template-directed manner. Then, through further evolution, the researcher attempts to coax the ligase to accept NTPs as substrates and to add multiple NTPs in succession.

Bartel and colleagues (*7*) have used one such in vitro evolved ligase, the class I ligase, and evolved it further to polymerize as many as 14 successive NTPs with high fidelity. Despite valiant efforts, however, it appears unlikely that this particular polymerase enzyme will ever be evolved to the point that it can copy RNA molecules as long as itself (~200 nucleotides). Nonetheless, it is likely that scientists will eventually apply a similar approach to a different set of RNA molecules to achieve more extensive polymerization and ultimately complete replication.

The class I ligase is the Ferrari of in vitro evolved ligase enzymes. Under optimal reaction conditions, it has a catalytic rate of up to 360 per minute. Like a Ferrari, however, it has very narrow tolerances and has been tweaked in imaginative ways to extract maximum performance. Three other RNA enzymes, the L1 ligase (*8*), R3C ligase (*9*), and DSL ligase (*10*), have substantial structural and biochemical similarity and may be regarded as three different versions of the family sedan. All catalyze the template-directed joining of an oligonucleotide 3′-hydroxyl and oligonucleotide 5′-triphosphate, but at a rate of only about 0.3 per minute. All have a simple three-helix junction architecture, in which the nucleotides that are essential for catalysis surround the junction and the site of ligation is offset from the junction by several base pairs. It is the L1 ligase that has been crystallized by Robertson and Scott, who solved its structure at a resolution of 2.6 Å (*5*).

Robertson and Scott crystallized the product of an autoligation reaction, in which the L1 ligase was configured to join its own 3′-hydroxyl to its own 5′-triphosphate (see the figure). Two different forms of the circular product were present in the asymmetric unit of the crystal: one in an "undocked" conformation, with the three-helix junction splayed out and no contact between the catalytically essential nucleotides and the ligation site, and the other in a "docked" conformation, with many of these essential nucleotides held near the ligation site. The docked conformation (which can reasonably be interpreted as the active form of the enzyme) is stabilized by tertiary contacts involving a guanine-adenine-uracil base triple and by ionic interactions between a single Mg^{2+} ion and three phosphate groups.

The crystal structure reflects the product of ligation rather than the reactants. One must therefore be cautious in drawing conclusions about the reaction mechanism. Rather than a free 3′-hydroxyl and a reactive 5′-triphosphate bearing four negative charges, the 3′,5′-phosphodiester is already in place. Nonetheless, some inferences regarding the reaction mechanism may be drawn from the structure, which reveals a network of hydrogen bonding and ionic interactions centered about the ribose sugar that bears the attacking 3′-hydroxyl. The adjacent 2′-hydroxyl appears to be kept out of the fray by its interaction with a tightly bound water molecule. If this were not the case, the reaction might instead result in formation of an unnatural 2′,5′-phosphodiester, rather than the 3′,5′-phosphodiester of RNA.

The L1 ligase is not a polymerase, let alone a replicase, but it performs the same chemistry that would be expected for an RNA molecule with RNA replicase properties. Its crystal structure gives us a view toward what may have been the first enzyme of biology, or at least the central enzyme of the RNA world. In the years ahead, we can expect to see the structure of other ligases, and eventually of polymerase and replicase RNA enzymes. These laboratory mimics of our deepest evolutionary ancestors will not appear to be alien objects. Like the L1 ligase, they will have comfortingly familiar structural features and an active site built of the usual stuff of biochemistry: hydrogen bonding, ionic, and hydrophobic interactions that have been crafted by processes of Darwinian evolution. Unlike the ancient RNA replicase enzymes that likely became extinct more than 3.5 billion years ago, these modern recreations will be available for detailed investigation.

References

1. C. Woese, *The Genetic Code: The Molecular Basis for Genetic Expression* (Harper & Row, New York, 1967), pp. 179–195.
2. F. H. C. Crick, *J. Mol. Biol.* **38**, 367 (1968).
3. L. E. Orgel, *J. Mol. Biol.* **38**, 381 (1968).
4. W. Gilbert, *Nature* **319**, 618 (1986).
5. M. P. Robertson, W. G. Scott, *Science* **315**, 1549 (2007).
6. D. P. Bartel, J. W. Szostak, *Science* **261**, 1411 (1993).
7. W. K. Johnston, P. J. Unrau, M. S. Lawrence, M. E. Glasner, D. P. Bartel, *Science* **292**, 1319 (2001).
8. M. P. Robertson, A. D. Ellington, *Nature Biotechnol.* **17**, 62 (1999).
9. J. Rogers, G. F. Joyce, *RNA* **7**, 395 (2001).
10. Y. Ikawa, K. Tsuda, S. Matsumura, T. Inoue, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 13750 (2004).

