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Review

Brownian Dynamics Simulations of Biological Molecules

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Brownian dynamics (BD) is a technique for carrying out computer simulations of physical systems that are driven by thermal fluctuations. Biological systems at the macromolecular and cellular level, while falling in the gap between well-established atomic-level models and continuum models, are especially suitable for such simulations. We present a brief history, examples of important biological processes that are driven by thermal motion, and those that have been profitably studied by BD. We also present some of the challenges facing developers of algorithms and software, especially in the attempt to simulate larger systems more accurately and for longer times.

Highlights

Many biological processes at the macromolecular and cellular level occur in the mesoscopic regime, where thermal motion drives diffusion and kinetics.

Brownian dynamics is a computer simulation method suitable for this mesoscopic regime, and has been used to study large biological molecules and cellular components.

Algorithms are being developed to help this method scale to larger length scales and longer times.

Modeling Living Systems Beginning with Atoms

Over the past several years, advances in biological experimental techniques, growth in the amount of available biological data, and the increase in computer size and speed have opened up new possibilities for building computational models of living systems. The potential rewards include increased understanding of living systems and more effective medical treatments. Although the field of biological modeling covers many areas, perhaps the most challenging and yet the most fundamental is the attempt to build useful models starting from the atomic level.

From Brown's Pollen to Atoms, and Back Again

One of the goals of science is to create mathematical models that can be used to make predictions, increase understanding, and devise useful substances and devices. Over the past few centuries, fundamental and general models, such as Newton's laws of motion, Maxwell's equations of electromagnetism, and more recently, the equations of quantum mechanics and general relativity were developed. In principle, because these are exact laws, it would be possible to exactly model any physical system. However, only the simplest systems, such as the harmonic oscillator, two bodies interacting through gravity, and the electron of the hydrogen atom, are described by equations that can be solved exactly by hand. The later development of computers made it possible to study larger systems by approximating the model equations by numerical algorithms, but the finite power and size of computational resources limit the size of such systems to that well below the size of most interesting biological systems. Thus, approximations of such models that could handle larger systems, while not sacrificing the interesting features, have been necessary.

Continuum models, such as the equations of solid and fluid mechanics, thermodynamics, and chemical kinetics, were developed alongside these fundamental models. These models were developed before scientists knew much about the details of molecules and their behavior, and are based completely on observed properties of the bulk materials, such as the elastic modulus, fluid viscosity, thermal conductivity, and kinetic rate constants. As more details of atoms and molecules came to light in the late 19th century and early 20th century, the field of statistical mechanics was developed to tie together the behavior of individual or small groups of molecules with macroscopic properties. For example, the van der Waals equation of state used to predict

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expected gas behavior (including condensation to a liquid) assumed that molecules could attract each other over long distances but repel each other at short [1].

In between these regimes of microscopic (atoms and molecules) and macroscopic (bulk material and continuum models) is the mesoscopic regime, where fluctuations caused by thermal molecular motion are significant, but, like the macroscopic regime, the knowledge of individual molecules is not accessible. In 1827, the botanist Robert Brown observed in his microscope pollen grains in water moving in a stochastic manner [2]. Although mathematical descriptions of such motion were later developed, the first physical explanation came from Albert Einstein in 1905 [3,4]. He was able to show mathematically that the mean-squared displacement of a mesoscopic particle immersed in a fluid of much smaller particles is proportional to the product of diffusivity and time. Using previous continuum theories of Stokes' law from fluid mechanics and Fick's Law from diffusion, he was able to show further that the diffusivity, D, of a spherical particle is

$$D = \frac{k_B T}{6\pi\mu a} \quad [1]$$

where k_B is Boltzmann's constant, T is absolute temperature, μ is the fluid viscosity, and a is the sphere's radius. As a bonus, the derivation provided an independent way of computing Avogadro's number, and along with further experimental confirmation by Jean Perrin, was seen as definitive proof of the atomic hypothesis [5].

