mechanism by which Gwl controls mitotic entry and progression. Activation of Gwl by Cdk1 leads to direct phosphorylation of Ensa or Arpp19, either of which then blocks PP2A-B55δ. The consequence of this decrease in dephosphorylation is an increase in the net phosphorylation of mitotic substrates, resulting in entry into mitosis (see the figure).

These results raise new questions. Are Ensa and Arpp19 the only relevant substrates of Gwl? Depletion of these proteins in *Xenopus* and human cells supports this notion, and there is precedent for cell cycle–regulatory kinases (such as Wee1) phosphorylating a limited number of substrates. Gharbi-Ayachi *et al*. and Mochida *et al*. disagree about the relative importance of Ensa versus Arpp19 in *Xenopus* mitotic entry, and this will require further study.

How is the phosphorylation of Ensa and Arpp19 regulated? Although Gharbi-Ayachi *et al*. and Mochida *et al*. suggest a simple mechanism—phosphorylation of a single serine residue by Gwl—other potential phosphorylation sites in Ensa and Arpp19 have been identified by phosphoproteomic screens (*12*), including two tyrosine phosphorylation sites immediately adjacent to the Gwl site. Perhaps these additional phosphorylation events, catalyzed by other kinases, alter the affinity of Ensa and Arpp19 for PP2A-B55δ or other PP2A B subunits, or the activity of Gwl on Ensa and Arpp19.

If phosphorylation of Ensa and Arpp19 is important for mitotic entry, are both proteins inactivated at mitotic exit so that mitotic substrates can be dephosphorylated? PP2A-B55δ may not be required for dephosphorylating mitotic proteins at exit from mitosis; indeed, a screen of phosphatases by RNA interference identified a different PP2A heterotrimer, PP2A-B55α, as a regulator of mitotic exit (*13*). There may be additional PP2A inhibitors to be discovered, which are inactivated through as yet unknown mechanisms.

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MATHEMATICS

Being Glassy Without Being Hard to Solve

The threshold for mathematical problems being easy or hard to solve can be extremely abrupt.

Federico Ricci-Tersenghi

The statistical mechanics that describes collective phenomena in disordered systems and solutions to large search problems have important mathematical connections. One of the models that describes disordered materials, the diluted p-spin model, is strongly related to the random XORSAT problem, a problem of finding variables that simultaneously satisfy a large number of logical constraints (*1*). This relation has provided insight into how small changes in a model can modify its computational difficulty.

Cooling a physical liquid creates an ordered crystal or a largely disordered configuration called a glass. Similarly, cooling a solid containing atoms with unpaired electron spins may lead to a spin-aligned state (for example, a ferromagnet) or to a disordered spin glass. Simple models of interacting particles or spins normally create the ordered state at low temperatures. Glass models, when cooled, form small regions of local order that mismatch at the boundaries, so that no ordered structure is evident on larger length scales.

A natural dynamics exists for these models: Particles or spins are allowed to move or flip according to the change in energy this would produce. In a glass model, a large amount of energy is needed to rearrange the local structures all along the boundaries; relaxation times become huge and diverge at the glass critical temperature T_g. Below T_g, the system will likely get trapped in one of many false local energy minima above the true equilibrium energy. In most models, when this situation occurs, the computation of the ground states can be unfeasibly long. However, there are glass models in which the relaxation dynamics indeed get stuck at a threshold energy value, yet a different algorithm can find all of the ground states in a very efficient way. Although such models (considered ideal glasses) are prototypes for complex systems, the problem of finding their ground state is easy to solve.

An example of these ideal glass models is the diluted p-spin model, which is defined in terms of N spins s that either point up or down (1 or –1). Their interactions are described by the Hamiltonian

$$H = -\sum_{\langle ijk \rangle}^{\alpha N} J_{ijk} s_i s_j s_k \qquad (1)$$

The sum runs over a set of αN randomly chosen triplets (i, j, k) of neighboring sites (so in this case, $p = 3$, only triplet interactions are included), and the couplings J_{ijk} are quenched random variables (e.g., they are randomly set to +1 or –1). The specifics will not matter in the limit of large N. Typically, the ratio α of interactions per variable is chosen so that not all sites interact, and some are more connected than others.

This model displays the desired dramatic increase of the relaxation times near T_g that reproduces glass phenomenology (*2*, *3*). Even when a spin configuration exists that satisfies all the interactions—which would favor ordering—a perfect glass still forms (*4*). This model has a mean-field nature—it reduces a difficult many-body problem to a simpler one-body problem—and could be solved analytically (*5*).

The figure summarizes the properties of the diluted p-spin model that are relevant for discussing possible relations between glassiness and computational hardness. In this sketch, potential energy E is shown as a function of α. The green region corresponds to energy values that can be reached by a stochastic algorithm—one with randomly cho-

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sen moves, such as a Monte Carlo Markov chain. These algorithms would get "stuck" at the threshold energy E_g separating the green from the red region. The red region is full of local minima (the glassy states) and large energy barriers (it looks like an "egg carton") and is hard to sample with stochastic local moves algorithms (and probably with any polynomial time algorithm). The blue line corresponds to unfrustrated ground states, that is, configurations with all interactions satisfied.

