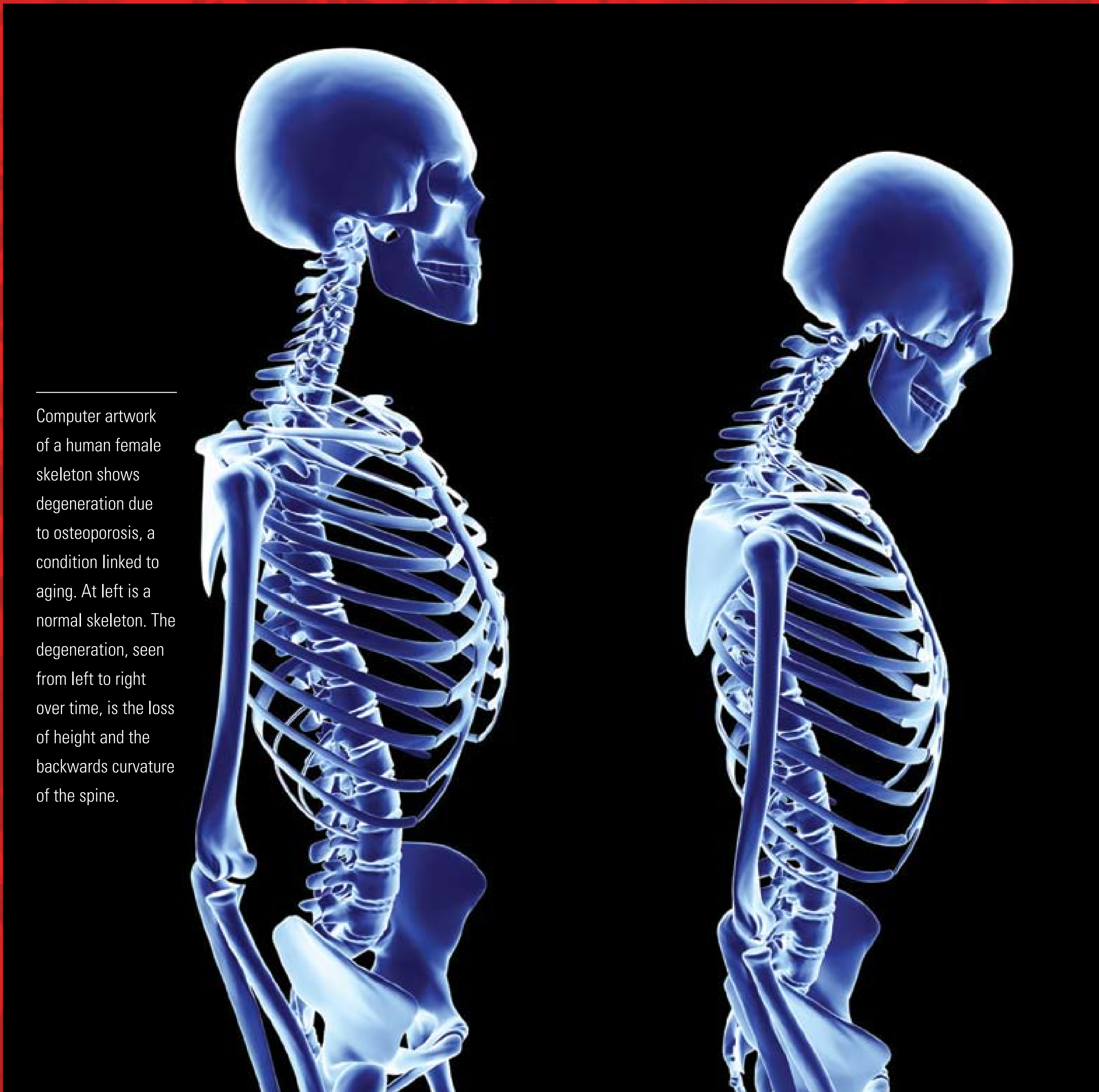

Computer artwork of a human female skeleton shows degeneration due to osteoporosis, a condition linked to aging. At left is a normal skeleton. The degeneration, seen from left to right over time, is the loss of height and the backwards curvature of the spine.

Toward a Theory of Aging

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Why are people born?
Why do they die?
And why do they spend so much time in between wearing digital watches?

—Hitchhiker's Guide to the Galaxy

By James Trefil

Santa Fe Institute scientists may not be able to help much with the first and last questions, but if a newly conceived initiative is successful, they may have quite a bit to say about the middle one. Starting with a planned workshop in March, the Institute will serve as the focal point for a major research effort devoted to the development of a comprehensive theory of aging.

The idea for this venture grows out of work done by President and Distinguished Research Professor Geoffrey West over the past decade. A theoretical physicist by training, West became interested in regularities that biologists had been finding when they looked at many different kinds of species in nature. From mice to elephants, quantities like metabolic rates and average lifetimes seem to scale in a predictable mathematical way. In 1932, for example, the Swiss biologist Max Kleiber made a graph in which he plotted the logarithm of the metabolic rate of organisms (essentially the rate at which the organism uses energy) against the logarithm of the organism's mass. The points fell on a straight line, as shown on the next page. Since then, scientists have found that the data for *all* organisms, from bacteria to whales, fall on the same kind of line. This law, which holds over an astonishing 20 orders of magnitude in mass, was known to be true, but for over half a century no one knew why. Scientists call such a relation a "power law," for reasons we'll explain in a moment.