Diffusion in Biology

It turns out that this more recently understood mesoscopic regime, where diffusional behavior predominates, critically influences the outcomes of many biological processes. At physiological concentrations, diffusion is known to influence or control the kinetics of ligand binding to many enzymes [6,7] and receptors [8,9] ; models based on this assumption have been used since the 1950s [6] . Such enzymes typically are ones where speed has provided an evolutionary advantage [10,11], for example, for efficient and accurate handling of amino acids on their way to protein synthesis [12], the removal of reactive toxic species [13], or for the rapid modulation of synaptic activity in the case of acetylcholinesterase [14]. The association of certain proteins is also known to proceed at diffusion-controlled rates with functional consequences [10,15–17], including some antibodies and antigens [18,19]. The rate at which drugs bind to their receptors also approaches diffusion control, which is generally a favorable situation [20,21]. Antibodies engineered for enhanced diffusion-controlled binding to proteins of the respiratory syncytial virus (RSV) have been developed as therapeutic agents for preventing RSV infection [22], and the importance of rapid binding in other therapeutic settings has been firmly established [23,24] . The assembly of cytoskeletal structures such as actin filaments and microtubules involves diffusion-controlled steps, substantially accelerated by electrostatic interactions [25–27] . Such mechanisms may also act in the targeting of transducin in signaling processes associated with vision [28]. Not only are the rates of association of many biomolecules limited by diffusion, but given the nonequilibrium nature of living organisms the relative probabilities of alternative outcomes of biological processes can be determined by the relative speeds of different diffusional events [10,29]. This, of course, is a very small and somewhat arbitrary sampling of the wide variety of biological systems governed by diffusion.

Computational Developments

Over the next several decades following Einstein's paper, general-purpose digital computers were developed, and the first atomic-level simulation of a substance, using Newton's laws of motion, was performed by Alder and Wainwright [30] in 1957 on an idealized hard-sphere fluid.

Ten years later, Verlet was able to reproduce thermodynamic properties of argon with a slightly more complex model [31]. Such atomic-level simulations, now known as molecular dynamics simulations, were extended to more complex systems, including protein molecules without surrounding water in the late 1970s [32]. However, it soon became apparent that adding solvating water molecules to such simulations would greatly increase the size and time required for such simulations. Fortunately, as seen earlier, when studying the motion of large biological molecules in water, it had been long observed that the motions of the large molecules, like Brown's pollen, follow a more diffusive trajectory with no appearance of inertia. Therefore, if one were not concerned with the details of the water, or even all of the details of the large molecule itself, using a more mesoscale approach might allow much faster simulations on much larger systems.

Along with the computer technology, the mathematical tools were developed to properly describe motion and fluctuation at the mesoscopic level. Although mathematical work describing the fluctuations was done as far back as the mid-1800s, and workers in different fields independently came up with useful formulations throughout the 20th century, more recent ideas such as the Wiener process and the Ito calculus were able to put the field on a unified foundation and allow the development of useful approximations and computational methods [33].

The starting point for Brownian dynamics (BD) is the Langevin equation, which is Newton's law of motion with several terms. There is the force originating from a potential energy function, a damping coefficient that gives a force opposing motion throughout the fluid, and a stochastic force. The stochastic force represents energy being added to the particle by collisions with the fluid molecules, and the damping term represents energy being removed from the particle from motion through the same fluid (Figure 1). As shown in Box 1, one can derive the final equation of BD

$$d\boldsymbol{x} = \frac{D}{k_B T}\boldsymbol{F}dt + \sqrt{2D}d\boldsymbol{W} \qquad [2]$$

