tainty, or otherwise, about them. But there's a catch: The computational demands of these programs are prohibitive.

As in any scientific field, molecular evolution has a long tradition of dramatic transformation. The development of a powerful computational and statistical arsenal to account for the uncertainty stemming from sequence alignments is heralding the first paradigm shift in the era of genome-scale analysis.

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SYSTEMS BIOLOGY

Enlightening Rhythms

Ovidiu Lipan

How yeast systematically respond to environmental change emerges from blending engineering, mathematical, and experimental analyses.

We live in a sea of vibrations, detecting them through our senses and forming impressions of our surroundings by decoding information encrypted in these fluctuations. Such periodic phenomena range from circadian oscillations in living cells (*1*) to acoustic oscillations in the primordial universe (*2*). Passively observing periodic phenomena is scientifically rewarding, but actively using periodic stimuli to observe the hidden wonders of nature is even more so. On page 482 of this issue, Mettetal *et al.* (*3*) report using oscillatory stimuli to decipher how an organism—the yeast *Saccharomyces cerevisiae*—responds to environmental changes. By constructing a predictive mathematical model for specific signaling pathways (*4*), they show that oscillatory stimuli can be used to study how networks of proteins and genes are engaged by a living system to control physiological behavior.

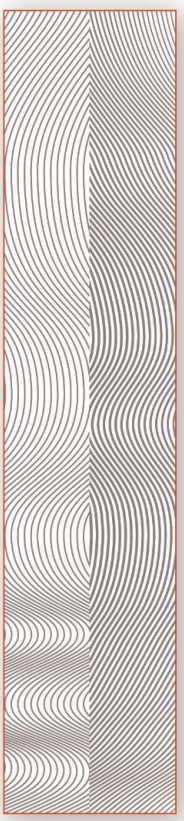
Many scientific studies hinged on creating oscillations to study natural systems. The idea of electromagnetic waves was implicit in James Maxwell's theory, but it was Heinrich Hertz's electric oscillators that created and measured their properties, thus confirming light waves as electromagnetic radiation, the most striking victory of 19th-century experimental physics (*5*).

Although the use of oscillatory stimuli to study how networks of proteins and genes regulate gene expression is theoretically valuable (*6*), implementation of this procedure is not obvious because the possibilities for constructing genetic oscillators are limited, at present. It takes ingenuity to find a molecular pathway that responds to an oscillatory signal, much less an experimental procedure to create these oscillations. Furthermore, these oscillations must produce detectable responses. Mettetal *et al.* fulfill these constraints by studying a signaling pathway in yeast that responds to changes in environmental osmolarity. Glycerol is the main yeast osmolyte and its concentration is controlled in part by the high-osmolarity glycerol (HOG) signaling pathway that involves the enzyme Hog1. By adjusting the export rate of glycerol through the cell membrane, yeast maintain osmotic balance.

Mettetal *et al.* studied three negative-feedback loops of the HOG pathway. One loop controls glycerol concentration through the membrane protein Fps1, and depends on the amount of active Hog1 in the nucleus. A second loop also involves Fps1, but is controlled by osmotic pressure across the cell's membrane and the concentration of intracellular glycerol. A third loop is Hog1 dependent and acts on glycerol concentration by increasing the expression of genes encoding the glycerol-producing proteins Gpd1 and Gpp2.

Which of the three negative-feedback loops dominate the dynamics of this osmo-adaptation system? Can system identification methods, such as those used by robotics engineers, describe the signaling dynamics of the dominant negative-feedback loops? To apply systems engineering methods, an input signal must be created and an output response signal must be recorded. Mettetal *et al.* varied the concentration of sodium chloride in the cell media, thus exposing cells to square-wave pulses (alternating between two values for an equal amount of time) of osmotic pressure. The output response recorded was the ratio between nuclear-localized, active Hog1 and Hog1 within the entire cell.

For designing complex systems, a success is claimed if the output response of a system to an external input signal can be mathematically predicted. Viewed only in terms of its input and output characteristics, the osmo-adaptation pathway loses its inner biological structure and becomes what is referred to as a "black box." The authors developed a black-box mathematical model for the osmo-adaptation pathway. They estimated parameters of the model from measurements using square-wave pulses of variable frequencies, then validated the predictive power of the model using a step input—one that switches on at a definite time and remains on indefinitely—of sodium chloride. Because gene regulatory networks contain many unknown molecular components, a black-box mathematical model is the best achievable solution in various situations.



Variable frequencies. Oscillating signals may unlock the complex organization of organisms.

The ultimate goal, however, is a mathematical model for a white box, in which all the molecular components and their interactions are known. The road toward this goal is paved with intermediate gray-box models containing some biological inner structures. Toward this end, Mettetal *et al.* transform the black-box mathematical model into a gray one that successfully incorporates the first two of the three osmo-adaptation feedback loops described. In doing so, they discovered that the dynamics of the osmo-adaptation response are dominated by the fast-acting Hog1-dependent negative feedback loop that does not require a change in gene expression.

