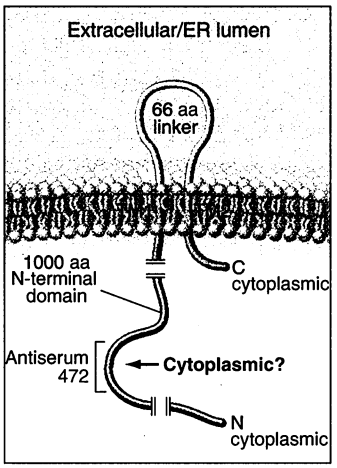
hibitory—which would imply that Nogo-A, -B, and -C should all be inhibitory. In contrast, Schwab and co-workers (*1*) report that the long N-terminal region of Nogo-A is its main inhibitory domain—which would imply that Nogo-B and -C are not inhibitory. Walsh and colleagues (*3*) agree that the isolated N-terminal region is inhibitory (and as potent as MAG) (*2*), and Schwab's group show that an antiserum against a peptide sequence in the N-terminal region (antiserum 472) can block the inhibitory action of myelin extracts (*1*).



Proposed topology of Nogo-A. The 66–amino acid (aa) linker is on the extracellular/lumenal side of the membrane, whereas the extreme N and C termini are cytoplasmic. It remains to be determined whether the entire N-terminal domain, including the region recognized by blocking antiserum 472, is completely cytoplasmic.

What accounts for these apparently divergent results? Does Nogo-A have two distinct inhibitory domains? If so, why does one antibody block both effects? Or do the differences reflect the varied assays used? No doubt these apparent contradictions will be resolved soon.

The precise membrane organization of Nogo-A also affects the interpretation of other experiments. The lumenal/extracellular 66–amino acid linker should be exposed on the surface of oligodendrocytes, but if the long N-terminal region of Nogo-A is cytoplasmic, it would not normally be accessible to extending axons. However, Schwab and colleagues report that the antibody to this domain facilitates the entry of regenerating axons into explanted optic nerves in vitro (*1*). If the epitope that is blocked is intracellular, how can the antibody promote regeneration?

One possibility is that Nogo-A contributes to inhibition when released from intracellular stores of damaged oligodendrocytes. Thus, at one extreme, if the N-terminal region is cytoplasmic and is the only inhibitory domain, then Nogo-A would contribute to inhibition only in pathological states. At the other extreme, if the membrane organization of Nogo-A is such that part of the N-terminal inhibitory domain is extracellular, and if this region and/or the 66–amino acid linker are inhibitory to regenerating axons in vivo, then Nogo-A may provide an ongoing source of inhibition in intact myelin. Either way, given the abundance of intracellular Nogo-A, one might expect damaged oligodendrocytes to be more inhibitory. Interestingly, some recent studies suggest that intact (as opposed to damaged) myelin may be less inhibitory than originally thought (*14*).

The most important question is whether inhibition of Nogo-A in vivo allows axon regeneration. The IN-1 antibody, which blocks the inhibitory action of Nogo-A in in vitro assays, has been shown to allow modest but clear axon regeneration after spinal cord injury (*15*). It is reasonable to attribute this important effect of IN-1 to inhibition of Nogo-A, although some of the effect could be contributed by blockade of NI35 or other cross-reactive proteins. The ability to make blocking reagents specific for Nogo-A and to generate Nogo-A knockout mice will now make it possible to establish the precise contribution of Nogo-A to the inhibition of regeneration.

If, however, the results with MAG are any guide, one might expect that blockade of any single inhibitory system might not permit more than a modest amount of axon regrowth. It is just as important, therefore, that this work will make it possible to determine how much more regeneration can result from blockade of multiple systems simultaneously—for example, by removal of both MAG and Nogo-A. A recent study showed that a vaccine against crude myelin extracts allowed much more regeneration than has been seen when any one protein alone is blocked (*16*). Although blocking multiple inhibitory systems may therefore be necessary, it may also be that all of these systems converge on a common signal transduction pathway (*17*). The identification of Nogo-A provides the tools to identify its signaling mechanism and to assess whether it converges on a common inhibitory transduction pathway, which might provide an even more effective target for regeneration therapies.

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PERSPECTIVES: GEOPHYSICS

The Strength of a Continent

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We can measure the strength of a small piece of rock by putting it in a press and watching it strain (deform) when we apply stress (force). But how can we measure the strength of an object that is 100 km or more thick and extends over a whole continent? On page 834 of this issue, Flesch *et al.* (*1*) attempt just that kind of measurement for the southwestern part of the United States.

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In their approach, the strength of the lithosphere—the rigid outer layer of Earth including the crust and the part of the upper mantle that sustains plate tectonics—is described by an effective viscosity, the ratio of applied stress difference to resulting strain rate. This may seem counterintuitive because the lithosphere is not obviously a viscous fluid. It does, however, slowly deform by multiple deformation mechanisms, including faulting, plasticity, and dislocation creep. Earthquakes are one sign of that deformation, but the major deformation mechanism in the lithosphere is probably viscous creep. Relatively low lithospheric viscosities might be caused by high local temperatures or high strain rates, because geological materials generally obey a nonlinear constitutive law. We are talking here about viscosities at least 20 orders of magnitude greater than that of water—effectively rigid on the time scale of human perception but flowing freely on the geological time scale. Describing the lithosphere's resistance to deformation by a viscosity parameter remains a great simplification but can give valuable insights in the context of an assumed level of applied stress difference. At any point the

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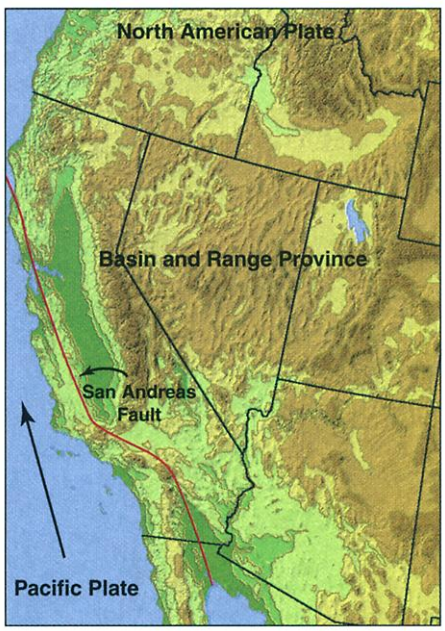
stress field, described by three principal stress axes, can be separated into an average compression plus a deviatoric stress field, which causes deformation.

