though no one has proved that such a sweeping solution is impossible, theorists are fairly certain the NP-complete problems really are as hard as they seem to be. If so, the 3D Ising model is intractable, too.

To reach that dismaying conclusion, Istrail started by translating the Ising model into terms of graph theory. A mathematical graph is just a collection of points called "vertices," pairs of which are connected by "edges"—just as in the Ising model pairs of neighboring atoms are linked by the interactions between them. The edges may be weighted with numerical values. In the traveling salesman problem, for example, the weights are the distances between pairs of cities. For the Ising model, the weights describe the amount by which parallel or opposing magnetic moments of neighboring atoms increase or decrease the energy.

Computing the lowest energy state for the Ising model, it turns out, is equivalent to cutting the corresponding graph in two by plucking off the edges whose weights add up to the smallest possible number. For planar graphs—that is, graphs that can be drawn on a piece of paper without any of the edges crossing—that calculation is a relative breeze. But 3D lattices are inherently nonplanar, and that, Istrail recognized, is the key. He has shown that any nonplanar graph throws up a barrier of computational intractability.

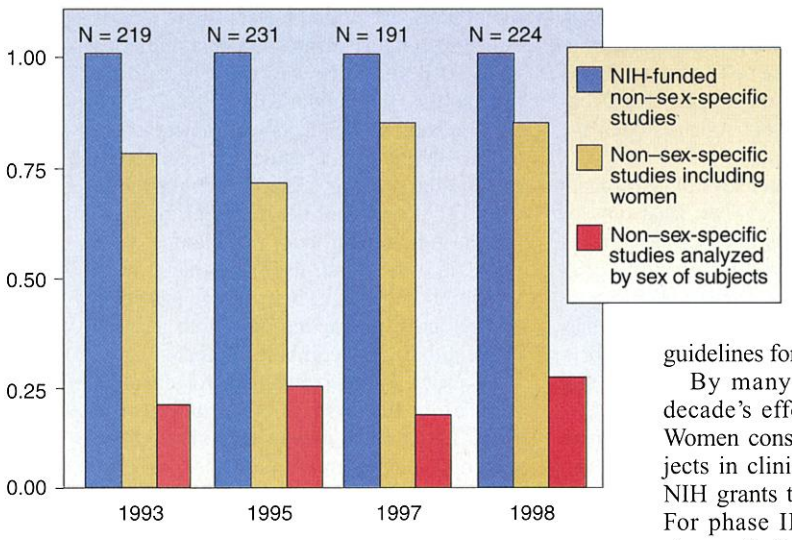
It might still be possible to find exact answers for some special cases of the Ising model, Istrail notes. In particular, the ferromagnetic case of the 3D Ising model may turn out to be simple enough to solve. Nevertheless, the overall message is clear. "We need a paradigm shift," Istrail says. "Instead of waiting for the mathematics to advance, we have to accept this impossibility." And the computational complexity of the Ising model could be just the tip of the iceberg. "There is something about this world that doesn't allow us to understand it." –BARRY CIPRA

WOMEN'S HEALTH

Reports See Progress, Problems, in Trials

Ten years after its scathing report on the National Institutes of Health's failure to include women in clinical research, the General Accounting Office (GAO) has concluded that the NIH is doing much better. Women are clearly taking part in clinical studies—in even greater numbers than men. And the amount of money devoted to diseases, such as breast cancer and depression, that disproportionately afflict women has risen steadily, outpacing increases in the NIH's overall budget. But NIH-supported researchers aren't always putting their data on women subjects to use.

The 2 May GAO report, amplified by a study in the June *Journal of Women's Health & Gender-Based Medicine*, shows that only a small fraction of publications based on NIH-funded research report a sex analysis of the data. "It's important to have women in clinical trials," says Phyllis Greenberger, head of the Society for Women's Health Research (SWHR) in Washington, D.C., "but not for the hell of it. The point is to do the gender analysis."



Room for improvement. Most publications in four major medical journals still don't report an analysis of the data by sex.

