

The notion of plant receptor kinases working with nonreceptor kinases in heteromeric complexes has emerged in other systems. The kinases in the heteromeric complexes can both be receptor kinases. For example, the BRI1 leucine-rich repeat receptor kinase detects the plant hormone brassinosteroid (11). Recently, an activation-tagging screen (12) and a yeast two-hybrid analysis (13) in *Arabidopsis* identified the receptor kinase BAK1 as a BRI1-interacting protein. Genetic and biochemical analyses suggest that the formation of BRI1-BAK1 heterodimers is required for brassinosteroid signaling (12, 13). Another example is provided by the NFR1 and NFR5 LysM receptor kinases identified in a screen for legume mu-

tants with defects in rhizobial symbiosis and nodulation (14). To recognize Nod factors, NFR1 is proposed to form a heterodimer with NFR5, which is missing the activation loop in the kinase domain (14).

The Murase *et al.* work presents a new scenario in which receptor kinases cooperate with plasma membrane-localized RLCKs. Perhaps this will become a common theme in plant receptor kinase signaling and certainly would account for the large number of RLCKs and RLKs found in plant genomes (8). Future studies will need to address the precise biochemical and cellular relationships among SRK, MLPK, and ARC1 in the plant self-incompatibility response.

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PHYSICS

The Cup of the Hand

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There is a memorable scene in the Japanese animé classic *Akira* in which two young protagonists are in a jail cell discussing the nature of the universe (1). They have a good excuse for doing so, for one of their school chums is at that very moment gleefully laying waste to Tokyo just by thinking about it, a victim of a powerful overdose of akira-hood administered by reckless military surgeons. Amid the peeling paint and dripping water of their prison they come to grips with their friend's terrible fate and the incomprehensible violence they have just witnessed—and will shortly witness redoubled and redoubled again—through an existential discussion of worlds within worlds not so different from what one might overhear late at night in a freshman dormitory. Their conversation reveals that the horror outside was made possible by a government research project into the ultimate power animating all things, which subsequently escaped and was rapidly leading to destructive rebirth of the universe. The latter actually comes to pass in the film, but a brave intervention by three other victims of the program at the last minute causes the new universe thus created to consolidate itself into a tiny luminous marble, which then drifts into the cup of the hero's hands and vanishes.

In discussing cosmic matters it is impossible not to draw analogies with sci-

ence fiction art from time to time, for the issues are as large as those depicted in such films and equally mysterious, despite being experimentally constrained. Our knowledge of the cosmos is still very primitive, and much of our thinking about it correspondingly speculative, more along the lines of what might plausibly have been than what is so. Plausibility is an interesting concept in theoretical physics, usually amounting to either a physical analogy with something observed to occur elsewhere in nature or a mathematical extrapolation of microscopic law. The latter, however, is actually a shibboleth, for the things that matter are nearly always collective organizational phenomena that cannot be reliably predicted from microscopics. The shapes of galaxies and the behavior of cosmic jets are simple cases in point, but the observation also applies to the grandest issues of modern cosmology: inflationary expansion and the hierarchical consolidation of matter after the big bang (2–4). The absence of predictive power is actually self-evident, because there would be no point in measuring these things if one could calculate them. As a practical matter, all plausibility arguments that count are analogies.

It may seem shocking to speak of the vacuum of space-time as an organizational phenomenon, but this is actually just a matter of semantics. The idea behind the words is mainstream and fully consistent with the facts. It has been known since the 1950s, and routinely verified by accelerator experiments since then, that empty

space is a kind of matter quantum-mechanically similar to a rock (5). The standard model of elementary particles is grounded firmly on the idea of space as a phase. A multiplicity of such phases and a complex sequence of transitions among them in the early universe are cornerstones of modern particle cosmology. The existence of such phases is implicated in the structure one sees on intergalactic scales, and the heat released in the transition between two of them is the ostensible power source of inflation. Inflation itself is partly motivated by these phases, because they make the observed uniformity of the universe unnatural and something requiring explanation.

The semantic incongruity, however, like the sublimated worries about modern life that give us science fiction nightmares, belies something important—unfinished business of the 1970s that has been slowly and systematically tearing physics apart (6, 7). Stripped of their confusing mathematical descriptions, the phases of the vacuum boil down to physical analogies with phases of ordinary matter, natural phenomena observed to exhibit universality. That means that their properties at long length and time scales, where we normally do experiments, do not depend on microscopic details at all, and thus do not constrain them when measured. A simple example of emergent universality would be sound propagation in fluids and solids, an effect perfectly well accounted for as the motion of atoms, but also a generic property of the phases not requiring atoms to make sense. Sound is an especially pertinent example because it has a second identity at low temperatures as an emergent elementary particle with properties identical to those of particles of light. In-sensitivity to microscopic detail thus

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turns the concept of fundamental on its head, in that it makes principles of self-organization the truly important thing, rendering the quantum underpinnings of the universe, whatever they are, unknowable in the absence of experiments that reach shorter scales and irrelevant to behavior we presently see. Little wonder that physicists remain bitterly divided over full acceptance of the vacuum as a phase (8).