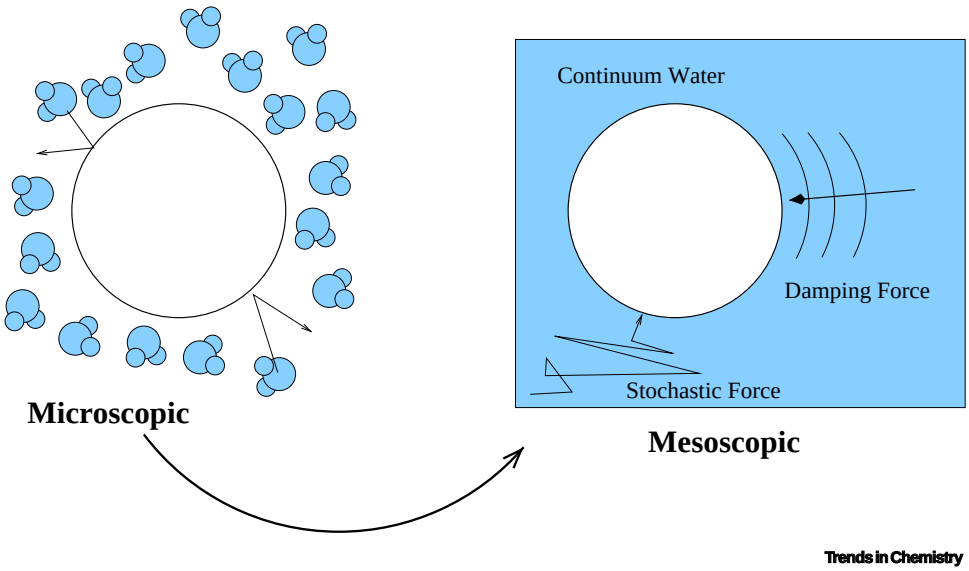

Figure 1. Going from the Microscopic Description to the Mesoscopic Description Is Done by Replacing Individual Atoms with a Continuum. Individual collisions are replaced by a damping force and a stochastic force.

Box 1. Derivation of the Brownian Dynamics Equation

The position and velocity of the particle are represented by 3D vectors **x** and **v**. The force is **F**, the damping factor is ζ, and the stochastic force is represented by d**W**. If the particle is a sphere, then the damping factor ζ is equal to $6\pi\mu a$, which is the Stokes law used by Einstein above. We show this for one particle:

$$m d\boldsymbol{v} = -\zeta \boldsymbol{v} dt + \boldsymbol{F} dt + \sigma d\boldsymbol{W} \quad [\mathrm{I}]$$

$$d\boldsymbol{x} = \boldsymbol{v} dt \quad [\mathrm{II}]$$

where σ is a constant to be determined. Because of the stochastic nature of the force, the time derivatives are not actually well defined, so it is more mathematically proper to keep the dt term on the top.

The term d**W**, called a Wiener process, is described in terms of its statistical properties. It is a 3D vector of uncorrelated random variables which follow a Gaussian distribution with a mean of zero and a standard deviation of dt. Mathematically, the limit is then taken as dt goes to zero. The velocity part of Equation II can be 'solved' for the case of zero **F** to get a solution for second moment of velocity

$$\langle v^2 \rangle = \frac{3}{2}\left[1 - exp\left(-\frac{t}{\tau}\right)\right]\left(\frac{\sigma}{m}\right)^2 \tau \quad [\mathrm{III}]$$

where $\tau = m/\zeta$ is a characteristic time scale. According to statistical mechanics, at large times the velocity distribution must approach the Maxwell distribution with the second moment of

$$\langle v^2 \rangle = \frac{3k_B T}{m} \quad [\mathrm{IV}]$$

In order for this to be true, the constant σ must be equal to $\sqrt{2\zeta k_B T}$. Next, the main assumption behind BD is this: the characteristic time τ for the velocity distribution of the particle to approach equilibrium is much less than the characteristic times of interest in the model. Therefore, we can divide the velocity part of Equation II by damping factor ζ, set time constant τ to zero, and combine with the position part to get the equation for BD (i.e., Equation 2 in main text), where the diffusivity $D = \frac{k_B T}{\zeta}$ is exactly that derived by Einstein.

The observed diffusional motion of large molecules can be summarized in Equation 2, where mass no longer appears. This relatively simple equation also lends itself well to computer simulations, where a finite time step is substituted for dt, the appropriate random numbers are generated, and the resulting value for $d\mathbf{x}$ is used to update the position. It is also possible to derive a version of Equation 2 for many interacting particles; the resulting equation has a diffusivity matrix instead of scalar D, which includes diffusional coupling and hydrodynamic interactions. The first simulations using the multiparticle equation were performed in 1978 by Ermak and McCammon [34], and it was in that paper that the term 'Brownian dynamics' was first used to describe models using Equation 2.