Obviously, the strength of something as large as the western United States can only be measured if nature obliges by applying a load sufficient to drive deformation. To estimate lithospheric viscosity then requires a measurement of the applied deviatoric stresses and an independent measurement of the resulting strain rates. This has only recently become possible, largely because of the increasing precision with which crustal deformation rates can be measured. In particular, the use of Global Positioning System (GPS) observations (*2*) in recent years has led to a remarkably detailed description of the distribution and rate of deformation over broad continental regions. These measurements are consistent with the evidence from long-term earthquake activity but are much more precise.

Measurements of the stress differences that drive deformation on a continental scale are somewhat more difficult, or at least are associated with larger uncertainties, than the strain-rate measurements. On this scale, the level of stress and, hence, its calibration and measurement are essentially determined by Earth's gravitational field. If the density structure of the lithosphere is known, the vertical stress component follows directly, but the lithosphere apparently deforms in a depth-coherent manner, and it is therefore the depth-averaged vertical stress component that drives deformation (*3*). This depth-averaged quantity is equivalent to the gravitational potential energy (GPE) of the lithospheric column. A column with greater than average GPE will tend to become thinner by spreading horizontally. In contrast, a column with lesser than average GPE will tend to be squeezed and thickened by neighboring high GPE columns.

For a large enough area, the depth-averaged horizontal stress component is just the spatial average of the GPE over the entire region. Wherever the local GPE differs from the average GPE, the difference between vertical and horizontal stress components can drive deformation of the lithosphere at a rate dependent on lithospheric viscosity. The GPE can be estimated directly from an assumed density structure. The thickness of the crust can be obtained from seismological measurements, and upper mantle density may then be estimated assuming isostatic balance. The resulting estimates of GPE are broadly consistent (*1*, *4*) with estimates obtained from the geoid (*5*), that is, Earth's gravitational equipotential surface corresponding to mean sea level.

If deformation is assumed to be driven entirely by variations in GPE, then the above approach gives a direct quantitative analysis of deviatoric stress, strain rate, and effective lithospheric viscosity. The method has previously been used to estimate lithospheric viscosity in the deformation zone of Central Asia (*6*). Suppose, however, that, in addition to variations in GPE, there also exists a background deviatoric stress field produced by relative movement of neighboring plates. In the western United States, the Pacific Plate (PA) moves in a northwesterly direction relative to the North American Plate (NA) (see the figure below), and the observed deformation in this region therefore results partly from variations in GPE and partly from a stress field created by the plate movement. Until now, it has been difficult to quantify what proportion of the stress field arises from the relative plate movement. Flesch *et al.* have now come up with a neat trick for estimating the relative magnitudes of the two parts of the stress field, in effect calibrating the magnitude of the plate-boundary stress field by means of the estimated GPE stress scale.



The western United States is slowly pulled apart by a stress field with two components. Movement of the Pacific Plate relative to North American Plate creates an overall shear; gravitational spreading causes extension in the Basin and Range and compression near the coast.

The two contributions to the stress field can be computed separately, accepting that there is an unknown magnitude factor associated with the PA-NA relative motion field. Each of these stress fields has its own geometric characteristics, that is, the distribution of directions of principal stress. For the GPE component, the principal stresses are perpendicular and parallel to contours of equal GPE. For the plate motion component, the principal stresses are roughly at 45° to the relative movement vector. The observed deformation field of course, depends on the total stress field and, in general, the directions of principal strain rate are assumed to be parallel to the directions of principal stress. Thus, by adjusting the unknown magnitude factor and comparing the directions of the computed total stress field with the directions of the observed strain rate field, Flesch *et al.* can choose the stress magnitude that gives the best match between these two sets of field directions. By doing so, they obtain the unknown magnitude of the plate-boundary stress field, together with the lithospheric viscosity distribution. The GPE-derived stress field is responsible for extension in the Colorado Plateau and the Great Basin and shortening in the Coast Ranges of California and Oregon. The GPE contrast across the Rocky Mountain front causes a transition from extension in the highlands to compression in the Great Plains. The plate motion–derived stress field causes shearing parallel to the San Andreas Fault system that gradually decreases in intensity with distance from the plate boundary.

Of course, the geometric agreement between computed stress field directions and observed strain rate directions is not perfect. The fields are not parallel in some places, perhaps because the lithosphere does not always obey an isotropic constitutive relation (in which case we would not expect the directions to be the same anyway) or perhaps because the GPE estimates are not sufficiently accurate. The quality of the match between computed stress field and measured strain-rate field thus remains uncertain. Nevertheless, in building on the steady development of methods, theory, and data within the last two decades, this study represents a important advance in our ability to quantify stress magnitudes within the continental lithosphere.

In the coming years, we may expect to see similar studies applied to other areas of continental activity, wherever we can measure the strain-rate fields with sufficient accuracy. These measurements will provide valuable insights into the driving forces behind lithospheric deformation.

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