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CLIMATE CHANGE

Rethinking Ice Sheet Time Scales

Satellite data show that ice sheets can change much faster than commonly appreciated, with potentially worrying implications for their stability.

Martin Truffer and Mark Fahnestock

According to glaciology textbooks, glaciers respond to climate change on time scales that vary from a decade or more for nonpolar glaciers to millennia for polar ice sheets. These numbers have lured the scientific community into thinking that while small glaciers undergo rapid changes, the big ice sheets adjust at a leisurely pace.

Lately, the ice sheets have been teaching us differently. Recent reports documented rapidly increasing discharge of Greenland's outlet glaciers (*1*–*3*). These glaciers are responsible for most of the ice sheet's mass loss, acting as "bathtub drains" to the vast interior ice mass (see the figure). On page 1559 of this issue, Howat *et al.* (*4*) report that ice discharge can also decrease at a high rate: Two of the major outlet glaciers in southeastern Greenland—Helheim and Kangerdlugssuaq—doubled their discharge of ice into the ocean within 1 year in 2004. Two years later, the discharge quickly dropped back close to its former rate.

Near the other pole, Fricker *et al.* [page 1544 (*5*)] report changes in ice surface elevation from data recorded by NASA's Ice, Cloud, and land Elevation Satellite (ICESat). These observations are interpreted as a sign of moving subglacial water under a large ice stream. At one ice stream location, the surface drop can be explained by the drainage of 2 km^3 of subglacial water. Elsewhere, the ice surface rose sufficiently to account for the storage of this water. Earlier studies had shown the existence of such elevation changes (*6*, *7*), but Fricker *et al.*'s analysis reveals a surprisingly active system of subglacial hydrology in a part of the world where little or no surface melting occurs.

Today, we can monitor ice sheets with unprecedented spatial and temporal resolu-

M. Truffer is at the Geophysical Institute, University of Alaska, Fairbanks, AK 99775, USA. E-mail: truffer@gi.alaska.edu M. Fahnestock is at the Institute for the Study of Earth, Oceans and Space, University of New Hampshire, Durham, NH 03824, USA.

tion, thanks to an array of Earth-observing satellites and many ground-based studies. The resulting news has consistently had an element of surprise with regard to time scales. Invariably, processes are happening more rapidly than previously thought possible (*2*–*4*, *8*, *9*). The discovery of moving water pockets underneath the West Antarctic ice streams by Fricker *et al.* and the rapidly oscillating fluxes at two of Greenland's outlet glaciers reported by Howat *et al.* further illustrate how rapidly ice sheets can change.

These observations of rapid change (*1*–*9*) highlight shortcomings in our understanding of relevant physical processes, such as the connection of ice to surrounding sediment, rock, and water. These boundary conditions help to regulate outlet glacier and ice shelf systems. In outlet glaciers, the ice/bed interaction is subject to a substantial flux of water. As recently highlighted by the Intergovernmental Panel on Climate Change (*10*), the largest uncertainty in sea-level projections lies in the ability to capture changes in such outlet systems in numerical models [see also the accompanying Perspective by Vaughan and Arthern (*11*)]. The modeling challenge is one of time scales: Water that moves rapidly under Antarctic ice streams and outlet glaciers that fluctuate on an annual basis do not mesh easily with the millennial-scale variations in ice mass, snow fall, and internal temperature required for modeling the thick interiors of large ice sheets.

It remains uncertain how important these rapid changes are for the future stability of the ice sheets. However, the closer we look, the more ice sheet outlet systems appear to behave like much smaller glacier systems in nonpolar regions.

The comparison is not reassuring. The closest analogs of Greenland's outlet glaciers are large tidewater glaciers, which also end in the ocean but are not fed by large ice sheets. Perhaps the best studied of these is Columbia Glacier, which has retreated ~15 km in the past 20 years and thinned by ~400 m near the current terminus (*12*). Columbia's retreat rates and ice discharge have been highly variable, with ice discharge at times reduced to pre-retreat rates, only to pick up again later. In that context, last year's reduction of ice flux at Helheim and Kangerdlugssuaq Glaciers (*1*) does not mean that they have stabilized. The question remains whether changes in the past 5 years have left the system as a whole more vulnerable.