Going into the 1980s and beyond, the field of BD on biological molecules started moving into two directions. One direction was the development of simplified models of peptides and other biopolymers, in which several atoms would be lumped into one rigid interaction center. The motions which were more local and rapid would be ignored, while the presumably more interesting larger-scale motions with longer time scales would be treated as diffusive in nature by using BD. Another direction was computation of kinetic rate constants for enzyme reactions and biomolecular associations, especially those that are diffusion limited. These calculations could use models of each molecule that treated it as rigid or mostly rigid, allowing great computational savings over all-atom molecular dynamics simulations. It should also be noted that outside of biology, the polymer physicists and engineers developed their own versions of BD in order to study rheological properties of polymers, especially in shear flows [35]. Although their derivations and nomenclature come from a slightly different tradition, the assumptions and mathematics are fundamentally the same.

Molecular Association and Channeling

A key advance in algorithms in BD came in 1984 with the Northrup–Allison–McCammon algorithm, which enabled the computation of second-order rate constants of diffusion-limited molecular association [36]. The usual method is to define a geometric reaction criterion, such as distances between opposing atoms, to decide when the association is complete. Then, a sphere is constructed around the center of the receptor molecule, large enough so that if the center of the other, ligand molecule is placed on it, the force between the molecules does not depend on their mutual orientation. A second, outer sphere is constructed, larger than the first but with the same center. The ligand is placed on the first, inner sphere, and (usually) the ligand is moved with a relative diffusivity according to BD until the association occurs or it reaches the outer sphere. This process is repeated many times, and the association rate constant can be computed from the probability of association versus escape to the outer sphere (Figure 2). A different formulation

