fungal pathogens also depends on the activity of NF-κB homologs. Tulin and Spradling find that this response is defective in PARP mutant larvae, which are exceptionally sensitive to bacterial infection.

How is PARP involved in the induction of gene expression? Tulin and Spradling envision that inactive PARP is recruited, presumably by certain transcription factors, to target genes where it becomes activated. PARP then adds long ADP-ribose tails to the histone proteins of nucleosomes around which the DNA is wrapped (see the figure). Nucleosomes containing poly-ADP-ribosylated histones are unable to remain tightly packed, resulting in "loosening" or decondensation of the chromatin. RNA polymerase is now able to transcribe the target genes without hindrance. In vitro experiments suggest that transcription is initially facilitated by PARP, but as soon as transcription factors dissociate from the DNA, they too become inactivated through poly-ADP-ribosylation, thus preventing repeated cycles of transcription (*11*). In this way, PARP

ensures a strong but transient transcriptional response to a heat shock or ecdysone stimulus. Ultimately, PARP poly-ADP-ribosylates itself and dissociates from the DNA, its poly-ADP tails later being removed by poly(ADP-ribose) glycohydrolase. The mechanism of PARP action seems adapted to facilitate sudden bursts of transcriptional activity in response to transient environmental signals. However, increasing evidence suggests that PARP activity may be involved in a variety of other chromatin transactions such as telomere elongation, DNA surveillance and repair, apoptosis, DNA replication, the activation of repressed chromatin, and possibly genomic remodeling during development and differentiation.

Many questions remain to be answered. Where is PARP parked when it is inactive? Which molecules recruit PARP to target genes and activate this unusual polymerase? What controls the glycohydrolase activity that removes poly-ADP tails from target proteins and from PARP itself? In the case of DNA damage, single-strand

nicks in the DNA are the recruiting agents for PARP, and binding of PARP to the damaged DNA induces catalytic activity. Perhaps DNA nicks are also involved in recruiting PARP to target genes. The work of Tulin and Spradling will undoubtedly stimulate renewed efforts to understand this remarkable enzyme, which is an unusual addition to the arsenal of molecules that modify chromatin and control gene expression.

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GEOPHYSICS

An Ensemble View of Earth's Inner Core

Malcolm Sambridge

Seismic studies show that Earth's inner core is solid. On page 552 of this issue, Beghein and Trampert (*1*) suggest that the structure of this inner core is more complex than previously thought. Their results indicate changes in the behavior of seismic properties in the inner core. The approach used by the authors also shows much promise in resolving other data-inference problems in geophysics.

More than 30 years ago, seismologists first realized that they could build models of Earth's interior by randomly generating large numbers of alternate models and retaining only those that satisfied observations to an acceptable level (*2*). Although initially appealing, this "Monte Carlo inversion" rather fell out of favor when it became clear that uniform random sampling is inefficient for large numbers of unknowns. Earth models found in this way were usually few in number, rather exotic in character, and often bore little resemblance to each other. It was therefore difficult to draw conclusions about which one (if any) resembled the real Earth (*3*).

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Attention turned to linearized inversion techniques, which dealt with the "nonuniqueness" problem by deliberately restricting the allowable character of the
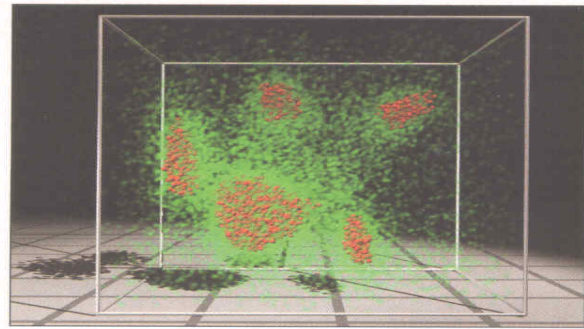
Neighbourhood sampling in five dimensions. Only three dimensions are shown. Transparent green spheres correspond to Earth models with poor fit to data. Solid red spheres represent those with acceptable data fit. Red "islands" correspond to multiple populations of solutions. Explorative direct search methods must be used to identify all potential solutions. This process has yielded new models for Earth's inner core.

Earth models (a procedure known as regularization). This approach has been widely used in geophysics, with numerical damping of linear systems of equations the most common way of imposing regularization.

The seismic study of Earth's solid inner core reported by Beghein and Trampert (*1*) suggests that the tide may have turned yet again, with direct search techniques providing new insights where linearized procedures fail. In truth, such direct search inversion techniques never really disappeared from the geophysicist's toolbag. Instead, they became more efficient with the advent of simulated annealing in the 1980s and genetic algorithms in the 1990s. Both of these methods are widely used to solve global optimization problems in many areas of the natural sciences (*4*).

Beghein and Trampert (*1*) use a new class of direct search technique, known as "neighbourhood sampling" (*5*), to constrain inner core anisotropy from seismic observations of normal modes (see the figure). Many regions of parameter space are explored simultaneously by randomly searching in the neighborhoods of earlier models, with preference given to those that fit the data relatively better.

This type of multiple sampling approach is known as ensemble inference. Rather than iteratively improving a single "best-fit" set of unknowns, as in linearized inversion, ensemble inference allows conclusions to be drawn from a population of alternate solutions. Attention is thus not confined to just one outcome. The downside is that the whole process can become computationally expensive.

