Research in Progress

Good Vibes

LIKE A BELL or a violin string, the earth vibrates in a discrete number of frequencies when it is "rung" or jarred by an earthquake. Theorized in the 19th century, the existence of these long-period free oscillations was not proven until the 1950s, when Caltech's Hugo Benioff developed a seismograph capable of measuring such long-period motions and, with some surprise, observed long-period vibrations that he thought were excited by the 1952 Kamchatka earthquake (magnitude Mw = 9.0).

He found on his record oscillations having a period of 58 minutes, which had been predicted by theoretical calculations as the period of the gravest (lowest in "pitch") of these oscillations. The earth's free oscillations were observed beyond any doubt by Benioff, Frank Press, and Stewart Smith after the 1960 Chilean quake (Mw = 9.5), and for this event they also first used the amplitude and phases of the oscillations to determine the properties of the earthquake source — the fault length and rupture velocity.

In the 20 years that followed, analysis of the earth's free oscillations with increasingly refined techniques has provided much information on the source mechanisms of earthquakes and on the earth's interior structure. During the last decade worldwide seismic networks (IDA — International Deployment of Accelerometers, and GDSN — Global Digital Seismographic Network) have furnished high-quality, digital data on the earth's "music" that is scanned, analyzed, and stored by computer, and made available to scientists studying the phenomenon.

One of those scientists is Hiroo Kanamori, professor of geophysics, who has made a number of contributions to the field, both in the development of new techniques and their application to the characterization of earthquake sources. His recent work on long-period surface waves (those oscillations of periods shorter than 300 seconds and wavelengths less than 1500 km) took an unexpected turn when he observed, again with some surprise, that the volcanic eruption of Mount St. Helens in May 1980 excited these waves, which were recorded by IDA and other networks. Since a volcanic eruption had never been observed by global seismological networks before, the event provided some unique data and an interesting picture of a volcanic source mechanism.

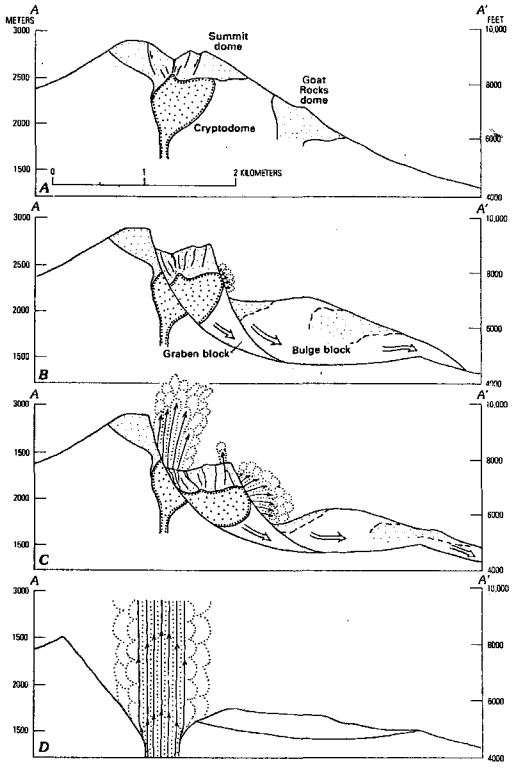
Kanamori and graduate student Jeffrey Given found that the source could be represented by an almost horizontal single force pointed in a S5°W direction and that the peak value of the force was about 10^{18} dynes. This is approximately equal to gravitational force acting on a conical mountain with a base diameter and height of about 1 kilometer. They also found that it was a relatively slow source process, much slower than ordinary earthquakes. At first they were not sure exactly what caused the seismic signal but concluded from the magnitude, the geometry (or direction), and time history of the force that the source was the massive landslide that touched off the eruption. The initial lateral blast (different from the vertical blast seconds later) may also have contributed to the horizontal force.

As magmatic activity increased the pressure inside Mount St. Helens, a bulge began to raise the incline of the north face of the mountain. The increase in slope led to the massive landslide down the north face (producing the southward force on the ground as it accelerated), removing the pressure near the vent and releasing the blast.