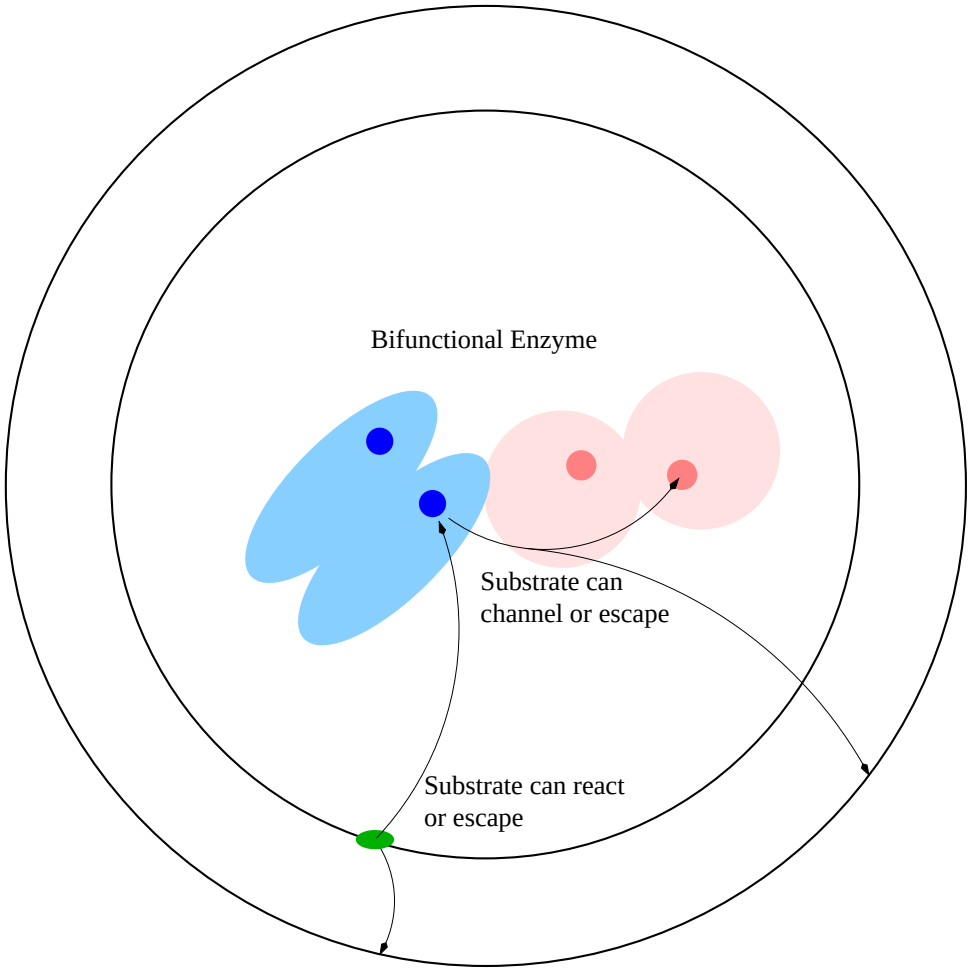

Figure 2. Computing Association Rate Constant and Channeling Probability. For computing a second-order rate constant of association, the substrate starts on the inner sphere and is propagated by BD until it either reacts or escapes to the outer sphere [36]. One variation of this technique allows the substrate to be placed back onto the inner sphere upon reaching the outer sphere, in order to continue the trajectory [38]. To compute a channeling probability, the substrate starts on one site and either reaches another site or escapes. Many trajectories must be run in order to obtain good statistics on the probabilities of reaction versus escape, which can be used, along with the total charges and diffusivities of the molecules, ionic strength, and solvent dielectric, to compute the rate constant.

was developed by Greives and Zhou in which a transient complex between the two molecules is determined, and BD trajectories take place starting from that complex [37]. A later formulation of the Northrup–Allison–McCammon model [38] also allows the study of channeling, in which the probability of a ligand moving from one site to another, versus escaping, can be computed to obtain channeling probabilities. For now, the reaction criterion remains an adjustable parameter, which can be adjusted for one case and kept fixed for different but related cases.

The first such detailed simulation on a biological system, in 1988, was on the interaction between superoxide dismutase and the superoxide ion [39]. A significant series of studies of triose phosphate isomerase followed in 1993 and 1994, with a detailed flexible model of the active site [40,41]. Protein–protein association simulations followed, starting that same year [42]. More recent interaction studies include CDC42 GTPase binding [43], linker histones [44], the p53 tumor suppressor [45], absorption of proteins to surfaces [46], protein kinase A [47], and the influenza virus [48]. The first substrate channeling study was performed on the protozoan dihydrofolate reductase–thymidylate synthase complex in 1996 [49], and more recent studies have included the same complex in humans [50] and a complex in the Krebs cycle [51]. In 1993, an idea was developed to simulate associations by tying together BD simulations for wider separations, and more detailed molecular dynamics simulations for closer encounters [52]. The idea has been further developed and used for prediction of kinetic parameters for several small molecules binding to a cyclodextrin [53].

A main area of ongoing research for such BD simulations is the computation of the forces between the molecules. The solvent is modeled as a continuum characterized by its viscosity and its effect on the electrostatic and other interactions between the solutes. A commonly used model for the electrostatic interactions is that represented by the continuum Poisson–Boltzmann (PB) equation [54]. Together with some model for apolar interactions, such as a generalized surface tension, this can provide a reasonable approximation to the effective force among diffusing solute particles [55]. A common further approximation is to use the PB equation to compute the electric field around the larger molecule, and let the charges on the smaller molecule interact with the field. For protein–protein association with more equal-sized molecules, approximations are included of polar desolvation effects that arise due to polarizability of the water [56], but these have much room for improvement.

In addition, for solutes that approach much more closely than about 1 nm in surface-to-surface distance, dewetting fluctuations can develop for incipient apolar contacts, dramatically altering the effective force for solute association [57]. These phenomena are observed in explicit solvent molecular dynamics simulations. These apolar interactions are significantly altered in the presence of polar interactions, and vice versa. At even closer approach, the atomistic details of the solvent and solute interactions must be recognized. Incorporating these apolar effects, and the polar effects mentioned earlier, into the simulations, while maintaining both accuracy and efficiency, will continue to be an important area for research.