There are other Kleiber-like regularities out there—regularities that remain unexplained. Andres Kriete, of Drexel University and the Coriell Institute for Medical Research—as well as a member of the nascent SFI collaboration—in a recent paper with Geoffrey West, summarizes previous findings that both growth rates of organisms and the rate of

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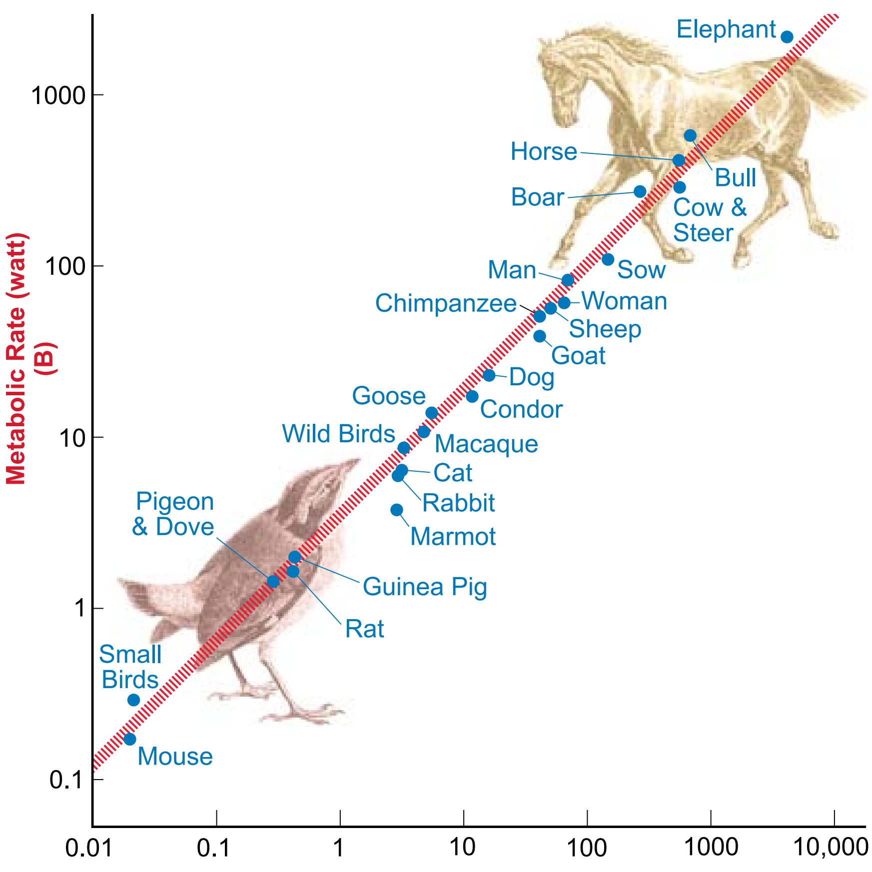
substitutions in their DNA, scale with the same power law as metabolism. In addition, average lifetimes scale as well, so that bigger animals live longer than small ones. Heart rate, on the other hand, goes in the opposite direction—the larger an animal is, the slower the rate, with the slowing obeying the same kind of power law as lifetimes. Interestingly enough, this leads to the conclusion that the number of heartbeats in the lifetime of any mammal is the same as the number in the lifetime of any other mammal, regardless of its size. A mouse lives a few years, but its heart beats fast, while a long-lived human has a correspondingly slower beat. Statistically speaking, we all get about a billion-and-a-half heartbeats.

To a physicist like West, the existence of regularities such as this suggests that there must be a deep law that governs the metabolism of all organisms—a law that transcends the details of the way individual species operate. In 1999, along with biologists J.H. Brown and B.J. Enquist, he showed that there was, in fact, a simple explanation for Kleiber's Law. Think about mammals as an example: As you go from mice to elephants, the main problem faced by the organism is to find a way to get nutrients to the increased number of cells. In mammals, this job is done by capillaries, the finest vessels in the circulatory system. Capillaries are basically just big enough to allow the passage of red blood cells, and since these cells are about the same size in all mammals, the size of the capillaries doesn't change much from one animal to the next. The increased quota of blood thus has to be supplied by making more capillaries, and what West and his



Kleiber's Law $B \sim M^{3/4}$ Body Mass (kg) (M)

JAN UNDERWOOD/INFORMATION ILLUSTRATED

colleagues showed was that the most efficient way to do this is to have the capillaries be the terminal units of what mathematicians call a fractal network.