Such analyses are crucial, she and others note, because women respond differently to some drugs, carry a higher risk of certain diseases, and can present with disease symptoms different from men's. Without a comparison of the sexes, both men and women miss out on sensitive diagnostics and tailored treatments. The director of NIH's Office of Research on Women's Health, Vivian Pinn, acknowledges the importance of gender-based analyses but points out that NIH has no control over whether grantees carry out and report them. "We don't dictate editorial policies for journals," Pinn says.

Researchers had historically been reluctant to include women subjects, says molecular biologist Regina Vidaver of the SWHR, because they didn't want to deal with potential birth defects or variability in responses due to hormonal changes during the menstrual cycle. The problem was exacerbated in 1977 after the Food and Drug Administration barred women of childbearing age from participating in early clinical trials because of fear of birth defects. In 1985 the U.S. Public Health Service pointed out the obvious repercussion: The lack of information could seriously compromise health care for women. The NIH, in response, urged researchers to include women in their clinical studies.

Not much had changed by 1990, according to a GAO study, which along with outrage over studies showing the benefits of exercise and of aspirin for preventing stroke—conducted in men only—prompted NIH to act. By the end of the year, the NIH began to require the inclusion of women and minorities in research. In 1993, Congress passed the NIH Revitalization Act that established guidelines for accomplishing that.

By many measures, the past decade's efforts have succeeded. Women constitute 62% of all subjects in clinical studies funded by NIH grants to outside researchers. For phase III protocols, the last stage of clinical trials before a treatment is approved for widespread use, 75% of subjects are women. Even when sex-specific studies, such as those focusing on ovarian or prostate cancer, are excluded from the analysis, more than half the remaining subjects are women.

The GAO report cautions that NIH bookkeeping methods preclude a detailed analysis of funding for women's health research. But funding for some conditions that disproportionately affect women grew steadily between 1993 and 1999. Research expenditures went up 78% for osteoarthritis, 59% for breast cancer, and 73% for depression and mood disorders. For comparison, the overall NIH budget rose by 29% during that time. The NIH also collaborates with other federal agencies in the Women's Health Initiative, a study of 164,000 postmenopausal women that is examining the effects of hormone replacement therapy, diet, and vitamins on cardiovascular disease, breast cancer, and the bone-thinning disorder osteoporosis.

The problem, Vidaver points out, is that NIH-funded researchers still aren't breaking down their data by sex. Her team examined hundreds of NIH-funded, non–sex-specific studies published in *The New England Journal of Medicine*, *The Journal of the American Medical Association*, the *Journal of the National Cancer Institute*, and *Circulation* between 1993 and 1998. Of those, 80% included women. But only 25% to 30% of the studies with women subjects reported a gen-

SOURCE: *JOURNAL OF WOMEN'S HEALTH & GENDER-BASED MEDICINE*

der analysis, which may have been as brief as a statement that there were no significant sex differences. That share remained constant over the period, Vidaver adds.

NIH's Pinn says that the analysis is premature, because the studies would have been funded before the 1993 law was implemented. But Greenberger counters that the NIH began urging the inclusion of women starting in 1986, adding that "we thought at least we'd see a trend" toward more gender analyses.

The society isn't waiting for NIH to make things happen. On 25 May, it wrote to the editors of 32 leading journals, calling on them to revise publication guidelines to require a sex analysis. **–LAURA HELMUTH**

VACCINE DEVELOPMENT

Radical Steps Urged to Help Underserved

BETHESDA, MARYLAND—These are miraculous times for researchers working on vaccines for the world's major scourges. For years, their plea for more funding, political attention, and greater involvement from the pharmaceutical industry fell on deaf ears. But recently, their cause has been embraced by politicians around the world—indeed, President Clinton seems determined to make it part of his legacy—and industry leaders have promised to do what they can. Suddenly, anything seems possible.

So when a broad group of researchers, big-pharma CEOs, and public health experts met last week at Clinton's request to discuss the main obstacles on the road to new vaccines for AIDS, malaria, and tuberculosis,* meeting organizers urged them to think big. "Now is your chance, folks!" beamed Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), who said the ideas would help shape the Administration's future policy. The participants were happy to comply, with proposals that range from a 10- or 20-fold budget increase to a new, more flexible funding agency to circumvent the National Institutes of Health's (NIH's) bureaucracy. A few even proposed a crash effort akin to the Apollo program that put a man on the moon within a decade.