The vacuum as an organizational phenomenon has the disturbing logical implication that the ancient dream of commanding the ultimate power of the universe just by thinking about it is a delusion, made so not by human frailty but by the very physical processes one is trying to understand. Ironically, nature abets this delusion. It can, and often does, happen that an experiment improved to reveal an ultimate cause reveals instead emergent universality of a nearby phase transition masquerading as one. This effect is unfortunately very likely to be occurring in the vacuum of space-time, for unstable renormalizability, one of its strangest attributes, is observed in table-top experiments to emerge very generally near phase transitions. If it is indeed the case that the vacuum is characterized by a hierarchical cascade of universalities, then all of our allegedly fundamental knowledge about it is temporary, and destined to pass away in the future as experiments improve.

The research article by Senthil *et al.* (9) on page 1490 of this issue is an attempt to address this problem mathematically. It deals specifically with a suspicion many of us have had that quark confinement, one of the most cherished features of the standard model, may be a collective effect that emerges at a phase transition and thus not fundamental at all. The paper is complicated, an unfortunate side effect of the difficulty of the task, for it is not generally possible to deduce emergent phenomena from first principles. The best one can do is postulate them and then demonstrate plausibility by showing that small corrections get smaller as the measurement scale increases. Such convoluted arguments are ripe with opportunities for mistakes, regardless of how careful the authors have been, so the test of emergent universality that counts is always experimental. This, in turn, forces the theory to address not quark confinement itself but an allegory of it one might

hope to test in a table-top experiment. The logic is maddeningly indirect, but unfortunately the only approach that is legitimately scientific.

The central idea of the paper is quite simple. It was discovered in the 1970s (10) that an ordinary antiferromagnet in one spatial dimension condenses at zero temperature into a quantum ground state with the curious property that its low-lying excitations carry spin 1/2, even though the underlying system of atoms from which it

delicately balanced at a zero-temperature phase transition. In other words, perhaps the missing fractionalization and our poor understanding of zero-temperature criticality are one and the same.

The potential relationship to quark confinement in the vacuum of space-time is similarly straightforward. If the objects with fractional quantum numbers do indeed emerge at low energy scales at phase transitions, then they must disappear utterly the moment the system is perturbed by



was built possessed only spin flips, which carry spin 1. Collective organization in this system thus caused half-integral spin to materialize out of nowhere, in the process defying one of the most basic lessons of quantum mechanics that the total spin of an assemblage is never less than the spin of its parts. In retrospect the lesson was subtly corrupted by postulating the number of atoms to be small. It is not true in general. While there was no doubt that the antiferromagnet result was correct, subsequent failure to find the effect experimentally in real three-dimensional materials created the widespread perception that it was a strange, unimportant mathematical curiosity unique to one dimension. But why one dimension should be so different was never explained. Recent events, notably the experimental discovery of electric charge fractionalization in the fractional quantum Hall effect, a related phenomenon, and our ongoing frustrations with correlated-electron materials, have led us to revisit this question and to wonder if the unique aspect of one dimension might simply have been its infamous ability to suppress ordering. The higher dimensional analog of the effect would then be quantum criticality, something that occurs only if the matter is

even the tiniest amount, since then it becomes one phase or the other, neither of which exhibits fractionalization in its low-energy spectrum. This can only happen if there are stupendous attractive forces between the particles that balance to zero at the transition but become unbalanced the moment one moves away. Moreover, these forces must work at extremely long length and time scales, since it is only the lowest energy particles that disappear. At higher energies, no experiment can tell whether one is exactly balanced at the transition or pushed slightly off into the phase, so the fractional objects must still be visible there. This very behavior—integrity at high energy scales but powerful binding leading to loss of identity at low ones—is exhibited by quarks and is codified as the principle of asymptotic freedom (5). Senthil *et al.*'s frequent use of the term “confinement” to describe their effect is tacit acknowledgement of this potential relationship.

Thus these ideas, if they are confirmed experimentally, have the potential to overturn some of the most deeply held beliefs in theoretical physics. The situation reminds us that scientific knowledge, even at its most fundamental, is never static, and

that the world of the mind, like the physical one on which it is built, is filled with incomprehensible violence that spins out of control from time to time. It is conceivable that this has now begun, and that we are in the process of discovering that the artist's vision of the universe in the cup of the hand is not fantastic nonsense at all but the essence of the matter.

