there is no indication whether the measured interactions are specific to active, GTP-bound Rac1. This is a key issue; the inactive GDP-bound forms of Rac1 are usually just that — inactive — so the differences between the interactions of the WRC with GDP- and GTP-bound forms will be crucial. And finally, the role of phosphorylation is merely touched upon. It is certain to be more complicated and wide-ranging than can be analyzed in a single paper — but the structure is a crucial starting point.

One interesting and ongoing point is that the function of the majority of the WRC is still unaccounted for. The recombinant complex used to resolve the structure is a masterpiece of protein chemistry, but the large polyproline-rich domains in the carboxyl termini of WAVE1 and Abi2 had to be removed to aid crystallization. The existence of polyproline domains is highly conserved — WAVE1's domains are also seen in all other WASP family members — and thus probably physiologically important. These domains are likely to form extended, unstructured arms that increase the effective size of the complex. Nearly half of Abi2, including an SH3 domain that is important in metazoans but not more distant organisms [19], is absent. The remainder of Abi2 transverses the entire width of the complex, potentially allowing the unseen carboxyl terminus to protrude near the bulk of Nap1.

This leads to the biggest mystery, the function of Nap1. Chen *et al.* [4] like most authors, portray this essential component of the WRC as a structural scaffold. However, it is not only very large, but conserved throughout is length from mammals to *Dictyostelium* and plants [20], implying a more central and specific role. Its conservation is curious, given its apparent separation from the action around Sra1 and the VCA domain, but this just goes to emphasize that the regulation of SCAR/WAVE still holds many secrets.

The structure of the WRC is not the end, or even the beginning of the end, as Winston Churchill said, of understanding how cells make actin protrusions. It is, perhaps, the end of the beginning. The physical arrangement of the subunits and a plausible mechanism for regulation by Rac1 represent a great step forward, but above all they make the prospects for future advances seem much clearer.

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Protein Dynamics: Moore's Law in Molecular Biology

The millisecond barrier has been broken in molecular dynamics simulations of proteins. Such simulations are increasingly revealing the inner workings of biological systems by generating atomic-level descriptions of their behaviour that make testable predictions about key molecular processes.

Michele Vendruscolo and Christopher M. Dobson

A fundamental understanding of the manner in which a protein molecule functions depends on a detailed knowledge of not just its structure but also its dynamical behaviour [1]. As molecular dynamics simulations carried out on modern computers make it possible to solve the equations that describe the motion of molecular systems [2], they are a supremely powerful way of providing information at atomic resolution about the way in which protein molecules move and interact with their environments [3]. Indeed, after the initial report of the first application of molecular dynamics simulations to studying the structural

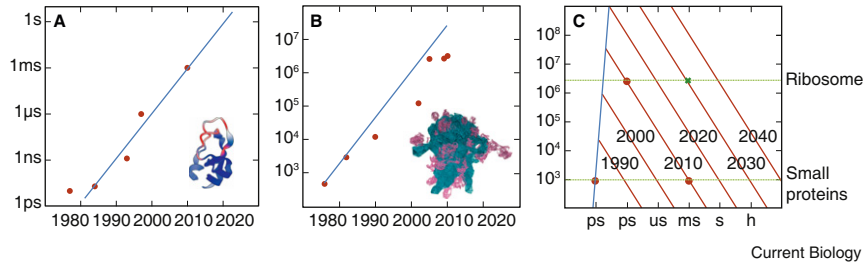

Figure 1. Moore's law in molecular biology.

(A) Growth in the timescale accessible to molecular dynamics simulations of proteins. After the first (*in vacuo*) simulation of a protein [4] (red point, bottom left), the timescale accessible to all-atom simulations in water has been increasing exponentially, indeed doubling every year, to reach the millisecond range [5] (red point, top right). By 2020, it should therefore be possible to follow the trajectories of small proteins for seconds and beyond. (B) Growth in the size (in number of atoms) of the protein systems studied by all-atom molecular dynamics simulations. The blue line is a theoretical limit derived by assuming that the growth in system size goes as the square root of the increase in timescale, as the number of interactions scales as the square of the number of atoms. The largest post-1990 simulations tend to fall below this limit, partly because of the lack of high-resolution all-atom structures of large macromolecular complexes, and partly because it is often not useful to devote a great deal of resources to simulating a very large system if it can be achieved only for, very short timescale. (C) Change with time in the limits of the timescales and system sizes accessible by molecular dynamics simulations. The blue and red diagonal lines define the boundaries at given times; for example, the current limit (red line labeled as '2010') runs through the millisecond simulation of small proteins [5], and the nanosecond multi-million atoms simulations of the ribosome [8], whose structure is shown in (B). If the current trends continue, it will be possible to simulate the dynamical properties of the ribosome for milliseconds by 2030 (green cross).

fluctuations of a native protein [4], this type of approach has become one of the most fascinating and widely used methods of enhancing our understanding of molecular processes in living systems.

With the recent report [5] of an all-atom molecular dynamics simulation of a protein on the millisecond timescale, a new milestone has been reached. By looking at the progress of such simulations with time, a steady and dramatic increase can be observed in the length of the trajectories that can be generated by this approach (Figure 1A). This result is a direct consequence of Moore's law [6], which is well known in computer technology and describes how the performance of integrated circuits has been increasing exponentially over the last half-century by doubling approximately every two years. Our analysis of the literature (Figure 1A) reveals that since the first report of an all-atom molecular dynamics simulation of a protein in water about 30 years ago [7], which was on the picosecond timescale, there has been an increase by nine orders of magnitude in the timescales accessible to this approach. If this trend continues, and there seems little reason to doubt that it will, within a decade it will be possible to define the trajectories of small proteins on the timescale of seconds and more. These advances are particularly remarkable when one realises that a picosecond is to a second as a second is to the time that has passed since the emergence of mankind on this planet.