Simplified Polymer Models

A very active area of research is of coarse-graining parts of large molecules to simplify the models and allow larger-scale simulations. This is intimately tied with BD, since these coarse-grained models typically move in a diffusive manner. A BD simulation using a one-body-per-residue model was used in 1980 to study the helix–coil transition in peptides [58]. Since then, many different schemes for reduced peptide models have been devised. Some of them are intended for general purposes, while many are *ad hoc* formulations for a specific problem. For peptides or nucleic acids, they typically use several beads to represent a residue or base (Figure 3), with

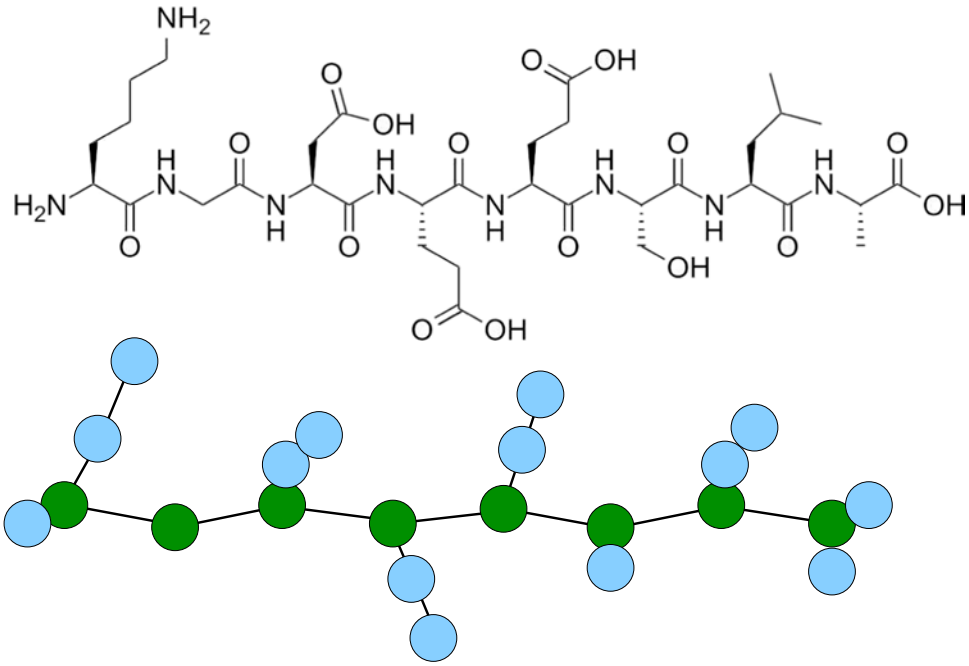

Figure 3. Coarse-Graining of a Peptide. In some models, several beads can be used to represent an amino acid, with the number of beads much less than the number of atoms. This is an example of the approach used by the COFFDROP model [70,72], which places a bead at each alpha-carbon and between zero and four beads to represent each side chain. The potential energy function depends on the bond lengths, bond angles, torsion angles, and distances between the beads.

a potential energy function to describe the bead interactions [59,60]. These coarse-grained models have been used with BD to simulate such intramolecular motions as flap displacements to allow drug binding in HIV protease, yielding correlations with drug binding rate constants [61]. Others have included the folding and conformational changes [62] of simplified models of proteins, the folding and unfolding [63] of RNA, the supercoiling [64], translocation [65] and compaction [66] of DNA, protein–DNA interactions, ion channels [67–69], and actin-binding proteins [70].

The main challenge in these types of models lies in devising the potential energy functions and computing their parameters. The parameters can be computed from equivalent atomic-level molecular dynamics simulations, experimental data, databases of structures, or physical reasoning. Although no single model has emerged as a universal, general-purpose model for biomolecules, general theories for molecular coarse-graining are being developed, which will likely lead to improvements and better understanding of these models [71].

Large-Scale Models

Beyond the peptide and nucleic acid models, it is possible to carry the coarse-graining even further to study larger systems, especially those with large numbers of separate biomolecules. In 2010, the first BD simulation of the cellular cytoplasm with significant molecular-level detail was performed by McGuffee and Elcock [72], and followed by further simulations to explore the effects of molecular crowding on biomolecular diffusion, thermodynamics, and kinetics [73,74] . Other models have been developed for microtubule growth [75] and bending [76], aggregation and assembly of protein complexes [77,78], retroviral infectivity [79], cytoskeletal molecular motors [80,81], chromosome organization [82,83] , the nuclear pore complex [84],

synapses [85], and endocytosis [86]. Although the level of coarse-graining depends on the model, many of these models treat entire protein molecules with a single interaction bead.