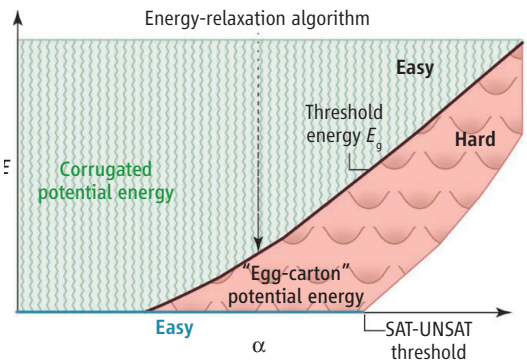
The search for the unfrustrated ground states of the Hamiltonian (Eq. 1) can be easily recast as solving a set of αN linear equations in N Boolean (true or false) variables of the type

$$x_i \text{ XOR } x_j \text{ XOR } x_k = c_{ijk} \qquad (2)$$

where XOR is the exclusive OR operation—the XOR statement is true if one but not both arguments are true. As before, the triplets are randomly chosen, and the known constants c_{ijk} are randomly fixed to true or false with probability 1/2. Equation 2 is a constraint satisfaction (SAT) problem (CSP)—each equation imposes a constraint on the Boolean variables—and is called a random XORSAT problem (*6*).

For small values of the ratio α of constraints per variable, true and false values can be found so that all αN linear equations are satisfied. However, as the ratio α increases, the random XORSAT problem becomes more and more difficult to solve and finally cannot be satisfied (UNSAT). The largest α value for which solutions exist is called SAT-UNSAT threshold. As long as α is smaller than this threshold, the problem is linear and all solutions can be found efficiently, for example, by the Gaussian elimination method, which takes a time of order N^3 in the worst case.

In a sense, the random XORSAT problem in computer science can be viewed as a limiting case (for temperature going to zero) of the diluted p-spin model in physics, and it is curious that its solution has been reached by the two communities independently and at the same time (*7*, *8*).



The line between easy and hard. A schematic picture for the potential energy E of a glass model (the diluted p-spin model) as a function of the ratio α of interactions or constraints per variable. The green region corresponds to configurations that can be easily sampled by a standard stochastic algorithm with local moves (e.g., Monte Carlo methods). In the red region, deep local minima separated by high energy barriers make the sampling of configurations a computationally hard problem. The zero-energy ground-state configurations along the blue line (at the horizontal axis) can be sampled efficiently, because this problem is not computationally hard before the satisfiability (SAT-UNSAT) threshold. However, configurations on the blue line cannot be accessed by cooling the glass model: In this case, a straightforward connection between physical glassiness and computational complexity cannot be made.

Returning to the figure, an important connection can be made about computational hardness. The blue line is computationally easy and can be sampled in polynomial time. However, it extends below the red hard region that cannot be accessed by the stochastic searches. The naïve connection between glassiness and hardness fails. Thus, it is not possible to say a priori that a complex physical problem does always correspond to a computationally hard problem. It is entirely possible to find an easy problem that looks "glassy" and difficult to solve if approached with a suboptimal algorithm.

Despite the existence of specific cases like the diluted p-spin model, scientists believe in a strong connection between the physical complexity of a model (i.e., the properties of its potential energy, which determine phase transitions) and the computational complexity of the corresponding CSP (*9*–*11*). Indeed, the peculiarity of the diluted p-spin model arises from an intrinsic symmetry in the model (*6*) that allows easy computation of configurations satisfying all interactions. As soon as this symmetry is broken, the computation of ground-state configurations becomes very difficult, even if these configurations satisfy all interactions (*12*).

In general, the connection between physical complexity and computational complexity may apply and may help in solving the following very important open problem. Computational problems fall into one of two complexity classes (*13*). The class P contains all of the problems for which a solving algorithm running in polynomial time is known, whereas the class NP contains all of the problems for which such an algorithm is not available, although a candidate solution can be checked in polynomial time. If the classes P and NP turn out to coincide—that is, if the "P = NP" conjecture is true—our world would change dramatically. For example, current cryptographic codes, based on the NP hardness of factoring large numbers, would be useless.

Scientists strongly believe P and NP classes to be different. In August 2010, some Internet blogs reported a claim of a proof that P ≠ NP by Vinay Deolalikar. A wiki site aggregates most of the information on the proof and the discussion about it (*14*). The proof tries to connect the complexity of the solution space of random CSPs (i.e., the structure of ground states of the corresponding physical model) and the complexity of algorithms for finding solutions to these problems.

In essence, Deolalikar tries to prove that those random CSPs in which solutions form clusters with frozen variables (that is, variables taking the same value for all solutions in the cluster) cannot be solved in polynomial time by any algorithm. However, the diluted p-spin model is a classical example that a simple connection cannot work. The solution space of random XORSAT problems shows clustering with frozen variables (*7*), but the problem is solvable in polynomial time. Certainly, we need to understand better this connection, and hopefully Deolalikar's work will help in this regard.

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