It has been generally thought that a magnitude 5.2 earthquake triggered the landslide, that the north slope was not sufficiently destabilized by the bulge to fail, but Kanamori now theorizes that the giant slide was caused by the instability of the slope and was responsible for the seismic signal. He suggests that there may not have been an ordinary earthquake at all, but only the force created by the removal of such a large mass from the mountain (a total of 5×10^{15} grams of material from the slide and the blast). Although the mechanism of the Mount St. Helens eruption is still not known precisely, interpretation of the earth's vibrations has added a new dimension to understanding the basic physics of the process.

Kanamori and Given have also developed methods of using long-period surface waves for rapid evaluation of an earthquake's tsunami potential. Tsunamis (tidal waves) are caused by deformations of the sea floor, primarily by earthquakes with a dip-slip rather than a strike-slip motion. Since surface waves travel faster than tsunamis, the Caltech scientists' method for retrieving a quake's fault geometry from global network data within minutes would make predictions and warnings of tsunamis possible. The system, according to Kanamori, would be relatively easy to implement. □ – *JD*

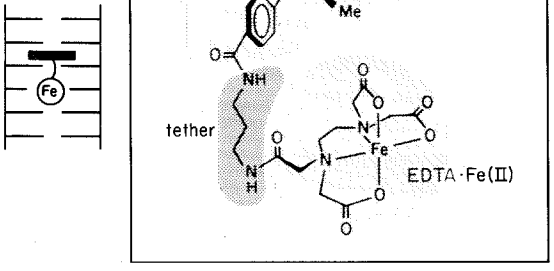
From *The 1980 Eruption of Mount St. Helens, Washington*, Professional Paper 1250, courtesy of the United States Geological Survey.



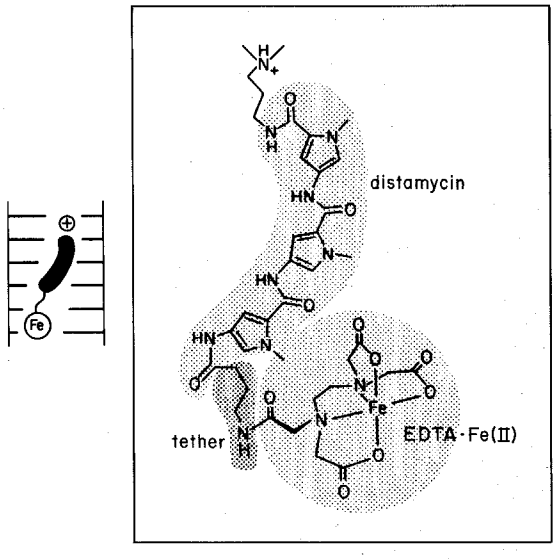
In the weeks preceding the eruption of Mount St. Helens, the increasing magmatic pressure (cryptodome) had caused the summit to split and a bulge to expand northward, lifting up the mountain's north side (A). The landslide that initiated the eruption removed the north face in two sections (B), exposing one side of the cryptodome and causing the lateral blast. As it slid farther (C), another explosion was triggered from the now exposed top of the cryptodome, and the vertical blast 20 km into the air followed (D) as the main volcanic channel was uncovered. Hiroo Kanamori's analysis of long-period surface waves suggests a new interpretation of the seismic signal excited by these events.

Drug Footprints

THE BINDING of small molecules and proteins on specific sites along double helical DNA is important in the regulation of many biological processes. For instance, many antibiotic, antiviral, and antitumor drugs useful in chemotherapy are small molecules that bind to DNA. To solve the problem *where* such drugs bind on the DNA template, Professor of Chemistry Peter B. Dervan and his students set out to design a new DNA-binding and DNA-cleaving molecule, whose function is that of a sequence-neutral DNA scissor. Their success in this effort has led to a rapid, direct technique for determining the locations and binding site sizes of small molecules bound on heterogeneous double helical DNA. Moreover, their design strategy has allowed them to create sequence-specific DNA-cleaving molecules that might be useful as new antiviral and antitumor drugs, as well as new powerful tools for the manipulation of DNA.



***MPE**•Fe (II) consists of the flat methidium molecule joined by a tether to the iron chelator EDTA. Methidium binds to the DNA ladder (left) by sandwiching itself between the base pairs. The attached EDTA with iron in its center acts like a wrecking ball to break the DNA.*



The banana-shaped antibiotic distamycin binds to DNA at a four-base-pair site by fitting into a groove of the double helix. By tethering the EDTA wrecking ball to the distamycin, the DNA can be cut at the specific site.

