Medical Xpress

Associations between aging and the loss of the ability to recover from stress

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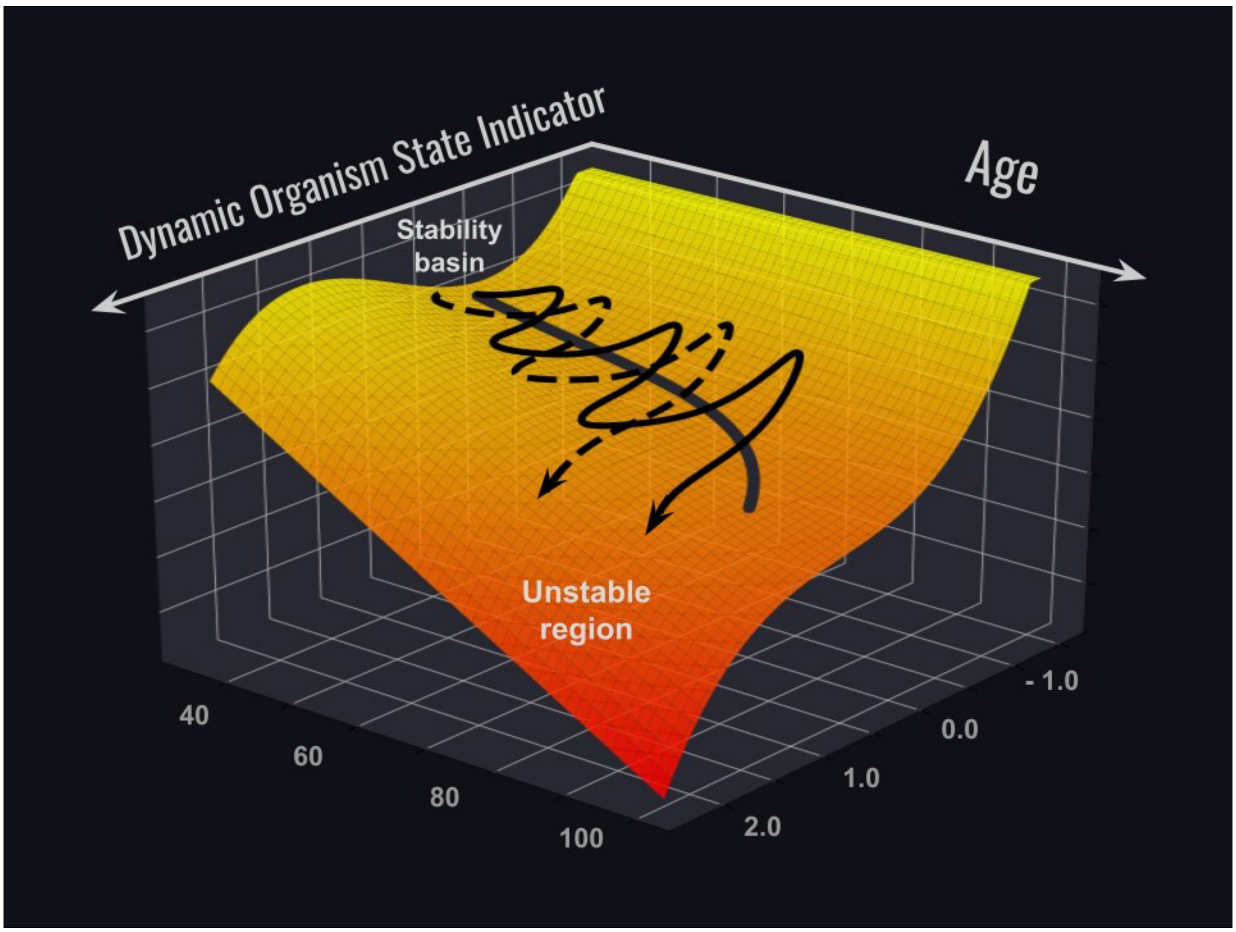

Schematic illustration of loss of resilience along aging trajectories. Credit: Gero

The research team of Gero, a Singapore-based biotech company in collaboration with Roswell Park Comprehensive Cancer Center in Buffalo NY, has presented a study in *Nature Communications* on associations between aging and the loss of the ability to recover from stresses.

Recently, scientists have reported the first promising examples of biological age reversal by experimental interventions. Indeed, many biological clock types properly predict more years of life for those who choose healthy lifestyles or quit unhealthy ones, such as smoking. Still unknown is how quickly biological age is changing over time for the same individual, and distinguishing between the transient fluctuations and the genuine bioage change trend.

The emergence of big biomedical data involving multiple measurements from the same subjects brings about a whole range of novel opportunities and practical tools to understand and quantify the aging process in humans. A team of experts in biology and biophysics presented results of a detailed analysis of dynamic properties of the fluctuations of physiological indices along individual aging trajectories.

Healthy human subjects turned out to be very resilient, whereas the loss of resilience turned out to be related to chronic diseases and elevated all-cause mortality risks. The rate of recovery to the equilibrium baseline level after stresses was found to deteriorate with age. Accordingly, the time needed to recover was getting longer and longer. Being around two weeks for 40-year-old healthy adults, the recovery time stretched to six weeks for 80-year-olds on average in the population. This finding was confirmed in two datasets based on two kinds of biological measurements—blood test parameters and physical activity levels recorded by wearable devices.

"Calculation of resilience based on physical activity data streams has been implemented in the GeroSense iPhone app and made available for the research community via web-based API," said the first author of the study, Tim Pyrkov, head of the mHealth project at Gero.