In addition to the challenges discussed earlier for smaller systems, perhaps the most difficult challenge is the inclusion of hydrodynamic interactions. When two or more large molecules move near each other in a solvent, their motions are coupled due to the movement of the solvent, and continuum fluid mechanics can be used to compute the effect [87]. These interactions have a large influence on diffusion and reactions in crowded environments. Although often referred to as forces, they instead manifest themselves in the diffusion matrix discussed earlier, and the time required for the most basic algorithm to properly include them scales as the cube of the number of particles. Recently, algorithms have been developed that scale linearly in certain cases for large systems, and useful approximations have been developed [88] but challenges remain [89,90].

Another challenge is the integration of BD simulations with Markov state models that have been developed to describe the internal motions of biomolecules [91,92]. Although both methods are used to reduce the complexity of the systems studied, BD is continuous in nature while Markov models are discrete. Because the two methods complement each other, this is an active area of research [93].

Outstanding Questions

Can we build efficient, yet accurate, models for solvent-mediated forces among biological macromolecules?

Will it be possible to accurately and generally predict the rates of protein–protein association and dissociation from first principles of physics, without using adjustable parameters?

Can Brownian dynamics algorithms be developed that favorably scale to larger sizes of biological systems and more powerful computers?

Will it be possible to use these models, based on Brownian dynamics, to simulate and better understand cellular-level phenomena, such gene transcription and translation, motion driven by molecular motors, or signal transduction?

Computer Software

Because of the wide variety of possible BD models and the relative simplicity of the algorithm, many investigators have written their own code. However, a number of software packages exist for various cases. The first academic BD code, UHBD, was released in 1991 [94], and used the Northrup–Allison–McCammon algorithm to compute rate constants. Another widely used code, useful for associations between two large molecules, is SDA [95], which provided the inspiration for others, such as Browndye [96] and GeomBD [97]. SDA was later updated with the capability of simulating many macromolecules [88,98]. Packages for larger-scale, more coarse-grained problems include BD_BOX [99], ReaDDy [100], and Smoldyn [101]. Perhaps the main challenge in future software development, besides improving the algorithms, is scaling it up to large, message-passing and multicore architectures [102], and adapting the algorithms for use on graphical processing units [103].

Concluding Remarks

In order to simulate larger and more complex biological systems for longer times, it is necessary to develop models that are simplified from the atomic-level details. It just so happens that such models on the macromolecular and cellular level often undergo a diffusive motion that can best be captured by BD. Although many useful and interesting models have already been developed, much research and development remains for better and more general theories, algorithms, and software (see Outstanding Questions). This will be especially important for studying phenomena at the cellular level, such as cytoplasm dynamics, gene expression, and pharmacokinetics, where the atomic-level simulations are no longer feasible but where continuum models used at the tissue level are not suitable either. Although it is impossible to discuss all of the BD models of biomedical interest from recent years, we have tried to provide a representative sampling of publications that illustrate the important points of this research area.

Future developments will likely be in several areas (Figure 4). Research will continue on coarse-grained models that span the scale from atom to organelle, particularly those that can be 'bootstrapped' from smaller scales. These models will include improved and more efficient