Beghein and Trampert (1) show that the character of the inner core structure obtained from linearized inversions of normal mode data depends strongly on the level of numerical damping. The major effect is on the depth variation of seismic anisotropy. It is already known that the inner core is anisotropic, but the amplitude and depth dependence of the anisotropy remain controversial. (Anisotropy means that the travel times of seismic waves depend on the direction of propagation. Inner core anisotropy is seen in differences in travel times between seismic core phases aligned with Earth's rotation axis and those aligned with its equatorial plane; the former are up to 3 s faster.) Beghein and Trampert's results suggest that the damping imposed in previous linearized studies may have led to bias in the inferred structures.

With ensemble inference, a new picture emerges. Because ensemble inference does not require damping, many more potential solutions could be explored. The search turned up some unexpected results. While searching for inner core structures consistent with normal mode data, the authors found a whole family of models that also fit differential travel time data at large epicentral distances (150° to 180°) with sampling well into the inner core. Previous models derived from normal mode data were unable to explain the travel time data. The reason seems to be that the more explorative search technique yields models in which anisotropy extends much deeper into the inner core (a feature that was suppressed by damping in previous linearized studies).

The new results have implications for the nature of the stable phase of iron in Earth's solid inner core, which is still highly controversial. Recent research—both experimental and theoretical—has indicated that the hexagonal close-packed (hcp) phase of iron can exist at the extreme conditions of Earth's core. But Beghein and Trampert's preferred models cannot be explained by any relatively simple texturing of an inner core composed solely of the favored hcp phase. Although their results are compatible with a progressively tilted hcp phase in the upper half of the inner core, they are not compatible with published mineral physics data in the deepest part of the inner core (radius 0 to 400 km).

This observation will undoubtedly provoke a new flurry of research and discussion in the mineral physics community. New suggestions (6) concerning the possible stabilization of the body-centered cubic phase at very high temperatures and/or by light-element impurities may be relevant. Indeed, it is possible that there is a transition to a different phase of iron in the innermost inner core (radius 300 to 400 km), which might correspond to variations in properties near the center of Earth, as suggested by Ishii and Dziewonski (7).

Another consequence is that our long-standing reliance on linear inversion techniques may need reconsideration. Fully nonlinear inversion is becoming practical for a wide range of inverse problems, with parallel computation now cheaply available through use of "Beowulf" clusters of personal computers (8). Over the next decade, this trend is likely to continue, with new insights being made in many fields.

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NOTA BENE: BIOMEDICINE

Weathering the Big Chill

Platelets are tiny disc-shaped cells devoid of a nucleus that are produced by the bone marrow. At sites of injury, platelets bind to von Willebrand factor (vWF) on the surface of endothelial cells, become activated by thrombin, and interact with plasma fibrin to form clots. For more than 50 years, platelet transfusions have prevented life-threatening blood loss in trauma, surgery, and bone marrow transplant patients. However, unlike red blood cells, which are amenable to cold storage, refrigerated platelets are cleared rapidly from the patient's circulation after transfusion. Unfortunately, the shelf life of platelets at room temperature is only 5 days, resulting in an acute shortage of platelets for transfusion. In a recent issue of Cell, Hoffmeister and colleagues (1) reveal why chilled, transfused platelets disappear rapidly from the circulation and propose a strategy to block this clearance.

The rapid disappearance of chilled, transfused platelets has been attributed to the cold-induced loss of their normal discoid shape, presumably leading to the ensnaring of deformed platelets in capillaries. Not so, say Hoffmeister et al., who show that even preserving the disc shape of chilled mouse platelets with drugs does not prevent their rapid clearance after transfusion into mice. The researchers next demonstrated that clearance of chilled platelets is due to their ingestion (phagocytosis) by liver macrophages called Kupffer cells.

Phagocytosis of platelets depends on their binding to an integrin called CR3 on the Kupffer cell surface. When chilled mouse platelets are transfused into mice lacking CR3, they circulate with the same kinetics as transfused platelets kept at room temperature. Seeking the platelet counter-receptor that interacts with CR3, the researchers first investigated GP1bα, the platelet surface glycoprotein that binds to vWF. They found that enzymatically cleaving the extracellular portion of GP1bα from chilled mouse platelets boosted platelet survival after transfusion. Furthermore, in an in vitro assay, enzyme-treated chilled human platelets were not ingested by macrophages, implying that GP1bα is the platelet counter-receptor for CR3.

Electron microscopy revealed that refrigeration induced the rearrangement of both mouse and human platelet GP1bα from neat, linear rows into clusters. This redistribution of GP1bα did not affect normal platelet behavior, because chilled platelets circulating in CR3-deficient mice were still able to bind to vWF, respond to thrombin and other mediators, and promote clot formation. If cold-induced platelet clearance could be blocked, then platelets could be stored in the cold and their shelf life dramatically extended. At a recent meeting, Hoffmeister and co-workers (2) presented a strategy to attain this goal. By using galactose sugar residues to shield the sugar molecules on GP1bα that bind to CR3, they prevented the clearance of chilled, transfused mouse platelets. Chilled platelets with sugar-modified GP1bα circulated with a normal life-span in transfused mice and fulfilled their normal functions. The Hoffmeister et al. work is a big step toward making platelet refrigeration a reality and alleviating the acute shortage of platelets for transfusion.

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