Parallel to the increase in the timescales accessible to simulations, there has also been a growth in the size of the systems that can be studied (Figure 1B). Following the first simulation of a small protein in water [7], which, even counting the surrounding water molecules, involved just a few thousand atoms, it is now possible to obtain a first glimpse of the dynamical processes that take place in the ribosome, involving several million atoms [8]. The computational power needed to carry out a simulation increases, at least in the most straightforward approaches, linearly with the simulation time (so that doubling the length of a simulation requires twice the power) and with the square of the number of atoms involved (so that doubling the size of a system quadruples the power required to simulate it). Therefore, from the increase in the accessible timescales (blue line in Figure 1A), it is possible to infer the corresponding increase in the accessible system sizes (blue line in Figure 1B). This type of procedure, rather than a direct analysis of the trends in the published 'record-breaking' system sizes, is likely to be more realistic, because there are at least two factors that come into play in the study of large systems. The first factor is that the biologically relevant timescales tend to increase as the system size increases, and therefore there is often limited value in simulating very large systems for very short timescales. The second factor is that high-resolution structures are still available for only a relatively few very large macromolecular complexes [9]. Thus, for example, within the next ten years it might become technically possible, at least in principle, to carry out an all-atom simulation of the nuclear pore complex [10], but such simulations cannot be carried out until an atomic resolution structure is available.

The type of argument that we have made follows from a general consequence of the application of Moore's law to biological systems. The data shown in Figure 1A,B indicate that every decade there is an increase of about three orders of magnitude in the timescale and about one and a half orders of magnitude in the system size accessible to molecular dynamics simulations. By combining these observations, we can rationalise the advances that have taken place in the last three decades concerning the types of system that can be studied by all-atom simulations in water, and make predictions about future possibilities (Figure 1C). Thus, we may expect, for example, that it will be possible to simulate the dynamics of the ribosome on the millisecond timescale by 2030, thus starting to provide us with a uniquely detailed description of a key biological process, here the biosynthesis of proteins from the information encoded in our DNA and the subsequent folding of the newly synthesised polypeptide chains.

Following an analogous argument, by 2050 it should be feasible to simulate the all-atom dynamics of an entire bacterial cell [11], although initially on a nanosecond timescale, bringing an atomistic description of the complete set of processes onto which life depends into the realm of possibility. For those without the patience to wait that long, however, we note that the direct integration of the Newton's equations of motion at atomic resolution over ever-increasing time intervals is not the only strategy that is possible in order to follow to simulate the properties of macromolecular

systems. Many other approaches are also being developed, including the use of low-resolution models in which collections of atoms making up chemical groups, or even entire molecules, are modelled as single entities [12], and the incorporation of experimental data into the calculations to restrict the extent of conformational space that need be explored in a simulation to those regions that are of interest for a particular problem [13]. The latter approach is of particular interest in the context of mechanistic studies, for example of protein folding or enzymatic action, as it enables the accurate determination of the structures of species present at low populations, such as intermediate states, or even just fleetingly, such as transition states [14].

The ability to carry out simulations for longer lengths of time, and of systems of increasing size, coupled with an ever-growing accuracy in the force fields used to describe the molecular interactions [15], will progressively enable some of the key problems in biology at the molecular level to be addressed. We find particularly exciting the possibility of generating accurate descriptions of the conformational ensembles corresponding to natively unfolded proteins and to unfolded or partially folded states of globular proteins; such descriptions are crucial for understanding the molecular processes that give rise to many of the highly debilitating neurodegenerative disorders that are proliferating with frightening rapidity in the modern world [16]. In addition, the ability to define the details of the interactions between small molecules and proteins promises unprecedented advances in the exploration of rational therapeutic strategies for other very common conditions, for example to combat infectious diseases and cancer. On a more fundamental level, the opportunity to probe large macromolecular systems offers exciting opportunities for exploring such issues as the nature of complex protein–protein interactions, and the mechanisms of trafficking of molecules to different regions of a cell, a process involving transport through membranes and diffusion over significant distances in the cytoplasm.

The progress illustrated by the recent report [5] of a millisecond simulation of a protein will steadily enhance our ability to use molecular dynamics simulations as a powerful strategy for proposing possible mechanisms for complex biological processes. This strategy will enable experiments to be devised in a rational manner to test and extend such mechanisms, and in addition will enable experimental data to be translated into descriptions of the astonishing intricacies of biological systems. Indeed, the application of Moore's law to molecular biology reveals just how much our understanding of the fundamental processes that characterise living systems is likely to develop in the next few decades.

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Motor Memory: A Declaration of Non-Independence

A new study shows that the 'fast' component of motor adaptation is distinct from its 'slow' counterpart and shares critical resources with declarative memory.

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Despite having to perform under a wide range of conditions that alter the relationship between motor commands and their consequences, humans have a dexterity that even the most sophisticated robotic devices are unable to match. For example, we can manipulate a variety of objects, even though grasping an object can dramatically alter the mapping between arm motor commands and arm motion. This ability is, in large part, the result of adaptive systems that are able to monitor and learn from sensory prediction errors [1,2]. Numerous studies have assessed human motor learning by applying novel and unusual loads to the hand via a vertical handle attached to a robotic interface during horizontal plane reaching movements (Figure 1A). Many of these studies have