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NEWS

Aging, in Theory: A Personal Pursuit

Do body system redundancies hold the key?

By A.J.S. Rayl

Courtesy of Natalia Gavrilova

Natalia Gavrilova and Leonid Gavrilov

Every human being has asked at least once, "Why do we have to age and die?" Leonid Gavrilov and Natalia Tuchnina (now Gavrilova), decide to really pursue the answer. They first met at a conference in 1975 when they were both fourth-year chemistry students at Moscow State University. Then, seven days after their first date, a smitten Gavrilov proposed, promising he would discover how to stop aging if she would marry him.

The couple went on a quest to find a general theory that could explain what aging is and why and how it happens. After more than 20 years of "sustained intellectual effort"—first at Moscow State University in Russia and recently at the University of Chicago's Center of Aging—they produced a "fundamental reliability theory of aging and longevity."[1] It is, they suggest, "a promising approach" for developing a comprehensive theory that integrates biological knowledge with systems repair principles and mathematical methods.

Since its publication, the Gavrilovs' paper has sparked discussion among those in theoretical biology and others interested in the evolution of aging, garnering comments ranging from "astonishing" to "a useful contribution," as well as "incredibly clever," "robust," "original," "thought-provoking," and "a pointer in the direction of how to understand the aging process."

The Theory

In essence, the Gavrilovs have taken general reliability theory from mathematics[2] and engineering,[3] where it is used to assess inanimate systems failure, and applied it to biological systems. Reliability theory, they write, "allows researchers to predict the age-related failure kinetics for a system of given architecture (reliability structure) and given reliability of its components." It also predicts that even systems composed entirely of non-aging elements, with a constant failure rate, will deteriorate and fail more often with age "if these systems are redundant in irreplaceable elements."

To adapt general reliability theory to biological systems and make it work, however, the Gavrilovs had to make a critical change in the initial assumption. "Reliability theory works with biological systems on one condition—that you assume that when we are born, we have a huge load of initial damage," says Gavrilov. An unwritten but prevalent assumption is that all living systems also begin more or less in an optimal state, created from perfect or near-perfect parts, he says, "but when you review the biological systems data, you see that this just cannot be."

From the point of conception, the cells from which biological systems are built are infused with faults and defective elements that would kill primitive organisms, the Gavrilovs posit. "Nobody can test the quality of each particular cell, so our systems are formed by self-assembly as they are and can be loaded with significant initial damage," explains Gavrilov. But humans and other complex organisms have "built-in redundancies," which help them survive random, destructive assaults, ensuring increased reliability and life span. However, these redundancies also ensure organisms will age and die. Hence, aging, according to this theory, is "a direct consequence or trade-off of systems redundancy exhaustion."

As defects accumulate, the redundancy in the number of elements eventually disappears, says Gavrilov, and the organism degenerates into a system with no redundancy. "At some point, one of those hits causes a critical system without a back-up redundancy to fail and we die." The simplest organisms that lack the redundancies built into more complex organisms do not age, they conclude, but "just die when damaged."

"The novelty of our approach," says Gavrilova, "is that we explain why living organisms die according to the Gompertz law," by taking into account the initial flaws or defects in newly formed systems. Named for British actuary Benjamin Gompertz, the Gompertz law holds that mortality rates increase exponentially with age in many adult species. The problem with Gompertz is that it does not account for why age-related increase in mortality rates vanish at older ages. The reliability theory of aging, they claim, provides the explanation.

Curve Shape

"What the Gavrilovs have shown in a very clean mathematical model is that the assumption you make about how many of these defects there are initially has a tremendous amount do with what a population mortality curve is going to look

like," says gerontologist F. Eugene Yates, professor emeritus at the University of California, Los Angeles. "They have shown that the shape of the curves comes out of the key assumption about initial defects and redundancy—those two assumptions and the notion of random hits. The beauty of their model is that just by tuning these three simple elements, the theory can fit any of the mortality curves that we have, including those of machines, the Weibullian ones."

The Gavrilovs first proposed the idea of applying reliability theory to aging and longevity more than 23 years ago. "In 1978, we published the two very first scientific articles suggesting the *reliability theory* idea in general," says Gavrilov.[4,5] As a result of those publications, they received permission from their scientific advisers at the Moscow State University in Russia to continue their research efforts independently.

In 1991, they published a further developed version of the theory in *The Biology of Life Span: A Quantitative Approach*. The book was well received, and was cited by Encyclopedia Britannica as a recommended reference on longevity studies. That work helped open the doors for them to find employment and immigrate to the United States in 1997—"the best place to be for researching aging and longevity," says Gavrilov.

At the University of Chicago's Center for Aging, the Gavrilovs secured a grant from the National Institute on Aging. Then in 2000, they accepted S. Michal Jazwinsky's invitation to contribute to the *Journal of Theoretical Biology*'s special issue on aging theories and "completed the development of the theory, at least as a theoretical concept," Gavrilov says.

"This theory provides a very flexible theoretical framework, a kind of scientific language and methodology, which can easily accommodate specific biological knowledge," says Gavrilov. "It does not introduce any heavy assumptions. Rather it helps to identify the research priorities and to organize the accumulated facts on aging in a manageable format."