A drain for Greenland's ice sheet. This photo of the calving front of Jakobshavns Isbrae, the major outlet glacier in West Greenland, was taken on 29 August 2006. At the lower right, broken-off pieces of ice are floating in the ocean. The ice cliff is >100 m high. The helicopter is a Sikorski S61, which can carry 12 passengers. Jakobshavns Isbrae currently dumps an estimated 46 km^3 of ice into the ocean every year (*4*).

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One difference between outlet and tidewater glaciers is the size of the ice reservoir that feeds them. It is an open question how much fluctuating ice discharge at outlets affects the interior ice. On the smaller scale, however, tidewater glacier retreat can draw down an entire ice field. In Glacier Bay, Alaska, an entire ice field disappeared within ~200 years. Some of this ice was more than 1500 m thick, and a total volume of more than 3000 km^3 was lost (*13*). Initial accelerated discharge depleted the ice reservoir, thinning it substantially. A positive feedback was established, because the ice surface was at lower elevation and thus exposed to higher temperatures and increased melting. The volume of the vanished ice at Glacier Bay is almost three orders of magnitude smaller than that of the Greenland Ice Sheet; nevertheless, it does demonstrate that relatively rapid collapse helped by outlet glacier dynamics is possible on the scale of an ice field.

Fricker *et al.* show that even the Antarctic Ice Sheet—where, in contrast to Greenland, only negligible surface melting occurs today—experiences rapid changes in basal conditions through transfer of subglacial water. The amount of subglacial water, its pressure, and its connectivity all influence basal slipperiness and hence ice discharge. The mapping of subglacial plumbing from space reported by Fricker *et al.* is a major breakthrough that should help to improve our ability to model these systems.

Many questions remain. In Greenland, as well as in Antarctica, large changes are always initiated at the ice-ocean interface. Furthermore, recent changes in Greenland have occurred while the climate has warmed. Are these changes caused by a warming ocean or by increased water runoff from the ice? How do quick changes in ice sheet boundary conditions affect its long-term behavior?

Substantial progress in understanding can only come from interdisciplinary studies exploring the effects of a changing ocean on outlet glaciers, of increased runoff of glacial freshwater on ocean and fjord circulation, and of meltwater on ice flow. Greenland differs from Antarctica in that it has a substantial zone where ice melts, and meltwater runs off and presumably reaches the base. Understanding the relative roles of the processes leading to flow acceleration will help to constrain potential differences between the two ice sheet's reactions to future climate change. As sci-

entists grapple with the spectrum of time scales that drive outlet glaciers in a changing climate, observations such as those documented in this issue will help to lead the way.

References and Notes

1. I. R. Joughin, W. Abdalati, M. Fahnestock, *Nature* **432**, 608 (2004).
2. A. Luckman, T. Murray, *Geophys. Res. Lett.* **32**, L08501 (2005).
3. E. Rignot, P. Kanagaratnam, *Science* **311**, 986 (2006).
4. I. M. Howat. I. Joughin, T. A. Scambos, *Science* **315**, 1559 (2007); published online 8 February 2007 (10.1126/science.1138478).
5. H. A. Fricker, T. Scambos, R. Bindschadler, L. Padman, *Science* **315**, 1544 (2007); published online 15 February 2007 (10.1126/science.1136897).
6. L. Gray *et al.*, *Geophys. Res. Lett.* **32**, L03501 (2005).
7. D. J. Wingham, M. J. Siegert, A. Shepherd, A. S. Muir, *Nature* **440**, 1033 (2006).
8. R. A. Bindschadler *et al.*, *Science* **301**, 1087 (2003).
9. A. M. Smith *et al.*, *Geology* **35**, 127 (2007).
10. The IPCC Working Group I Fourth Assessment Report Summary for Policymakers was released on 2 February 2007 (www.ipcc.ch); the full Working Group I report will be released in May 2007.
11. D. G. Vaughan, R. Arthern, *Science* **315**, 1503 (2007).
12. S. O'Neel, T. W. Pfeffer, R. Krimmel, M. Meier, *J. Geophys. Res.* **110**, F03012 (2005).
13. C. F. Larsen *et al.*, *Earth Planet. Sci. Lett.* **237**, 548 (2005).

