to overexpress an active form of Drac1. Thus, activated Drac1 is able to direct the necessary cytoskeletal organization that is otherwise lacking in the rhodopsin deficient flies (*4*). Given these observations, the authors propose that Drac1 links rhodopsin to assembly of the RTW and hence to the development of photoreceptor cells. It will be intriguing to determine whether it is the rhodopsin present in the rhabdomere or the small amount of rhodopsin located in the RTW (presumably en route to the rhabdomere) that is directing Drac1 activity.

Small GTPases, such as Rho, Rac, and Cdc42, are pivotal in a variety of cytoskeletal-dependent processes, including cell shape changes during embryonic development, the directed movement of the growth cone in developing neurons, formation of stress fibers and assembly of focal adhesions in the cell, progression through the cell cycle, transcriptional activation, and signaling during apoptosis. In contrast, the larger heterotrimeric G proteins typically transduce more specialized neural and endocrine signals such as those produced in response to light, odor and taste molecules, hormones, neurotransmitters, and peptides (*3, 5, 6, 12–14*). There is increasing evidence for cross talk between the various signaling pathways (*13*). Notable examples include odorant receptors that assist in the guidance of axonal projections on the olfactory bulb to generate a precise topographic map (*12*) and G protein regulation of Rho GTPases through a Rho guanine nucleotide exchange factor (*15, 16*).

The finding that Rho GTPases are involved in the organization of the actin cytoskeleton in photoreceptor cells may shed light on some forms of the inherited neurodegenerative blinding disorder retinitis pigmentosa (RP) (*17*). This devastating group of genetic diseases is characterized by loss of rod photoreceptor cell function, often leading to a progressive decrease in peripheral vision and eventual blindness. About 30% of cases of autosomal dominant RP are caused by mutations in rhodopsin; thus far, 23 additional genetic loci have been identified in RP patients (*7–9*).

The actin cytoskeleton is essential for the correct development of outer segment disks in mammalian rod cells (*18*). Mutations in the cytoskeletal molecule myosin VIIA have been identified in patients with a form of RP called Usher syndrome type 1B (*19*). Human rhodopsin carries the Asn-Pro-X-X-Tyr motif implying that it, too, may interact with Rho GTPases (*11*). So, as Chang and Ready point out, there are several striking parallels between development of the retina in humans and fruit flies, including the conservation of molecules that regulate the actin cytoskeleton. These parallels imply that human rhodopsin may also regulate the photoreceptor actin cytoskeleton and that defects in this process could underlie some forms of RP (*4*).

The Chang and Ready findings demonstrate the startling likelihood that rhodopsin has another job besides its day (or night) job. This versatile photopigment is not only a phototransducing receptor, it also directs the actin cytoskeleton to orchestrate the formation of the elegant architecture of the photoreceptor cell.

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PERSPECTIVES: COMPUTING

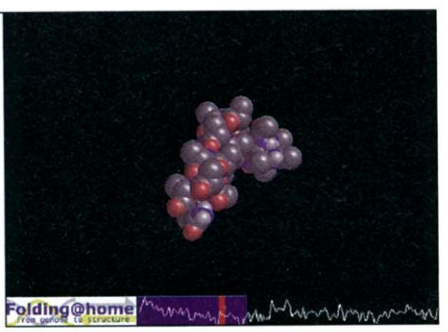
Screen Savers of the World Unite!

Michael Shirts and Vijay S. Pande

Recently, a new computing paradigm has emerged: a worldwide distributed computing environment consisting of thousands or even millions of heterogeneous processors, frequently volunteered by private citizens across the globe (*1*). This large number of processors dwarfs even the largest modern supercomputers. In addition to the scientific possibilities suggested by such enormous computing resources, the involvement of hundreds of thousands of nonscientists in research opens the door to new means of science education and outreach, in which the public becomes an active participant.

A handful of projects have already demonstrated how such large-scale distributed computing power can be utilized. For example, SETI@home has totaled over 400,000 years of single-processor CPU time in about 3 years in its search for alien life (*2*). Similarly, distributed.net has used the power of this huge computational resource for the brute-force cracking of DES-56 cryptography codes.

Virtually any other computationally intensive project could be aided by distributed computing, from the simulation of nuclear reactions or star clusters to atomic-scale modeling in material science. Perhaps the most exciting possibility, however, is in the biological realm. In the last few years, the huge amount of raw scientific data generated by molecular biology, structural biology, and genomics has outstripped the analytical capabilities of modern computers. Novel methods, algorithms, and computational resources are needed to process this wealth of raw information. For example, we need to compute the structure, thermodynamics, dynamics, and folding of protein molecules, the binding ability of drugs, and the causal events in biochemical pathways. Many of the newest distributed applications have thus focused on biological systems.



Merging research and education. The Folding@home screen saver shows a graphical representation of the protein and its potential energy as it is folding, making the research more visually accessible to the public contributing to the project.