"Fractal" is a mathematical term that refers to a network that looks the same no matter the scale of the observation. In a fractal network, the pattern of arteries will look like the pattern of intermediate blood vessels, which in turn, will look like the pattern of capillaries. The researchers also showed that a necessary consequence of this fact is that the relation between energy usage and mass will follow exactly the power law seen in the graph. With this work, a 70-year biological mystery was solved, and the explanation was seen to be a consequence of a deep common property of living things.

Scientists refer to this sort of data as a power law because it says that the amount of energy an organism uses over its lifetime depends on its mass raised to some power. Many quantities of biological interest (including metabolic rate and lifetimes) seem to depend on power laws. In the figure, the metabolic rate depends on the mass raised to the ¾ power.

Since power laws seem to be ubiquitous in biology, it is important to ask how those powers are to be interpreted. Usually, when we see a number raised to a power, we understand the symbols to say "multiply the bottom number by itself as many times as the number that appears in the power." Thus, 3^2 would be interpreted as three multiplied by itself, which would be 3x3 or the number 9. If the power is a fraction like ¼, we ask, "What number, when multiplied by itself four times, will give us the number being raised to a power?" For example, if we multiply 3 by itself four times (3x3x3x3) we get 81, a fact that we would represent by saying that $81^{1/4}$ is 3 or, alternatively, that 3 is the fourth root of 81. Finally, when we see a ¾ in the exponent, we are being told to (a) find the fourth root and (b) multiply that root by itself 3 times. Thus, $81^{3/4}$ is just 3x3x3 = 27.

A comprehensive theory of aging might unify the aging of biological organisms with that of airplanes, bridges, cities, and even cars.

The larger sequoias on the planet are believed to be some of the oldest living things—existing a few thousand years.

To give a concrete example of how a power law works, the fact that metabolism scales as the ¾ power means that when we compare a 5-pound animal (a small cat) to an animal that is 81 times as heavy (a large calf or small cow), the energy requirement of the calf will only be 27 times that of the cat, not 81 times. One way of looking at this result is to say that the cells of a calf require only a third as much energy to operate as the cells of a cat.

Hidden in these regularities, SFI scientists believe, is the explanation of why biological organisms grow old and die. "I would like to understand," West says, "why humans live about a hundred years, and not a few months or a few centuries." His approach to the problem, involving the search for grand overarching regularities between organisms, can be thought of as a sort of "top down" method.

There is, of course, another way to come at the problem, and that is to start with genes and cells and try to understand how they program both obsolescence and death. This could be characterized as a "bottom up" approach. Many of the scientists in the workshop have long histories of work in this sort of biology.

SFI External Faculty Professor Walter Fontana, now at Harvard, points out that virtually all of the research done on aging is aimed at dealing with its clinical consequences, rather than with its deep causes. "Our ambition," he says, "is to understand the nature of aging and follow its roots in molecular biology, organization and network theory, and evolution." He points out that the development of a serious quantitative theory of aging and mortality could have important medical consequences, and perhaps allow us to increase both human longevity and health. At the moment his laboratory at Harvard is engaged in an attempt to obtain a massive, fine-grained data base on normal aging in a microscopic worm known as *C. elegans*. "The lab will look at the process of aging," says Fontana, "and not just at lifespans."

Eugenia Wang of the University of Louisville Medical School, who has done significant work on the genetic mechanisms involved in healthy aging, will also be involved in organizing the SFI conference and guiding future research. Her work has included investigations of the molecular mechanisms that prevent certain human cells from dividing forever *in vitro,* a search for genes responsible for defenses against oxidation in long-lived mice, and using cells from long-lived mice to identify unique genetic "fingerprints" that go with healthy aging.

Using both "top down" and "bottom up" approaches, and perhaps providing the vital link between them, will be the main focus of the work in Andres Kriete's laboratory. Kriete stresses that many people have studied the aging process (indeed, he found a paper that listed no fewer than 300 different theories of aging!). Nevertheless, a theory of normal healthy aging remains outside our grasp. "We really don't have a deep understanding of why we age," he says, "nor why older cells are more susceptible to disease, which is a rising concern for health care in post-industrial graying societies."

Talking to him, you get a picture of a living organism as a complex system of networks linking genes, proteins, metabolism, cell signaling, and all of the other chemical processes of life. His goal, part wet lab and part computer modeling, is to look at cells and organs from the standpoint of the systems engineer, trying to understand the complex feedback system that makes them operate as they do. He refers, only half-jokingly, to his work as simulating life "*in silico,*" as opposed to the usual laboratory *in vitro* process.

Right now, the development of a comprehensive theory of aging is still basically a gleam in the eye of SFI researchers. The hope is that the upcoming workshop will develop a framework to guide future research. In the end, the role of SFI will be to focus scientific attention on an extremely deep and important topic—biological aging—that looks to be ripe for exploration.

But don't expect things to stop there. When asked about his long-range plans, West got a far-away look in his eye. "I wonder," he said, "whether there might not be a general theory of aging. It's not only biological systems that get old—what about bridges, cars, planets? Someday I'd like to get people who know about these things to talk to each other here in Santa Fe."

Now *that* would be a conversation worth listening to! ◀

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