14. We acknowledge NSF grant ARC 0531075.

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DEVELOPMENT

Built to Run, Not Fail

Networks of genes that control organism development are organized in a basic architecture that is conserved across processes and species.

Paola Oliveri and Eric H. Davidson

On first encounter, gene regulatory networks for development often seem so complicated as to defy intuitive understanding. But the overall maze of gene interactions that they represent is actually composed of subcircuits that perform separate functions. The subcircuits are often of elegant and sometimes counterintuitive design, even more so, the ways they are combined in the overall network. As the underlying subcircuit structure is clarified, we see that gene regulatory networks in fact provide a direct and simply organized bridge from the phenomena of development to the detailed genomic programs that encode it. Among the most fascinating aspects of gene regulatory networks are their design principles, for these are often interestingly different from what would seem the "simplest" solution. Gene regulatory networks for development are the direct product of evolution, and the character of their design both illuminates evolution and is illuminated by it.

Each of the specific biological functions which together make up a developmental process is programmed by a specific subcircuit of the network. In other words, large gene regulatory networks have a modular structure: They are composed of different subcircuits that work together to accomplish whole "pieces" of development, such as specification of dorsoventral pattern in the fly embryo or of the endomesoderm territories of the sea urchin embryo. Overall, such gene regulatory networks involve scores of genes [>50 in these cases (*1*)] organized into many subcircuits, where a single subcircuit controls a specific developmental task. These tasks include specifying regulatory states of a group of cells (i.e., determining which regulatory genes they will express); mounting molecular signals that induce new regulatory states in recipient cells; coordinating the expression of genes that control cell differentiation; stabilizing newly established regulatory states; defining tissues and setting their boundaries; and interpreting prior regulatory instructions. There is a plethora of regulatory jobs different from one another—such as the development of embryos, or of stem cells, or of adult body parts—that all require different kinds of subcircuits. The subcircuit components of gene regulatory networks have evolved independently of one another, and at different rates (*2*), and are assembled in different contexts in related organisms. Both in their functional organization and in the separate evolutionary histories of their subcircuits, gene regulatory networks are modular in construction.

The individual subcircuits each consist of a few regulatory genes, including their genomic cis-regulatory information processors, which respond in a combinatorial and conditional manner to the transcription factors encoded by other genes of the same module. In considering structure-function causality in gene regulatory network subcircuits, the architecture of the module tells it all. The architecture is the design of the causal linkages between genes of the subcircuit. This is a hard-wired feature because it is constructed by the inherited cis-regulatory control sequences of these genes. The biological function depends on the architecture. For example, positive cross-regulatory interactions among a set of genes that encode transcription factors can stabilize the particular regulatory state generated by these genes. As another example, it is the particular set of genes regulated by a given gene that is turned on in response to an inductive signal that determines what the developmental effect of the signal will be.

There are two essential consequences of this concept of a modular network architecture and subcircuit design. First, subcircuit architectures are as varied as the biological jobs they do. Thus, although subcircuits are indeed the modular functional components of developmental gene regulatory networks, they are to be distinguished from simpler "building blocks" or "motifs" that are used for many diverse developmental functions (e.g., feedforward or feedback elements, per se). For instance, feedforward motifs are to be found in every conceivable context in diverse gene regulatory networks (*3*), whereas the individually designed subcircuits here considered are specific to the type of biological job they do. Second, subcircuit architectures are built from diverse classes of transcription factor, and by and large, a given type of factor is not dedicated to any given type of subcircuit. In terms of logic outputs, circuits that transduce signals and distribute their outputs may operate very similarly, whatever the nature of the signaling system or the identity of the immediate early response factor. The same is true of cross-regulatory subcircuits. It is the genomic architecture of the subcircuit, and not the nature of the factors the genes encode or the families they belong to, that uniquely indicates subcircuit function [multiple examples of subcircuits from diverse developmental systems can be found in (*3*)].

As we have come to understand developmental gene regulatory networks, there arises an impression of "overlayered" circuit design—or more precisely, deployment of multiple subcircuits—that in different ways support the same end result. In development, the major regulatory task is to specify spatial domains of gene expression. Typically, multi-

The authors are in the Division of Biology, California Institute of Technology, Pasadena, CA 91125, USA. E-mail: davidson@caltech.edu; poliveri@caltech.edu