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IMMUNOLOGY

The Tangled Webs That Neutrophils Weave

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Neutrophils are the body's first line of defense against invading microorganisms. The high incidence of bacterial infections in neutropenic patients, and the associated high mortality rate among these patients, underscore the importance of neutrophils for microbial clearance (1). Most studies of microbial killing by neutrophils investigate the ability of these immune cells to engulf pathogens by phagocytosis, and the complex armamentarium they deploy to eliminate engulfed pathogens within intracellular phagocytic vacuoles. Such antimicrobial tools include toxic oxygen radicals, cationic proteins that disrupt the pathogen membrane, and an assortment of lytic enzymes that contribute to the death and degradation of invading microorganisms. These cationic peptides and lytic enzymes are packaged in specialized membrane-bound granules that fuse with the phagocytic vacuoles, delivering their lytic contents to the vacuole interior (2). However, neutrophils can kill extracellular pathogens in the absence of phagocytosis. The killing of extracellular bacteria by neutrophils may seem advantageous, providing a more rapid and disseminated means of controlling infection. On the other hand, extracellular killing may be riskier, because neutrophils can potentially damage surrounding host tissues. Brinkmann and colleagues (3) describe, on page 1532 of this issue, a tool that neutrophils produce to kill extracellular bacteria in a way that minimizes damage to host cells.

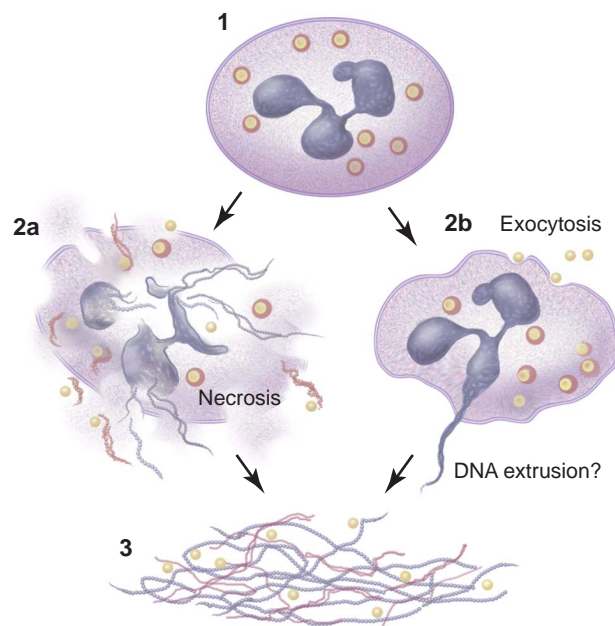
Brinkmann *et al.* observed that when neutrophils are stimulated with cytokines or bacterial endotoxin, these cells generate a web of extracellular fibers composed of DNA, histones, and granule proteins such as elastase (see the figure). These fibers, nicknamed neutrophil extracellular traps (NETs), bind to both Gram-positive and Gram-negative bacteria and display bactericidal activity. The authors also demonstrate that the elastase component of NETs effectively degrades bacterial virulence factors. Dispersal of NETs with the enzyme deoxyribonuclease (DNase),

which degrades extracellular DNA, eliminates their antimicrobial properties. The investigators postulate that NETs immobilize a high concentration of extracellular antimicrobial peptides and, by trapping and killing invading bacteria, provide rapid control of infection.

Although neutrophils are known to secrete granule proteins, the finding that NETs contain DNA and histones raises an obvious question: How are NETs formed? In particular, what are the mechanisms by which neutrophils might release some of their nuclear contents? Neutrophils are terminally differentiated cells and therefore do not divide; they normally die within hours through a tightly regulated and noninflammatory process of programmed cell death called apoptosis. This process, however, seems not to be involved in the generation of NETs. Brinkmann *et al.* note that NET formation occurs much more quickly than apoptosis, and that stimuli known to delay apoptosis in

fact induce NET formation. Explosive neutrophil death by necrosis would therefore seem a more likely alternative. However, the authors do not favor this mechanism, as they failed to detect abundant cytoplasmic proteins, such as actin and tubulin, in the NETs. Instead they speculate that neutrophils may have developed an active process of extrusion of nuclear material while conserving cellular integrity (see the figure). This daring hypothesis needs to be validated by direct observation of the extrusion event and by detection of intact neutrophil remnants selectively depleted of their nuclear contents.

However they are formed, the discovery of NETs may help to explain some puzzling observations about what neutrophils do. Elastase,



Making NETs. Neutrophils generate extracellular fibers called NETs that kill bacterial pathogens without the need for phagocytosis. A resting neutrophil becomes activated (1), leading to the release of DNA, histones, and granule proteins that assemble into NETs (3). The cellular constituents of neutrophils are released either through necrotic cell death (2a) or by exocytosis of granule contents coupled with active extrusion of DNA via an unknown mechanism (2b).

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