CREDIT: AP PHOTO/T. HADEBE

Unmet need. Malaria kills a million people a year, mostly in Africa, but no vaccine exists. Momentum is building to change that.

Epidemiologists say vaccines are the only practical way to cut the death toll from AIDS (currently estimated at 2.6 million annually), TB (which kills 1.5 million to 2 million), and malaria (more than a million). Doing so would also be a boon for development, economists point out: In Africa, especially, sickness and death take a huge toll on the economy.

Yet funding for most types of vaccine research has been hard to come by because the big killers overwhelmingly afflict the developing world. NIH currently spends a paltry $6.5 million a year to find a vaccine for TB and $25 million for malaria. (Vaccine studies for AIDS, which poses more of a threat to the U.S. population, will get an estimated $250 million this year.) Pharmaceutical companies have been reluctant to bet much of their R&D budgets on these vaccines, as expected returns are low, and developing countries don't always respect industry patents. For the same reasons, cash-starved small biotech companies have a hard time attracting venture capital.

To help break the pattern, Clinton proposed a Millennium Vaccine Initiative in January, which includes increased funding for NIH, a $50 million contribution to the Global Alliance for Vaccines and Immunization, and a $1 billion tax break on vaccine sales to stimulate industry investments. Several bills before Congress would do more or less the same, and some European countries are considering similar steps. The issue will also be on the agenda when leaders of the eight major industrial nations meet next month in Okinawa, Japan.

Not all of the proposals to come out of the NIH meeting, however, are likely to make it onto the table, at least in their current form. The malaria researchers, for instance, want the president to initiate an "aggressive malaria vaccine program" and raise funding to $500 million a year. The group also thinks the U.S. should agree to purchase $500 million a year worth of vaccines, if one gets developed, to guarantee that there is a market. The AIDS group pleaded for a 10-fold funding hike for vaccine studies in general, while the TB researchers suggested setting up something

* Vaccines for HIV/AIDS, Malaria and Tuberculosis: Addressing the Presidential Challenge, 22 to 23 May, at NIH.

ScienceScope

Vaccine Variation The National Institutes of Health (NIH) is restructuring its HIV vaccine research in a move designed to spark flagging efforts to combat the global AIDS epidemic. The agency recently abandoned its current two-pronged approach, which used separate networks of academic and clinical centers to run early-stage domestic and late-stage international vaccine trials. In its place, NIH is forming a single HIV Vaccine Trials Network, a system of nine U.S. academic centers. Most will be paired with clinics in countries suffering the brunt of AIDS deaths.

The shift is a response to criticism that the existing networks—the U.S.-based AIDS Vaccine Evaluation Group and the international HIV Network for Prevention Trials—lacked coordination. Critics also argued that scientific priorities were being set by NIH bureaucrats, not researchers. The new approach will move much of the administrative control and priority setting to a Core Operations Center run by Lawrence Corey of the Fred Hutchinson Cancer Research Center in Seattle, Washington.

The makeover isn't a sure bet to succeed, says Mark Mulligan, who runs one of the new network's centers at the University of Alabama, Birmingham. But, he adds, "when there's not success, the structure gets changed to try to stimulate some new vitality."

Family Quarrel Energy Secretary Bill Richardson moved quickly last week to break up an internal fight over the future of the world's largest laser. While publicly supportive of the National Ignition Facility (NIF) being built at California's Lawrence Livermore National Laboratory, some officials at New Mexico's Sandia and Los Alamos national laboratories have long privately attacked the project as ill conceived. And recent news that NIF is $1 billion over budget (*Science*, 5 May, p. 782) has only added to fears that Livermore may eat into its sister labs' budgets.

To prevent that, Sandia vice president Tom Hunter told the *Albuquerque Tribune* on 25 May that NIF should be downsized so that it will not "disrupt the investment needed" at the other labs. But Hunter's statement was "out of line," "the type of lab divisiveness which is extremely unhelpful," and "will be totally disregarded," Richardson promised in a statement. The discord, however, may raise questions in Congress, which will vote on NIF's budget later this year.

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