the conformational space for small peptides (as used frequently in the protein folding community, for example, [40]), but as the size of the molecule grows, the usefulness decreases. Of course, conventional molecular dynamics, including its high-temperature variant, is the standard against which the 'improved' sam-

pling methods must be judged—thus the 'hypothetical enemy', as it were.

2.3. Outnumbering the odds: multiple-copy dynamics

There are two types of multiple-copy dynamics. In one, the copies do not feel one another in any way—the advantage comes purely in avoiding computing the environment as many times as the number of copies; in the other, the molecule copies, whilst existing in distinct systems, cooperate indirectly in a 'swarm' over the landscape in hope to finding the target—the advantage is more than the sum of the parts due to the cooperation.

The first method, named locally enhanced sampling, has only been used in sampling the ligand conformation under the influence of a protein [41]. Sadly, so far no clever adaptation to sampling protein conformations has come to attention.

Two Hubers independently explored the type of swarming methods, intended for optimisation of structure and protein folding [42,43]. In these methods, the copies of molecules reach a consensus of which direction in the conformational space to explore next; they then proceed to move over there, until the target—usually set to be the global minimum—is found. Recently, the Folding@Home project has popularised (in more ways than one) a method of this type [44,45].

Though useful for its original purpose, these second types of multiple-copy methods are not readily applicable for dynamics and functional studies of proteins without adaptation. Unlike folding studies, which are most concerned with the global minimum, dynamics and studies are often concerned with local minima that are (say) the second or third lowest in energy, or those close to the global minimum. Happily, such adaptation does not appear to be conceptually prohibited [44].

2.4. Replica-exchange MD

Several Monte Carlo methods have been proposed in the context of small protein folding [46–48], of which we note particularly replica-exchange molecular dynamics (REMD) [49] (compare with parallel tempering [50]) for its potential applicability to large proteins.

Combining the ideas of multiple-copy simulation, simulated annealing, and Monte Carlo methods, REMD runs several non-interacting replicas of the same molecule over a range of temperatures. With a transition probability (similar to that in conventional Monte Carlo simulations) the replicas may exchange in temperature by re-assignment of velocity. Thermodynamic quantities at a temperature within the range may be calculated by reweighting.

As mentioned, it has been applied [51,52] and extended [53] in the context of small proteins in folding and structural prediction studies. However, applications to large molecules have yet to appear in the literature.

3. Atomic-scale biased methods: fighting it out of the minimum

Unlike methods in the previous section, the ones following are biased in a struggle to get out of the energy minimum and achieve sampling a wider space in the conformational space. Much development has occurred in the field of material science [54–57]; most of the methods covered here, however, have been designed with protein dynamics and functional studies in mind, to search for interesting spots (minima or conformational transitions) in the energy landscape of biopolymers.

3.1. Landscape engineering: padding and filling

To avoid the molecule hanging around in an energy minimum for too long, the local elevation method [58] adds a penalty potential against any conformations previously visited. In essence, this is a search method with 'memory', recording a history in order to penalize visiting the same conformation. It was intended only for small molecules, using only a few bits to record the conformational state.

The conformational flooding method [39] cleverly applies PCA [15,16] to define the 'essential' degrees of freedom of the (bio)molecule in which the landscape should be lifted. (Compare with

Becker's visualization method [21].) Using a multi-variate Gaussian potential padded upon the original landscape, the molecule can be nudged out of an energy minimum, thus achieving a wider conformational search. This method has been applied to carbonmonoxy myoglobin [59] and appears theoretically and practically robust.

Rather than padding the energy landscape, the recent puddle-skimming method [60] (and its improvement, puddle-jumping [61]) fills the minima in the original energy landscape up to a flat energy level. Though this simple modification may achieve wider conformational sampling, this reviewer has reservation about possible artefacts that can arise due to the resulting non-smooth potential in the context of MD.