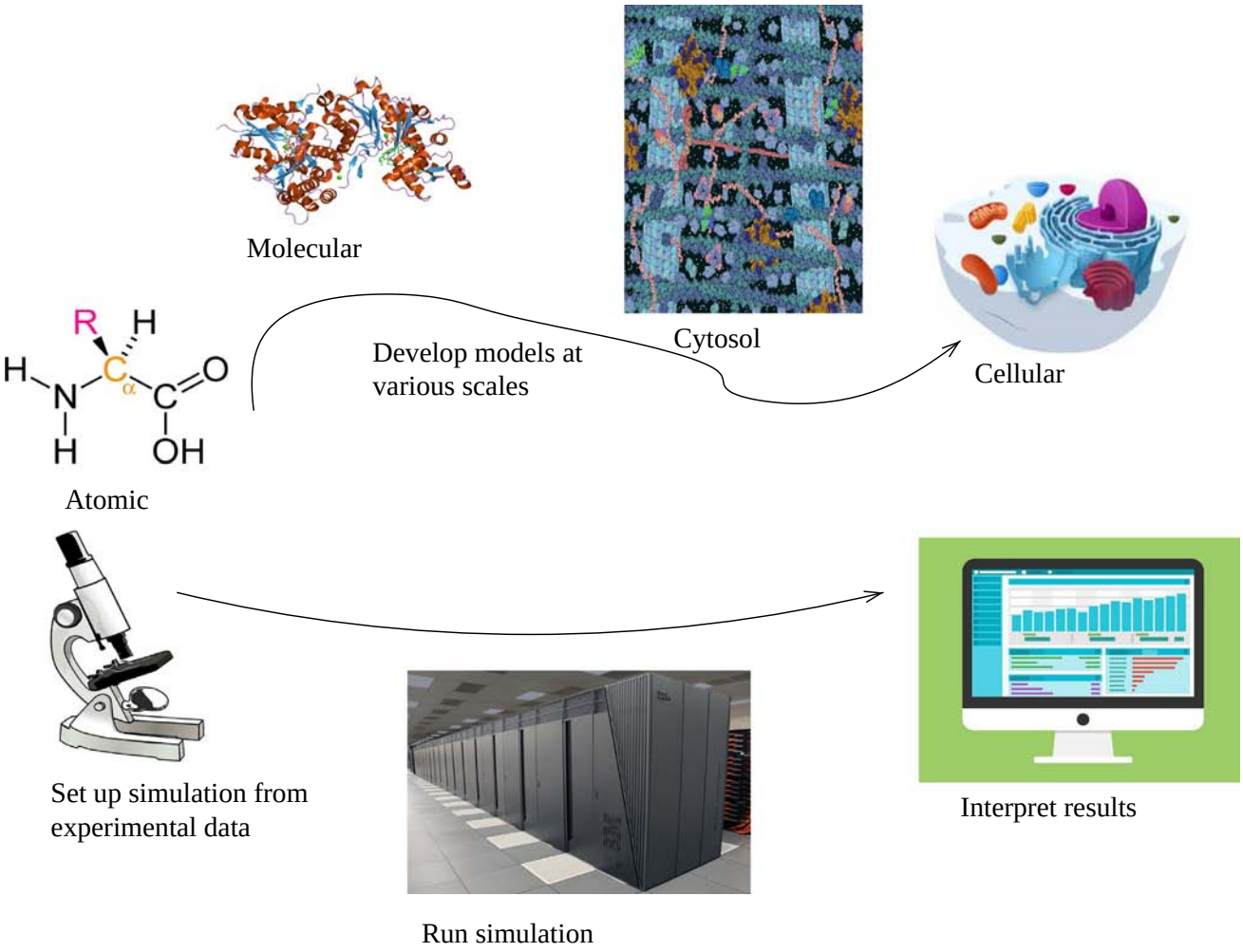

Figure 4. Future of Brownian Dynamics Simulations. The main challenges are building the models at various scales, setting up simulations using previous information, developing algorithms and software, and analyzing and interpreting the results.

descriptions of the internal motions of the coarse-grained bodies and the surrounding solvent. The three main components of such models will be: (i) a description of the dynamic variables, or degrees of freedom, and how they are mapped to higher and lower scales; (ii) the effective potential energy as a function of these variables; and (iii) a description of the response of the variables to the gradients of the effective potential energy and to external forces. Development will continue on algorithms to efficiently compute these three components, and to propagate them through time in the most efficient manner without losing important information. As simulated systems become larger and more detailed, these models and algorithms will be implemented on modern computer architectures in such a way that they can scale effectively with the amount of available resources. Constructing the initial conditions and starting point of such simulations from experimental data, especially at the cellular level, will continue to be a challenge. Finally, devising methods for interpreting the resulting vast amount of data resulting from such simulations will be necessary for using BD simulations to answer biologically and medically interesting questions.

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