If the trend holds at later ages, the extrapolation shows a complete loss of human body resilience, that is the ability to recover, at some age around 120 to 150 years. The reduced resilience was observed even in individuals not suffering from major chronic disease and led to the increase in the range of the fluctuations of physiological indices. As we age, more time is required to recover after a perturbation, and on average, we spend less and less time close to the optimal physiological state.

The predicted loss of resilience even in the healthiest, most successfully aging individuals, might explain why we do not see an evidential increase of the maximum lifespan, while the average lifespan was steadily growing over recent decades. The divergent fluctuations of physiological indices may mean that no intervention that does not affect the decline in resilience may effectively increase the maximum lifespan and hence may only lead to an incremental increase in human longevity.

Aging in humans is a complex and multi-stage process. It would, therefore, be difficult to compress the aging process into a single number, such as biological age. Gero's work shows that longitudinal studies open a whole new window on the aging process and produce independent biomarkers of human aging, suitable for applications in geroscience and future clinical trials of anti-aging interventions.

"Aging in humans exhibits universal features common to complex systems operating on the brink of disintegration. This work is a demonstration of how concepts borrowed from physical sciences can be used in biology to probe different aspects of senescence and frailty to produce strong interventions against aging," says Peter Fedichev, co-founder and CEO of Gero.

Accordingly, no strong life extension is possible by preventing or curing diseases without interception of the aging process, the root cause of the underlying loss of resilience. We do not foresee any laws of nature prohibiting such an intervention. Therefore, the aging model presented in this work may guide the development of life-extending therapies with the strongest possible effects on healthspan.

"This work by the Gero team shows that longitudinal studies provide novel possibilities for understanding the aging process and systematic identification of biomarkers of human aging in large biomedical data. The research will help to understand the limits of longevity and future anti-aging interventions. What's even more important, the study may help to bridge the rising gap between the health- and life-span, which continues to widen in most developing countries," says Brian Kennedy, distinguished professor of biochemistry and physiology at National University Singapore.

"This work, in my opinion, is a conceptual breakthrough, because it determines and separates the roles of fundamental factors in human longevity—aging, defined as progressive loss of resilience, and age-related diseases, as 'executors of death' following the loss of resilience. It explains why even most effective prevention and treatment of age-related diseases could only improve the average but not the maximal lifespan unless true antiaging therapies have been developed," says prof. Andrei Gudkov, Ph.D., sr. vice president and chair of the Department of Cell Stress Biology at Roswell Park Comprehensive Cancer Center, a co-author of this work and a co-founder of Genome Protection, Inc., a biotech company that is focused on the development of antiaging therapies.

"The investigation shows that recovery rate is an important signature of aging that can guide the development of drugs to slow the process and extend healthspan," commented David Sinclair, Harvard Medical School professor of genetics.

"The research from Gero surprisingly comes to a similar quantification of human resilience—a proposed biomarker of aging—based on two very different kinds of data: blood test parameters and physical activity levels recorded by wearable devices. I'm very excited to see how Person-generated Health Data, including data from commercial wearables, can help create individual, longitudinal profiles of health that will be instrumental to shed light on lifetime-scale health phenomena, such as aging," said Luca Foschini, co-founder and chief data scientist at Evidation Health.

Two aging markers

The authors characterized the dynamics of physiological parameters on time scales of human lifespan by a minimum set of two parameters. The first is an instant value, often referred to as the biological age, and is exemplified in this work by the Dynamic Organism State Index (DOSI). The quantity is associated with stresses, lifestyles and chronic diseases and can be computed from a standard blood test.

The other parameter—the resilience—is new and reflects the dynamic properties of the organism state fluctuations: it informs how quickly the DOSI value gets back to the norm in response to stresses.

When does aging start?

Age-related changes in physiological parameters start from birth. However, various parameters change in different ways at different stages of life, see, e.g., a previous work by the same authors published in *Aging US* in 2018).

The data from the *Nature Communications* work shows that there is a good differentiation between the growth phase (mostly complete by the age of 30 and following the universal growth theory by Geoffrey West and aging. At 40+ years, aging manifests itself as a slow (linear, sub-exponential) deviation of physiological indices from their reference values.

How often should one measure biological age?

Physiological parameters are naturally subject to fluctuations around some equilibrium level. Glucose levels rise and drop after having a meal, the number of sleeping hours is slightly different each day. Yet, one can collect a longitudinal dataset, that is a series of such measurements for the same person, and observe that the average levels are different between individuals. Resilience also requires repeated measurements, since one needs to know exactly when recovery was achieved to calculate the resilience.

Importantly, resilience also provides a convenient guide on how often repeated measurements should be taken. As a rule of thumb, the period of observation required for the robust bioage determination should comprise multiple stress and recovery events. For the most healthy individuals such an observation period would amount to several months and should increase with age. During that time, a robust bioage determination would require several data points per recovery time, that is ideally one measurement in a few days.

Wearable technology comes into play

In 2021, the only practical way to achieve a high (once-per-day or better) sampling rate is to use mobile/wearable sensor data.

In another paper, the authors have focused on wearable/mobile sensor data. They have built a wearable DOSI, which they called GeroSense, and reported its validation tests in Pyrkov et al. Aging (Albany NY) 13.6 (2021): 7900. GeroSense can be used to compute resilience. Population study shows that the number of individuals showing signs of the loss of resilience increases exponentially with age and doubles every eight years at a rate matching that of the Gompertz mortality law (the observation by B. Gompertz from 1827, who observed for the first time that the all-cause mortality rate doubles every eight years).

More information: Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23014-1 , www.nature.com/articles/s41467-021-23014-1

Provided by Gero