Signaling Through Cooperation

Emmanuel D. Levy *et al.*

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anisotropy. Circulating flow due to thermal convection is one possibility (*11*). Interestingly, the observed seismic anisotropy also exhibits hemispherical variations. The strongest anisotropy is observed in the Western Hemisphere, which coincides roughly with the region where Monnereau *et al*. require melting. Lateral motion transports any existing crystal texture from west to east, where little anisotropy is observed. The absence of anisotropy in the east requires some mechanism to erase the crystal texture that originates in the west. There are several ways to accomplish this task (*12*), but a resolution requires further investigation.

One of the impediments to progress is a lack of observations. The inner core represents only 0.7% of Earth's volume, and the sampling provided by available seismic wave propagation paths is far from complete. Observations of normal modes (low-frequency oscillations of Earth as a whole) provide a complementary source of information, because the oscillation frequencies represent spatial averages of the elastic properties and density of Earth, including the inner core. However, conventional analysis of normal-mode observations cannot recover hemispherical structure because of the nature of the averaging in this approach. These limitations can be overcome by accounting for the interaction of oscillations with nearby frequencies.

Deuss *et al*. now show that the additional work is worth the effort. A key step in their study lies in the choice of normal modes. The authors consider pairs of modes that have strong sensitivity to the inner core. One mode contributes to motion at the surface, whereas the other is typically confined to the inner core and would not be directly observed at the surface. In the presence of hemispherical inner core structure, these two modes interfere, perturbing the frequency of the first mode. By measuring these perturbations, the authors retrieve the hemispherical structure of the inner core. The results provide evidence for strong anisotropy in the west and relatively little anisotropy in the east. In fact, the region of strong anisotropy appears to be confined in longitude to a region that is narrower than an entire hemisphere. The origin of this feature is not known, but better observations, like those reported by Deuss *et al*., are crucial to making progress.

Earth's solid inner core is an enigma. Expectations of a simple radial structure have been replaced by hemispherical variations and other surprising complications. These features probably reflect events and processes that have occurred over geological time. Our ability to read the geological history of the core will ultimately depend on better data and new ideas about the structure of this tiny iron-rich sphere at Earth's center.

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CELL SIGNALING

Signaling Through Cooperation

Protein kinases and phosphatases may form a collaborative network of interactions to mediate cellular responses.

Emmanuel D. Levy,[1] Christian R. Landry,[2] Stephen W. Michnick[1]

Living cells are complex systems that are constantly making decisions in response to internal or external signals. Among the most notable carriers of information are protein kinases and phosphatases, enzymes that receive inputs from cell surface or internal receptors and determine what actions should be taken in response, by phosphorylating or dephosphorylating substrates. How are these enzymes organized in the cell to capture and relay information in coordinated responses to signals? On page 1043 of this issue, Breitkreutz *et al*. (*1*) provide a key clue to this puzzle, describing how protein kinases and phosphatases in budding yeast are associated with other proteins and, most notably, with each other.

[1]Département de Biochimie, Université de Montréal, Montréal, Quebec, Canada H3T 1J4. [2]Université Laval, Département de Biologie, PROTEO and Institute for Integrative and Systems Biology, Québec, Québec, Canada. E-mail: stephen.michnick@umontreal.ca

The structure of the kinase and phosphatase interaction network revealed by Breitkreutz *et al*. does not have the command and control organization suggestive of textbook-depicted linear cascades. Indeed, the authors observed about ~30% more interactions among kinases than would be expected by chance, suggesting extensive cross-talk between signaling pathways. This observation is also consistent with several recent findings—for example, kinases are more highly phosphorylated compared to other proteins, implying that kinases frequently target other kinases (*2*). Further, specific inhibition of a kinase results in extensive depletion (as expected) but also enrichment of phosphorylation of many proteins, suggesting substantial functional dependencies among kinases and phosphatases (*3*). Finally, kinases and phosphatases have more genetic interactions with each other than with other proteins, also pointing to substantial collaboration in the cell decision-making apparatus (*4*).

Conceptually, the kinase-phosphatase interaction network described by Breitkreutz *et al*. suggests a distributed organization of information flow. Such a structure might confer robustness to the system in that contributions to decisions are distributed across many proteins. Observations from genetic experiments are in line with this view, whereby relative contributions of proteins to cellular processes follow a continuum. Surely canonical components usually have the largest contribution, but many other proteins often exert a large influence (*5*) (see the figure). Interestingly, the kinase-phosphatase interaction network also resembles recent descriptions of transcriptional regulatory networks, seen as a collaborative layer rich in interactions among transcription factors (*6*, *7*). Such a collaborative layer can be pictured as a table around which decision-makers debate a question and respond collectively to information put to them, akin to

