ing transmitted to daughter cells, mechanisms called checkpoints either halt cell division so that the damage can be repaired before division occurs, or even kill the damaged cells. If the DNA is not repaired because an essential protein is missing, the cells might never pass the checkpoint, and so either fail to divide or simply die.

That raises the question of how cells in the adult organism can keep proliferating—and form breast or ovarian tumors—when *BRCA1* or *BRCA2* is inactivated by mutation. One possibility, Bradley suggests, is that the checkpoint controls are much tighter in the embryo than the adult. Livingston proposes another: that checkpoint genes, too, have to get knocked out before cancer can develop.

Causing defective DNA repair may not be the only way in which *BRCA* mutations lead to cancer, however. Both proteins are very large—BRCA1 contains 1863 amino acids and BRCA2 has 3418—and they may well have activities other than DNA repair. In the second *Nature* paper, Tony Kouzarides of the Wellcome/CRC Institute in Cambridge, U.K., and his colleagues present evidence that BRCA2 can activate gene transcription. They found that when they linked a particular region of BRCA2 to a known DNA binding sequence, it activated transcription of a so-called reporter gene in yeast. What's more, one BRCA2 mutation found in families with inherited breast cancer abolished the activity—an indication that its loss might be involved in development of the cancers. Other researchers have made similar observations with BRCA1. Still, the test systems used for all this work were artificial, and the results need to be confirmed—say, by identification of genes that the BRCA proteins activate normally.

But even though the understanding of how *BRCA1* and *BRCA2* lead to cancer is tentative and incomplete, researchers feel that after years of frustration, they are finally making headway. Says Duke's Futreal, "Hopefully, we are moving toward [finding] a role for these things. It certainly looks like a trend."

–Jean Marx

MATHEMATICS

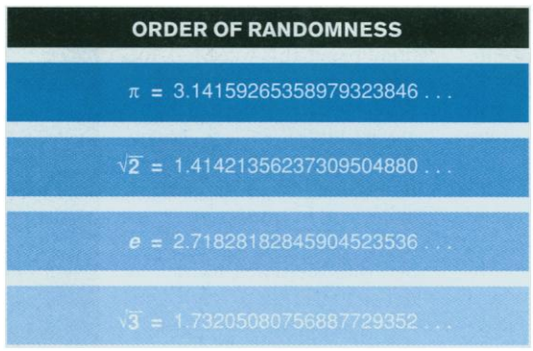
New Test Sizes Up Randomness

Finding a random sequence of numbers is as easy as pi—or is it? Mathematicians often depend on irrational numbers like π, e (the base of natural logarithms), and $\sqrt{2}$ to give them an unpredictable stream of digits. But a paper in last week's *Proceedings of the National Academy of Sciences* is upsetting the conventional wisdom about randomness by showing that some of these numbers are far more predictable than expected. The finding is an early result of a new test of randomness that is also raising concerns in other fields where random-looking sequences crop up, such as cryptography. Ultimately, though, the new test could put those fields on firmer ground.

Randomness has been hard to quantify. Any mathematician could tell you that 01101100 is more random than 01010101, but none could tell you just how much more random. Then, two researchers—Steve Pincus, a free-lance mathematician based in Guilford, Connecticut, and Burton Singer, a mathematician and demographer at Princeton University—created a method for measuring a sequence's "entropy," or disorder. "[Their method] is one of those tools that makes you say, 'Hey, that's a good one!' and you put it in your tool kit," says Max Woodbury, a mathematician at Duke University.

Pincus and Singer built on the observation that all possible digits are represented about equally in a perfectly random stream of numbers. For example, the binary sequences 01101100 and 01010101—each with four 1s and four 0s—pass this test. But the researchers also noted that when the digits are taken two at a time, a random sequence should have an equal number of all possible pairs: 00, 01, 10, and 11, in this case. The sequence 01010101 fails this test miserably; there are no 00s or 11s at all. The same reasoning can be extended to larger groups of digits, taking them three at a time, four at a time, and so on. By comparing groups of digits to the expected frequency of those groups, Pincus and Singer come up with the "approximate entropy" (ApEn) of the sequence—a measure of its randomness.

Pincus and Rudolf Kalman, a mathematician at the Swiss Federal Institute of Technology in Zurich, have now applied this tool to calculate the ApEn of various irrational numbers. Some, like $\sqrt{3}$ and $\sqrt{2}$, are "algebraic" numbers: They are the solution to a polynomial with a finite number of terms. Others are "transcendental," or nonalgebraic, numbers like π and e. Because algebraic numbers are in a sense simpler than transcendental numbers, Pincus—like most other mathematicians—expected that when written out in decimal form, they would be less random than the transcendentals. He was wrong.



"π is the most irregular," says Pincus. "But I was very surprised that e was not next in line." In fact, $\sqrt{2}$, an algebraic number, was more random than the transcendental number e. Mathematicians are still scratching their heads over this. "It's an interesting open question if the transcendental and algebraic numbers are mixed together" in order of randomness, says Kenneth Wachter, a mathematical statistician at the University of California, Berkeley.

Pincus and Singer think other researchers should be taking note of this new tool, which they have incorporated into a computer algorithm. Cryptographers often try to make messages look like random sequences by adding a sequence of binary digits that is nearly random—preserving just enough order for the message to be retrieved. Given enough data, ApEn could tell the difference, distinguishing encoded messages from random noise. "Theoretically, you can bust them all," says Pincus.

Experiment designers could exploit ApEn as well, says Singer. In scientific experiments such as drug trials, researchers randomize the test subjects to avoid bias. But randomizing by coin toss or luck of the draw can occasionally produce an orderly pattern—with all the women assigned to the control group and all the men to the study group, to take an extreme example. ApEn, however, gives researchers an objective yardstick of randomness, so they can decide when the draw is too orderly and redo it. "[ApEn] allows you to increase the power of testing," says Woodbury.

ApEn may also provide a quick and easy way to screen data for randomness. Geriatricians and endocrinologists at two veterans' hospitals in Virginia, for example, sent Pincus the data from a hormone-sampling experiment. "We looked at the degree of disorderliness of the secretion of testosterone and luteinizing hormone in men," says Thomas Mulligan, a geriatrician at the Hunter Holmes McGuire Veterans Affairs Medical Center in Richmond. Thanks to ApEn, Mulligan and his team found—and quantified—an effect of aging. "In older men, the disorderliness is markedly greater than in younger men," he says.

Pincus expects that his randomness test will uncover many more puzzles. "If I can bring nothing else to the party," he says, "I want to ask a different set of questions."

–Charles Seife

Charles Seife is a writer in Riverdale, New York.