3.2. Self-guided molecular dynamics

Halfway between changing the landscape (discussed above) and biasing the sampling (reviewed below), the principal component restraint method [62] observes the landscape sampled before using PCA [15,16] (again; compare with conformational flooding) and, guided thereby, restrains the distribution of the ensemble.

In contrast to the multiple-copy methods, where the copies vote for the direction of exploration, the self-guided molecular dynamics method [63–65] invites previously-sampled conformations in the selfsame simulation to vote. Since it was initially intended for protein folding, the 'guiding force' (and its 'momentum'-version [66]) rewards 'systematic motion' (that is, perpetuates rather than penalizes as in the local elevation methods).

So far the method has been applied to small host–guest [67] and peptide [63] systems. There is research into the correlation between the guiding force and the force due to the original energy landscape, and the impact of such correlation upon the enhancement in barrier crossing [68]; sadly, that inquiry limited itself to positive guiding factors. Those interested in protein dynamics are eager to get out of energy minima and may want to see the guiding force anti-correlated to the original force. Investigation into a negative guiding factor may be in order.

3.3. Filtering

The digitally-filtered MD method [69] and its reversible variant [70] amplify or suppress atomic motions by frequency. Using a recipe favouring low-frequency motion, conformational change may be enhanced. Indeed these methods, by performing a series of MD simulations with monitoring of spectral density and adjustment of digital filters, make it possible to home in to motions at any desired frequencies. The authors have applied the methods to peptidic systems as large as a prion protein [69,71] at the time of introduction.

4. CONCOORD: a non-dynamical method of generating conformation sets

The popular CONCOORD ('from constraints to co-ordinates') method [72] has now been applied to a wide variety of proteins, some as large as the GroEL chaperonin [73]. Unlike MD or most of the other methods reviewed here, it is not a dynamical method—the set of conformation generated cannot be considered as a timeseries. Rather, the resulting set contains conformations satisfying a list of distance criteria. It is also notable that the idea of energy does not take a direct role; this perhaps allows for some (reasonable) 'surprises' that may not be so readily generated by the other energy-dominated methods.

5. Coarse-grain methods

5.1. Network models

The Gaussian network model [74,75] has a residue-level (as opposed to atomic-level) model of a protein. The residues are connected by harmonic potentials governed by a single Hookean parameter (anharmonic terms are added in a later variety [76]).

It very aptly reproduces isotropic temperature (B) factors observed in crystallography, and has been applied to proteins such as tryptophan synthase [77], HIV-1 reverse transcriptase [78] and influenza virus hemagglutinin [79]. Clearly, global motions can be seen on this level of granularity; but surprisingly, finer interpretations have also

been made on the kinetically-hot residues in the hemagglutinin case.

Recent forays of improvement on this front include: (a) using coarser grains than residues [80]; (b) doing away with the notion of sequence altogether (!) [81,82]; (c) enhanced sampling by coupling the slower modes with higher temperature [83] in a similar manner to the biased methods reviewed above; and (d) using the network model to assist conventional MD sampling [84].

5.2. *MBO(N)D and related methods*

A step up the length scale from the conventional united-atom MD, MBO(*N*)D (multiple-body O(*N*) dynamics) [85] provides a framework of coarse-grain dynamical simulation that scales linearly with the number of bodies in the system. It modestly claims a 5–30-fold speed-up over MD. It has been applied to the C-terminal domain of calmodulin [86], a peptide of 70-some residues.

MBO(*N*)D relies on the user to determine the level of granularity, though empirical comparisons of different levels and analyses of their influence on the molecular behaviour observed are lacking. When this problem is rectified, the method may lead to a tour de force of coarse-grain 'molecular' dynamics.

6. Summary

Distinct exhortations are directed to two constituent groups in the scientific community. To those who are eager to sample the conformations of larger proteins and interested in dynamical behaviours, this review commends the RESPA, replica-exchange MD, CONCOORD and Gaussian network methods. For those who are keen to develop better methodologies for conformational sampling, endeavours in the directions of the Langevin, swarming, self-guided MD and MBO(*N*)D methods may prove effective. May this short review be of use to the impatient.

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