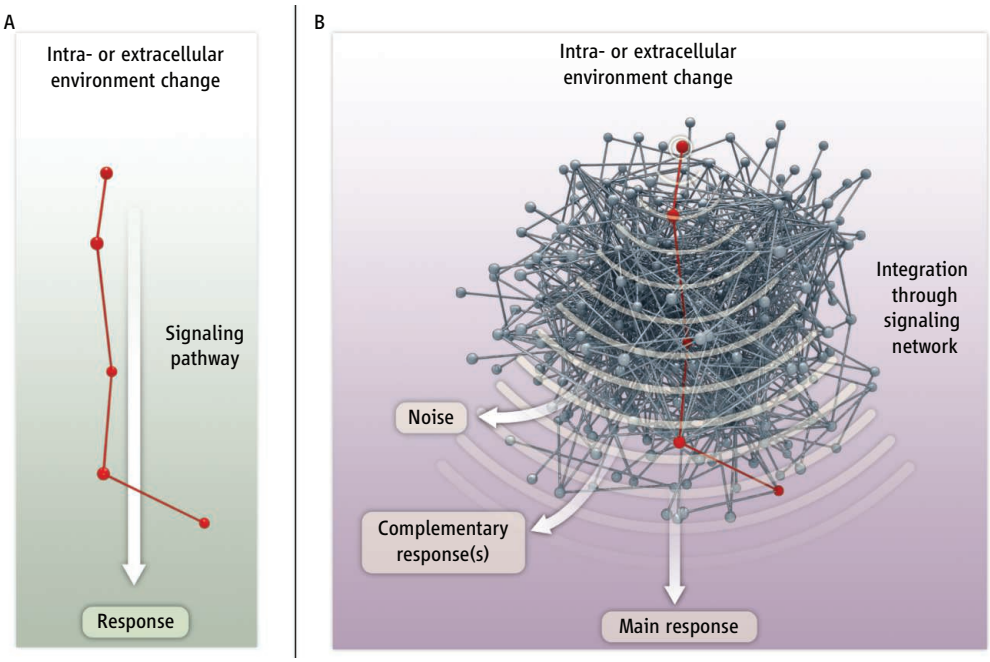
a "democratic" network (*6*). The similarities between the kinase-phosphatase interaction and transcriptional regulatory networks could suggest evolutionary principles guiding the assembly of networks that organize information flow in cells. These networks have evolved from simpler ones and, to use the terms of the French biologist Jacques Monod, there might have been a great deal of "necessity" at play that shapes their structure, but a lot of "chance" as well, the relative contributions of which have yet to be quantified (*8*, *9*).

A side effect of the kinase-phosphatase interaction network collaborative structure is that it creates the conditions for indiscriminate chatter within and outside of the network, as seen for transcription factor–DNA binding networks (*10*). This is especially true given that substrate specificity is particularly degenerate among kinases and phosphatases (*8*, *11*). Importantly, this could result in noisy interactions and phosphorylation events, even if recognition of substrates is augmented by auxiliary subunits or binding domains (*12*–*14*). Supporting this notion is the fact that phosphorylated sites (or "phosphosites") of known function are more conserved than phosphosites of unknown function (*8*, *14*). This leads to an estimated 50% or more of phosphosites detected in phosphoproteomic screens, and hence of kinase-substrate interactions, that have no or little functional relevance. Compensation of phosphorylated sites (e.g., loss of one phosphosite but gain of another nearby) could help explain their limited evolutionary conservation (*3*), but the extent to which this mechanism occurs remains controversial (*14*).

The functional importance of phosphosites and kinase-phosphatase interactions could be better assessed on the basis of stoichiometry of phosphorylation and of interactions, and as importantly, on the basis of their conservation. By analogy, transcription factors appear to discriminate between nonspecific versus specific functional binding sites on the basis of their affinities; those sites with the highest affinity are likely those that are functional (*15*, *16*). Similarly, the most abundant phosphosite on a given peptide is frequently the most conserved phosphosite on that peptide (*13*). Data on absolute phosphorylation abundance and kinase-phosphatase interaction intensity are not yet available, but may reveal a trend analogous to that seen for transcription factors. In this respect, the study by Breitkreutz *et al*. is an advance toward considering relative strengths and specificities of interactions.

Although the authors used standard affinity purification of "bait" proteins followed by mass spectrometry, they introduced important biochemical and computational twists. In particular, minimal washes of captured protein complexes were conducted to increase the detection sensitivity of unstable associations. In combination, they used a computational data-filtering scheme that enabled the differentiation of specific versus indiscriminate binding proteins on the basis of spectral counts. Such an approach might better reflect interactions that occur in the interior of cells, in that it relies more on the relative probabilities of interactions than on binary detection information under artificially stringent conditions. In parallel to such novel data acquisition and filtering approaches, careful analysis of how and at what rates phosphosites and kinase-phosphatase interactions have evolved should prove an efficient way to distinguish true functional signal from evolutionary noise in signaling networks.

Further progress in understanding signal transduction will require exploring the dynamic structure of kinase-phosphatase networks on both immediate and evolutionary time scales. This will require time-dependent experimental and computational reconstructions of local signaling networks (*5*) and a better understanding of the role of chance and necessity in shaping these networks.



Network organization of cellular signaling. The kinase-phosphatase interaction network **(B)** revealed by Breitkreutz *et al*. contrasts with linear signaling cascades classically depicted in textbooks **(A)**. The high degree of connections among kinases and phosphatases suggests a "board of directors" type of organization, whereby many proteins outside of the canonical pathway (in red) can influence its output. Such cooperative organization might allow the network to integrate several inputs and output complex responses. A certain degree of noise is expected to emanate from such a network.

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