"The idea that the redundancy systems that keep living organisms alive are also the systems that ensure we age is consistent with natural selection, because it keeps us alive and functioning at a high-enough level long enough to reproduce within the adaptive space of our body plan in ecology—and that's what natural selection is after," says Marc Tatar, evolutionary biologist, Brown University. "The Gavrilovs' theory addresses with some pretty clever models what is really the kind of central problem with biodemography—which is how to relate individual biology to these patterns we see in the population."

"It does provide people who are thinking about the evolution of aging with some mathematical tools from which they can frame questions, from which they can begin to develop models that in some realistic way generate relationships among organisms at different ages or impose dynamics that are common among complicated systems, to generate and impose constraints that were previously somewhat ad hoc ¼ random assumptions," offers mathematically trained biologist Scott Pletcher, assistant professor, Baylor College of Medicine.

Gerontologist Yates views the Gavrilovs' theory in a bigger-picture perspective.

"In my observations of theorizing, and in my experience doing theoretical biology, I have found theories that have a lot of range lack precision, and theories that are very mechanistic have precision but not range. The Gavrilovs' model has both range and precision to a degree that is astonishing," he says.

Beyond Genes and Free Radicals

"They have gone beyond pinning it on any particular gene, and beyond pinning it on free radicals and those sorts of mechanisms, and they're taking a statistical view, saying if this is the overall design picture you're working with then you're going to get these mortality curves and the theory works with transistors, drosophilae, and humans," Yates continues. "And they allow the possibility that whatever the defects—even if they were all cleaned out before you reach maturity, the model would still hold. I went through the arithmetic and it really does, which is all the more remarkable. Still, the theory requires, above all, the idea of redundancy and they still require polymorphisms and heterogeneity and random hits as their statistical mechanism for generating these beautiful population dynamics."

Therein will be the rub for biologists. The notion that humans and other organisms are chock full of defects from the get-go will be a difficult idea for many biologists and reductionists to embrace. And, the issue of mechanism will cause biologists to balk, says Pletcher. "I appreciate the Gavrilovs' theory for its approach and I respect the work, but I don't believe that it biologically explains aging. It's just not sort of particular enough in mechanism to capture the variation in biological organisms. I don't think that organisms are composed of underlying, redundant, non-aging components—for various reasons," opines Pletcher, who is finishing postdoc work on the genetics of aging at University College London. "But I do think it's a useful contribution, because it really outlines what we expect to see from a wide range of complicated systems. Therefore, I see this more as a framework that can help biologists better model and better work toward developing realistic models of aging, than I think of it as a truly biological mechanistic explanation for why organisms age." Compositional heterogeneity, for example, is another alternative theory, Pletcher points out, "that offers a very simple explanation to explain mortality deceleration, as well as mortality convergence, two of the things that the Gavrilovs bring out here."

The Gavrilovs welcome dialogue and interaction with other scientists. As they see it, there are "promising opportunities" for merging the reliability and evolutionary theories, such as, offers Gavrilova, "studying the whole mortality curve to see how it evolved over time … and studying how different species managed to increase and evolve their reliability."

"Further analyses using the reliability approach may help to test hypotheses on the mechanisms of gene action in long-lived humans," she adds. "Our preliminary analyses [not yet published] demonstrated that the progeny of long-lived parents may have higher redundancy in important elements [cells] compared to the progeny of short-lived parents. This may suggest that 'longevity genes,' or genes that ensure long life, may act early in life, increasing the redundancy of the organs in vital elements [cells]."

"If this theory does turn out to be true—and it seems to be moving toward testability—then it might help us perhaps start making sense of this," says Tatar. "A potentially very exciting implication of the work is that it might [direct researchers] to study development." While people have proposed the critical importance of the developmental experience before, this theory goes the extra mile, saying, basically, that the trajectory of an individual's aging depends on developmental experiences. "That," says Tatar, "is a different magnitude of relationship between the adult and juvenile experience."

"This idea does change the emphasis in life extension intervention and health issues," says Gavrilov. "It emphasizes the importance of early life conditions, which may determine the level [load] of initial damage, and, therefore, the health outcomes in later life [including longevity].[6,7] The message of reliability theory is that we consider the initial damage of our organism and start earlier to prevent rapid aging," adds Gavrilova.

"The most important implication [of this theory] is that the intellectual Berlin Wall between the gerontologists and the reliability experts is demolished—at least we hope so," says Gavrilov. "Now when the intellectual apartheid between the two large groups of scientists ends, the biological aging research may be greatly accelerated and facilitated by using the rich experience and knowledge accumulated in reliability engineering, as well as in the mathematical reliability theory. There is a remarkable resemblance between aging of biological species and technical devices (in terms of age-related failure kinetics), which literally invites for broad large-scale interdisciplinary collaborative research efforts."

In about five years, gerontological research could be transformed into a new powerful bioreliability approach, Gavrilov boldly predicts, "that may allow the human species to postpone and perhaps even to prevent some of the unpleasant manifestations of aging." Neither Tatar nor Pletcher is willing to make that leap. "It's another set of mathematical tools," says Pletcher.

Convinced they are on the right track, the Gavrilovs plan to continue work on their theory. In addition, they are now studying longevity inheritance and the effects of early-life conditions on human mortality later in life, among other things. They are determined to find the answer. "My promise to Natalia," chuckles Gavrilov, "is still not fulfilled."

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