pedigree, others are skeptical that it has been cracked so easily. Susan Coppersmith of the James Franck Institute of the University of Chicago describes the new model as "quite speculative" and points out that the basic assumption of the model "has not been explicitly tested."

The root of the sand-pile problem is a frustrating facet of mechanics called indeterminacy. For a perfectly rigid table, for example, it is not possible to work out the downward forces on each of the table legs because the number of unknown forces exceeds the number of equations relating those forces, so the system of equations cannot be solved. The traditional way physicists tackle this type of problem is by making the table mathematically slightly elastic so that it sags. This provides additional relations between forces via the sagging, and the problem then becomes determinate.

Sand piles are indeterminate in the same way, but Cates and his colleagues dismissed the idea of an elastic sand pile, because the bigger the pile, the more it would sag. This, Cates explains, will give a pressure dip pattern that depends on pile size, which is at odds with experimental results. Instead the researchers introduce the idea that the lines of stress propagation in the pile are a set of fixed parallel straight lines, and this additional relationship between the forces within the sand pile means there are enough equations to fix all the forces. "These directions are remembered by the packing of the grains from the moment at which they are first deposited," says Cates.

Based on this "fixed principal axis" (FPA) assumption, the model can reproduce the classic pressure dip for a sand pile created by pouring grains. But piles created in different ways should, according to the FPA model, show different stress patterns. For example, a pile of flour formed by a cook's swirling sieve should have virtually no pressure dip. "The local stress propagation rules depend on how the pile was constructed," says Cates, adding, "There are definitely new predictions from this theory which new experiments will be able to put to the test."

Cambridge University's Sam Edwards welcomes the FPA model because the stress lines create "a nest of arches" in agreement with a model he proposed in 1989. He points out that a child's sand castle can withstand having a tunnel dug through it, so there must be arches in sand piles shouldering the load. But in his model, Edwards included only vertical forces. "If you bring the other [forces] in you find it turns into coupled differential equations, and that's what Cates *et al.* have done," says Edwards.

Joe Goddard of the University of California, San Diego, acknowledges the success of the FPA model, but he thinks a "soft," elastic approach to sand piles could still be useful. Within a more classical approach one could get "localized yielding" of an elastic material, he says, and provide an even better explanation of the pressure dip. Only time will tell if the sand-pile problem yields to a hard or soft approach, or a mixture of the two.

–Andrew Watson

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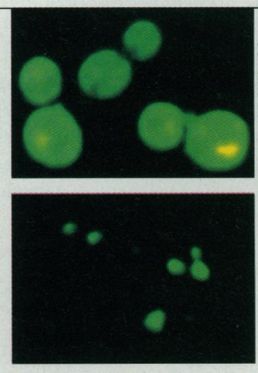
BIOCHEMISTRY

Yeast Prions: DNA-Free Genetics?

Prions—infectious protein particles thought to cause "mad cow disease," human Creutzfeldt-Jakob disease (CJD), and other neurological afflictions—now seem to be running rampant in yeast. But there is no reason to stop eating bread or drinking beer, for there's not even a hint that yeast prions pose a health threat. On the contrary, they may help scientists figure out how a protein can perpetuate a trait—or a disease—from one cell to the next by assuming an abnormal form and recruiting normal proteins in the new cell to its cause. Whether prions can perform that feat—supposedly beyond the ability of anything without DNA or RNA—is a major argument in the debate over whether prions are real (*Science*, 12 July, p. 186).

On page 622, geneticist Susan Lindquist and her colleagues at the University of Chicago show that a form-changing protein in yeast appears to create a trait called [PSI$^+$] in daughter yeast cells, after they bud off a mother cell, by causing newly synthesized proteins to become relatively insoluble and clump together. It does so without altering the DNA in the cells, which are clones. The finding does not prove that proteins alone can infect other cells in mammals, but it is evidence that a protein is able to pass on a trait just by its presence in a cell. "It's genetics without DNA," Lindquist says.

That notion has caught the attention of scientists on all sides of the prion debate—although they disagree on its interpretations. Reed Wickner, the geneticist at the National Institute of Diabetes and Digestive and Kidney Diseases who first proposed that yeast prions existed, says this work—which builds on previous studies—greatly strengthens the argument for a prion model for [PSI$^+$]. "The biochemical evidence had been lagging," he says. And Laura Manuelidis, a neuropathologist at Yale University who believes a virus, not an infectious protein, lurks behind CJD and other diseases, calls the research "very elegant, inherently interesting work." She says that by studying the clumping and insolubility patterns, researchers may be able to home in on the infectious agent.



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Prion model. Normally, the protein sup35 (green) is evenly spread in yeast *(top)*, but in a prionlike condition it clumps *(bottom)*.

The work centers on a protein called sup35. In normal strains of yeast, it helps translate DNA into proteins. But in [PSI$^+$] strains, the protein doesn't work. And the malfunction does not appear to be based on DNA: Strains with apparently identical DNA can show up as the normal [psi$^-$] or the unusual [PSI$^+$]. Researchers have found that they can trigger the condition in [psi$^-$] cells by causing them to overexpress sup35.

What scientists had not been able to do was link the heritability of [PSI$^+$] to any particular physical change in the sup35 protein. Lindquist and her colleagues set out to pin down that link by analyzing sup35 in both [PSI$^+$] and [psi$^-$] cells. They spun cell extracts in a centrifuge to separate soluble material from insoluble clumps, and quickly spotted a difference: The sup35 protein is soluble in normal cells but insoluble in the [PSI$^+$] cells. They also attached a fluorescent molecule to the sup35 protein and observed it in living cells. It turned out to be evenly distributed in normal cells, but in [PSI$^+$] cells it clumped, a finding that corresponds to mammalian prion research. The researchers theorize that the protein clumps are passed from mother to daughter cell in the cytoplasm when the daughters bud off, and that the clumps form "seeds" that attract newly formed sup35 to them, tying up the protein and preventing it from doing its usual job. In separate work published in July in the *EMBO Journal*, Michael Ter-Avanesyan and colleagues at the Institute of Experimental Cardiology in Moscow found other evidence for soluble and insoluble forms of the protein.

Lindquist acknowledges that the yeast work does not prove the infectivity of prions in mammals, where prion diseases don't involve budding cells. But she says transmitting protein conformations shouldn't be underestimated. "It's suggesting there's a mode of inheritance that we haven't been paying attention to," she says. And that has implications that even go beyond mad cows.

–Gretchen Vogel