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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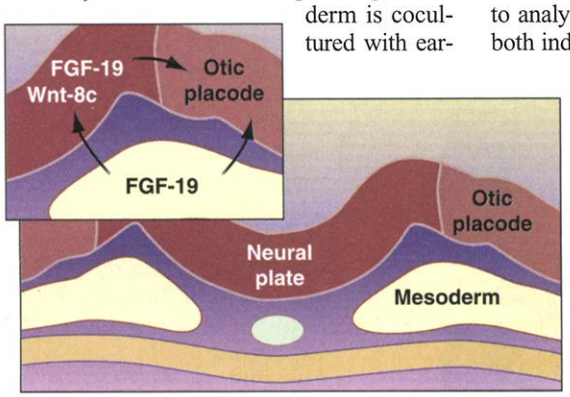
Ladher and co-workers identified and characterized a new chick member of the fibroblast growth factor family of signaling molecules, FGF-19, which they found to have a particularly interesting expression pattern in the early embryo. In the developing chick head at about the one-somite stage of embryonic 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

transiently expressed in the now-closed neural tube. An important facet of the expression pattern of *FGF-19* is that, as the authors demonstrate, it colocalizes with otic-inducing activity. If the *FGF-19*–expressing mesoderm is cocultured with early embryonic ectoderm in the laboratory, then the expression of a broad range of otic markers is induced in this tissue, including the formation of auditory hair cells, which mark the terminal stages of inner ear differentiation. By contrast, other mesoderm that did not express *FGF-19* could not induce otic markers in this ectoderm. Similarly, otic markers could be induced in early ectoderm when it was cocultured with *FGF-19*–expressing neuroectoderm and its adjacent mesoderm. Although *FGF-19* expression colocalizes with otic inducing activity, Ladher *et al.* found that the FGF-19 protein alone could not promote the expression of otic markers in either nonotic ectoderm or presumptive otic ectoderm. This protein could, however, elicit an otic response in these tissues if neural tissue was included. Thus, FGF-19 itself can only direct otic development provided another neural-derived signal is also present.



Breaking the silence. A transverse section through a chick embryo showing the relative positions of the mesoderm, neural plate, and presumptive otic placode, which develops into the inner ear. Also shown are the signaling molecules that induce formation of the otic placode. First, the mesoderm produces FGF-19, which then signals to the overlying neural plate and ectoderm. The neural tissue then produces Wnt-8c, which acts in concert with FGF-19 to induce the adjacent ectoderm to become the otic placode.

Taking their cue from studies in the frog *Xenopus* showing that FGFs often work together with another group of signaling molecules (the Wnts), Ladher and colleagues investigated whether Wnt-8c was the second otic inducer. This signaling molecule was already known to be expressed in the ar a of the neural tube closest to the region (.) where the otic placode forms. On close scrutiny, they found that *Wnt-8c* was exp ssed in the neural tissue overlying the *FGF-19*–expressing mesoderm, and that at later stages Wnt-8c and FGF-19 were located in the same area of neural tissue. These authors also showed that FGF-19 could induce the expression of *Wnt-8c* in early embryonic ectoderm in culture. Thus, Wnt-8c is a prime candidate for the neural signal working with FGF-19 to induce the otic placode. So, they proceeded to analyze the abilities of these two factors, both independently and together, to promote otic development. As before, they found that FGF-19 alone could not promote otic development, but that Wnt-8c, on its own, induced the expression of one otic marker, *FGF-3*. However, Wnt-8c was unable to direct the robust expression of any other otic marker. In contrast, if ectoderm was treated with both FGF-19 and Wnt-8c, there was strong expression of a gamut of otic markers and the ectoderm began to acquire the morphology of the otic placode. It is noteworthy that the otic induction driven by the combined action of FGF-19 and Wnt-8c is direct, and does not require the prior induction of neural tissue. However, because these two factors did not elicit the formation of cochlear inner hair cells in the cultured ectodermal explants, other signals may be required to promote full inner ear development.

Although previous investigations of otic induction identified the mesoderm and the neural tissue as inducers, the new work provides us with a clearer picture of how the inducer tissues initiate inner ear development (see the figure). This process begins with the mesoderm: Through production of FGF-19, the mesoderm signals to the overlying neural plate inducing the expression of *Wnt-8c* in this tissue, and to the ectoderm, which then gives rise to the otic placode. Subsequently, Wnt-8c and FGF-19, emanating from the hindbrain, act together on this ectoderm to induce the otic placode and thus to initiate inner ear development.

The fact that FGF-19 can induce expression of *Wnt-8c* in presumptive neuroectoderm also suggests that FGF-19 plays a part in patterning the neural tube. This is in keeping with previous work on neural patterning that implicated an undefined FGF activity in regionalizing the neural plate into midbrain and hindbrain territories (*4*). Hence, it is likely that FGF-19 is acting specifically to pattern the central hindbrain territory alongside which the otic placode forms. It is within this territory that the auditory nuclei of the brainstem arise (*5*). Thus, FGF-19 could be pivotal in ensuring the coordinated development of both the inner ear and its neuronal transducing apparatus.

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PERSPECTIVES: PALEOCLIMATE

Glacial Climate Instability

Laurent Labeyrie

Throughout the last glacial period, rapid climatic changes left their mark in the glacial ice in Greenland. During each of these Dansgaard-Oeschger (D-O) events, named in honor of the initial leaders in their study, an initial warming of 10°C or more within a few decades was followed by a gradual cooling over about 1000 years. Twenty-one such events occurred between 75,000 and 15,000 years ago (75 to 15 ka). Because the events were so similar over tens of thousands of years, they are ideal targets for testing our understanding of climate change and developing climatic change models. Important steps toward understanding D-O events, particularly regarding the role of the low latitudes, are now reported by Hughen *et al.* (*1*) on page 1951 and Peterson *et al.* (*2*) on page 1947 of this issue.

Preliminary low-resolution studies (with a resolution of ~500 years) of North Atlantic sediment cores have indicated that D-O events are probably driven by oscillations of the polar front and associated changes in the convective thermohaline ocean circulation. The slow cooling may be caused by input of melt water from continental ice sheets into the surface waters of the high-latitude Atlantic Ocean, interrupting deep water formation. At the end of the melt water event, the thermohaline circulation would restart rapidly, at the same time as a northward shift of the polar front and warm conditions over Greenland (*3*–*6*). Low latitudes may also be affected but are not necessarily in phase with the high latitudes (*7*).

To fully understand the mechanism that drives D-O events requires well-dated ocean paleoclimatic records with much higher resolution (a few decades to a century). Such

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