Their source of inspiration was bleomycin, a glycopeptide natural product used as an antitumor drug in man. Bleomycin binds a two-base-pair site on the DNA chain, and in the presence of iron and oxygen cleaves at that site. Because bleomycin is a complex structure, the details of the binding and DNA cleaving are still poorly understood by researchers. Bleomycin's biological activity is presumed to be related to the DNA cleaving event.

Dervan and graduate student Robert Hertzberg mimicked bleomycin's efficient DNA-cleaving activity by connecting two molecules that each performed one of bleomycin's functions. Methidium, a flat, aromatic molecule that binds to DNA by sandwiching itself between the base pairs was linked by a tether to ethylenediaminetetraacetic acid (EDTA), a simple and well-known iron chelator. EDTA • iron acts like a "wrecking ball" and cleaves the DNA helix where the methidium is attached.

Although Dervan claims that the resulting molecule, (methidiumpropyl-EDTA) iron(II), or MPE • Fe(II), is only a primitive model of the much more "exquisite" bleomycin, MPE is quite efficient at what it was designed to do. And it goes bleomycin one better for Dervan's purposes in that it is *not* sequence specific. It will cut DNA at any set of bases, thereby mimicking in function a DNA-cleaving enzyme called DNase I. But DNase I can be very sensitive to DNA structure (conferred by different base sequences) so its use as sequence-neutral DNA scissors sometimes suffers from the lack of complete non-specific DNA cleaving.

Non-specific DNA cleavage makes MPE a new useful tool to determine drug-binding sites on the DNA template. The rapid technique developed by graduate student Michael Van Dyke is called "footprinting with MPE•Fe(II)." When small molecules bind DNA, they protect that site, so that when the MPE•Fe(II) scissor happens along it can't cleave it where that drug is sitting. When DNA strands of known sequence are radioactively labeled on one end and a very small amount of MPE•Fe(II) is added, so that it cuts each strand just once, the resulting segments can be analyzed on a Maxam-Gilbert sequencing gel. Since MPE•Fe(II) will cut anywhere that the drug has not bound, when the ladder of base pairs is observed on the sequencing gel, there will be gaps where the drug has bound. This DNA-cleavage inhibition pattern is called the drug's "footprint," and while footprinting had been done previously with protein-DNA-binding sites, Dervan and Van Dyke are the first to adapt it for small molecules. Thus far they have used this rapid and direct method for identifying the DNA binding sites of seven drugs — actinomycin D, distamycin A, netropsin, chromomycin, mithramycin, olivomycin, and echinomycin. Many of these molecules are important in antibiotic, antiviral, and anticancer chemotherapy. A knowledge of where drugs bind on DNA is one step forward in understanding the molecular basis of antitumor, antibiotic action.

With the knowledge of these binding sites on DNA and the proven efficiency of his attachable "wrecking ball," the Dervan group was then able to construct molecules that would cleave DNA sequence specifically. The goal is to design and construct DNA-cleaving small molecules that would act like restriction enzymes, proteins that recognize and cleave DNA at sequences four to six base pairs in size. The ability to cut and paste DNA at a particular site in DNA is the basis for much of genetic engineering. The longer the recognition sequence, the less often it occurs and the more precisely the target can be defined in the DNA polymer, which is thousands to hundreds of thousands of base pairs long. By equipping the antibiotic distamycin with EDTA•Fe(II), graduate student Peter Schultz and postdoc John Taylor successfully constructed a molecule they called distamycin-EDTA that binds and cleaves at a specific four-base-pair site, rich in adenine and thymine. This same strategy can be used to construct other molecules that can recognize DNA sequences four to six base pairs in size, creating in effect a new set of "artificial restriction enzymes." Dervan envisions the construction of opposite strand DNA-cleaving agents at defined sequences as large as 8 to 16 base pairs. Once that happens, chemists will have gone beyond the sequence specificity nature has provided, affording a new class of useful DNA-cleaving machines for site-specific cleavage of viruses and chromosomes. □ – *JD*