The hope is to include other molecular components and feedback loops into a

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more detailed mathematical model. This will require new techniques to generate molecular input signals—perhaps based on photons rather than chemicals—for tuning gene expression and protein degradation (*7*, *8*). The study by Mettetal *et al*. is part of a large effort to blend the biological and mathematical structure of living systems and understand living systems not as collections of machine parts, but as stable, complex dynamic organizations (*9*). Hopefully, 21st-century systems biology will claim victories as striking as those of Maxwell and Hertz.

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GEOCHEMISTRY

The Rise and Fall of a Great Idea

Heterogeneities in Earth's mantle create ambiguity about the origin of hot-spot lavas.

Anders Meibom

On page 453 of this issue, Luguet *et al.* address a key question in geology (*1*): Can we determine the provenance of hot-spot lavas by geochemical means? The authors show that the chemistry of Earth's mantle is too heterogeneous to allow the detection of chemical or isotopic signatures of the "mantle plumes" widely held to cause hot-spot volcanism (see the figure).

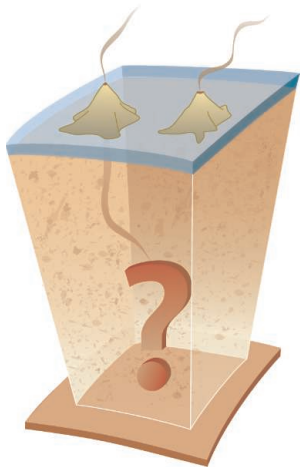
For decades, mantle geochemists have tried to find a clear isotopic or chemical signature of Earth's outer core in oceanic basalts, which are produced along mid-ocean ridges or at isolated, intraplate islands such as the Hawaiian chain. The latter are often assumed to be associated with deep-rooted upwellings called mantle plumes. Detection of a geochemical signature unambiguously linked with the outer core in such an intraplate basalt would make a very strong case for mantle plumes that originate at the core-mantle boundary (~2900 km below the surface). This would, in turn, have important implications for our understanding of large-scale mantle convection, the long-term stability of different mantle regions, and other fundamental aspects of Earth's interior.

The platinum-osmium (Pt-Os) and rhenium-osmium (Re-Os) isotopic systems have played a dominant role in these studies. ^{190}Pt is a rare platinum isotope that decays to ^{186}Os with a very long half-life of ~450 billion years. ^{187}Re is the most abundant rhenium isotope and decays to ^{187}Os with a half-life of ~42 billion years. Over time, a system with fractionated (that is, changed) Pt/Os and Re/Os elemental ratios will develop ^{186}Os/^{188}Os and ^{187}Os/^{188}Os ratios that are different from those in a system in which these elements were not fractionated. (The stable isotope ^{188}Os is used for normalization.)

Earth's mantle was strongly depleted in osmium, platinum, and rhenium during core formation, because these elements tend to move into metallic phases. If the osmium concentration is much higher in the liquid outer core than in the surrounding mantle, mixing a little bit of outer-core material back into the mantle at the core-mantle boundary will change the local osmium isotopic composition to resemble that of the outer core. And if the osmium isotopic composition of the outer core is very different from that of the upper mantle, it might be detected in lavas brought to Earth's surface.

This is a great idea. Excitement therefore followed the discovery of enhanced ^{186}Os/^{188}Os and ^{187}Os/^{188}Os ratios in Hawaiian basalts; a case was made for an outer-core origin of this isotopic signature (*2*). The logic was that the measured osmium isotopic ratios, particularly ^{186}Os/^{188}Os, would not normally exist in the mantle, but that inner-core solidification could produce the required fractionation of osmium, platinum, and rhenium in the remaining outer core. Finally, geologists had what looked like proof of a deep origin of a proposed mantle plume.

But as the assumptions behind the model were examined, problems appeared.



Mantle complexities. Thermally driven upwellings in the mantle—so-called mantle plumes—are often envisioned to originate at the core-mantle boundary, from which they rise to create the hot-spot volcanism seen, for example, in Hawaii. Unambiguous geochemical signatures of the outer core in such hot-spot basalts would prove the existence of deep-rooted mantle plumes, with important implications for large-scale mantle dynamics. But the detection of geochemical signatures uniquely tied to the outer core is severely complicated by a very high degree of upper-mantle heterogeneity, as shown by Luguet *et al*.

First, modeling of osmium, platinum, and rhenium fractionation between the solidifying inner core and the molten outer core is largely unconstrained. We do not know with certainty either the light-element composition of the outer core or the crystal structure of the solid inner core. We know even less about the fractionation behavior of these elements between the inner and outer core.

Second, when the fractionation of osmium, platinum, and rhenium between the inner and outer core was tuned in the model to fit the data from the Hawaiian basalts, the extremely long half-life of ^{190}Pt required the inner core to have started to crystallize early in Earth's history. This conclusion is in direct conflict with geophysical studies of the evolution of the inner/outer core system (*3*).

Third, an osmium isotopic signature from the outer core should be accompanied by a distinct signature in the isotopic composition of tungsten. This signature was not found (*4*).

Finally, osmium isotopic analyses of other mantle-derived materials showed that the upper mantle is very heterogeneous and that the Os isotopic "anomalies" detected in the Hawaiian basalts were probably not that anomalous (*5*). For example, certain mantle sulfides could have the appropriate Pt/Os and

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