Both SETI@home and distributed.net tackle so-called "embarrassingly parallel" problems, in which the desired calculation can easily be divided between many computers. For example, SETI@home looks for alien life by Fourier-transforming radio telescope data from different parts of the sky. These chunks can easily be assigned to different computers to be processed. However, not all problems are so easily broken down into independent parts ("parallelized"). Just as having 1000 assistants

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does not necessarily mean that one's work will be done 1000 times faster, the great challenge for distributed computing is the development of novel algorithms that allow calculations previously deemed unparallelizable to be performed on hundreds or thousands of computers with very little communication between the processors.

Even if an algorithm can be parallelized, it may still be poorly suited for distributed computing. Consider, for example, simulations of the dynamics of biomolecules at the atomic level. Such simulations are traditionally limited to the nanosecond time scale. Duan and Kollman have demonstrated that traditional parallel molecular dynamics simulations can break the microsecond barrier (*3*), provided that one uses many tightly connected processors running on an expensive supercomputer for many months. This style of calculation requires, however, that the processors frequently communicate information and is thus poorly suited for worldwide distributed computing, where computer communication is thousands of times slower than the interprocessor communication in today's supercomputers.

Recently, an algorithm has been developed that helps address the problems of both parallelization and communication by allowing loosely connected multiple processors to be used for molecular dynamics (*4*, *5*). The Folding@home project (*5*) has shown that this algorithm can reach orders of magnitude longer time scales than have previously been achieved when used for distributed atomistic biomolecular dynamics simulations. The design of similar algorithms for parallelization will likely play a major role in adapting other problems in computational biophysics (such as the design of more effective drugs) and other fields for distributed computing.

The ability to engage users to run the simulation software is central to the success of worldwide distributed computing. First, the user must have some interest in volunteering his or her computer. SETI@home and distributed.net have had great success in generating excitement about their projects. Biological and biomedical applications may have an even greater potential for generating public interest. Some commercial ventures even plan to expand this resource by paying users for their excess CPU time (*6*).

Second, distributed systems must not interfere with the user's personal use. This is most commonly (and perhaps most elegantly) done using screen savers (see the figure). The user downloads and installs the screen saver from the project's Web site. The vast majority of idle computer cycles will then be used for the project, without interfering with the user's work. To perform a calculation, the screen saver downloads some task from the project's server, performs the required calculation, returns the results to the server, and then repeats the cycle. To address networking and security issues, many projects use the same techniques as Web browsers and Web servers, because these methods of distributing data from client to server are well developed and secure. The project's server(s) must be carefully designed to handle the enormous number of clients in distributed computing.

There are at least 300 million personal computers on the Internet (*7*). Up to 80 to 90% of their CPU power is wasted. If each distributed computing project involved 500,000 active users, as SETI@home currently claims, and half of all PCs now connected to the Internet participated, there would be sufficient capacity for 300 SETI-sized projects worldwide.

The world's supply of CPU time is very large, growing rapidly, and essentially untapped. Used to analyze the data generated by recent genomic and proteomic efforts or conduct other important calculations, distributed computing could raise biological and other scientific computation to fundamentally new predictive levels.

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PERSPECTIVES: DEVELOPMENT

Hear, Hear, for the Inner Ear

Anthony Graham

The inner ear, a complex sensory organ that enables sound to be heard and balance to be maintained, has long been a favorite study tool of biologists. Composed of the fluid-filled cochlea (which transforms sound waves into nerve impulses) and the semicircular canals (which provide a sense of orientation and balance), the inner ear is formed from a focal thickening of the embryonic ectoderm called the otic placode (see the figure). The otic placode can be readily identified and isolated during early embryogenesis and its morphogenesis into the inner ear can be easily followed because it generates an elaborately patterned, discernible structure. Indeed, in the premolecular era, tissue manipulation experiments that induced inner ear formation in amphibian embryos, were at the forefront of investigations into key developmental processes. Such experiments identified the mesoderm and the neural tube as the source of inductive signals directing otic development. This process, with its multiple serial cues, was thought to be generally indicative of the inductive processes that underlie the formation of other organs of the vertebrate body (*1*). Beyond the identification of the inducing tissues, further advances in our understanding of otic placode induction have been slow, particularly with regard to the molecules that drive this process. On page 1965 of this issue, Ladher *et al.* now report that two signaling molecules, FGF-19 and Wnt-8c, work together to initiate inner ear development in chick embryos (*2*). Their work not only elucidates two of the key molecules directing the induction of the otic placode, but also clarifies the sequence of events underlying this phenomenon.

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Ladher and co-workers identified and characterized a new chick member of the fibroblast growth factor family of signaling molecules, FGF-19, which they found to have a particularly interesting expression pattern in the early embryo. In the developing chick head at about the one-somite stage of embryonic development, the *FGF-19* gene is first expressed in the mesoderm underlying the neural plate in the hindbrain. As the neural plate folds up, the ectoderm that lies alongside it also comes into contact with the *FGF-19*–expressing mesoderm, and it is in this region of ectoderm that the otic placode forms. Subsequently, the expression of *FGF-19* is lost from the mesoderm, although it is