Aging as a Process of Deficit Accumulation: Its Utility and Origin

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Abstract
Individuals of the same age differ greatly with respect to their health status and life span. We have suggested that the health status of individuals can be represented by the number of health deficits that they accumulate during their life. We have suggested that this can be measured by a fitness-frailty index (or just a frailty index), which is the ratio of the deficits present in a person to the total number of deficits considered (e.g. available in a given database or experimental procedure). Further, we have proposed that the frailty index represents the biological age of the individual, and suggested an algorithm for its estimation. In investigations by many groups, the frailty index has shown reproducible properties such as: age-specific, nonlinear increase, higher values in women, strong association with mortality and other adverse outcomes, and universal limit to its increase. At the level of individual, the frailty index shows complex stochastic dynamics, reflecting both stochasticity of the environment and the ability to recover from various illnesses. Most recently, we have proposed that the origin of deficit accumulation lies in the interaction between the environment, the organism and its ability to recover. We apply a stochastic dynamics framework to illustrate that the average recovery time increases with age, mimicking the age-associated increase in deficit accumulation.

People age at different rates. Even so, everyone ages, and to an end: the mortality rate is characteristic, rising exponentially with age. This is the case even though not everyone dies from the same illness. Despite the remarkable progress that has been made by studying how each individual illness arises, and how each contributes to mortality, there remains a strong rationale to consider illnesses in their totality. Multiple aging processes can be studied with profit by employing a systems biology approach [1–3]. Mathematical modeling, at the heart of systems biology, allows the useful insights and apparatus developed in other scientific fields to be brought to bear on understanding
ageing. Here, we discuss how ageing can be understood as a process of deficit accumulation, which likely scales from the molecular level to produce macroscopically visible deficits [4]. After briefly reviewing major facts about the deficit accumulation approach to quantifying aging, we discuss a very general stochastic framework to explain how the origin of deficit accumulation stems from the interaction between the environment and the organism. Because the deficit accumulation approach to aging has many reproducible characteristics, we suggest that the biological age of an individual can be estimated in relation to how many deficits they have accumulated, compared with how many are accumulated, on average at their chronological age. We also discuss how this approach can be applicable in understanding differences in health status not only in individuals, but also between countries with differing socioeconomic status.

The Accumulation of Deficits as a Proxy Measure of Aging

However aging is defined, it should be measured. The simplest measure of aging is chronological age, not least because mortality rate increases exponentially with age, in accordance with the Gompertz law of mortality [5]. Even so, the mortality rate is a population characteristic, and its application to individuals is quite limited. That is because individuals at the same age differ from each other not only because of differences in their genetic profile, but also reflecting how the external environment affects the multiple biological pathways of damage control and repair. This variability in damage potential and control leads to variable changes in physiological functions, loss of homeostatic regulation, shrinkage of the homeodynamic space, and flexibility, and vulnerability to stressors [6]. In these ways, subcellular processes scale up to affect life expectancy and health span. This variability in the vulnerability to adverse outcomes (worsening health, mortality) is often referred to as frailty [7, 8]. In short, different people age at different rates, making the idea of biological age (which is intrinsically individual) quite attractive; even so, how to estimate biological age remains a matter of dispute. Despite great individual variability in how aging manifests, there is a universal characteristic – the number of health problems increases with age [9, 10]. In 2001, we suggested a method for appraising health status in older adults [9] later extended to younger ages [11]. We demonstrated how to use a simple count of deficits (symptoms, signs, functional impairment, and laboratory abnormalities), and in order to make the deficit count comparable across different datasets, we defined the frailty index as a ratio of the number of deficits that individuals accumulated to the total number of deficits available in the database. Remarkably, from this simple measure, it is possible to predict mortality and other adverse outcomes [7]. Since then, our group and many others have investigated the properties of the frailty index in multiple databases (~300,000 cases) from different countries including Canada, the United States, Australia, Mexico, China and most European countries. Together, the results
are similar across databases that use different data collection methods (e.g. clinical vs. self-reported data), different designs (e.g. cross-sectional vs. longitudinal) and different numbers of variables. Specifically, the frailty index robustly shows that: (a) the average rate of deficit accumulation has a narrow range (in community-dwelling people between 2.5 and 4% per year, on a log scale) [7]; (b) men have lower mean frailty index values than do women of the same age; (c) women show better mean survival than do men who have the same frailty index value; (d) there is an empirically determined limit to the frailty index value close to 0.7; (e) the frailty index is a strong predictor of adverse outcomes; (f) the frailty index outperforms chronological age in all survival models.

The statistical distribution of the frailty index for older adults shows typically skewed pattern (fitted by the gamma density function). Of some note, people from institutions or with severe illnesses show bell-shaped patterns approximated by the normal distribution [9]. The frailty index can be regarded as a *clinical state variable*, in that it characterizes the whole health of individuals [7] and validly classifies risk across a wide range of people. In short, the frailty index, although nonspecific (but note, aging itself is *nonspecific*), is a very sensitive measure of health in older adults.

Remarkably, the values and age trajectories of frailty indices are not sensitive to the exact nature of the variables that might be included in the frailty index. Indeed, when some dozens or more variables are included, individual variables can be selected at random and still yield comparable results [12]. For this reason, and usefully for epidemiological inquires, the frailty index can be created from virtually any set of health-related variables if they cover a range of systems, are associated with adverse outcomes and increase with age [13]. The reason that the frailty index characterizes individuals’ health independently of the variables it comprises can be understood if we recognize that the variables (health deficits) are not independent, even though this typically is assumed in the various risk factor models. Indeed, whatever statistical techniques might be employed to suggest otherwise, in any pragmatic sense the deficits are predominantly interdependent; each of them is linked with many others, i.e. each of them contains information about many others [9, 14].

One property of the frailty index is of considerable practical and theoretical interest. Each new deficit decreases the probability of surviving. There is an empirical limit to the frailty index around 0.7, beyond which further deficit accumulation is incompatible with life independently on their age [15]. A frailty index can also be constructed from clinical data using a Comprehensive Geriatric Assessment (CGA) from the items available in typical CGA forms [14]. This so-called FI-CGA has the usual properties of other versions of the frailty index – i.e. it is correlated with age, shows a skewed distribution, is higher in women, and correlates with several adverse outcomes, including institutionalization and health care use. It could aid clinical decision-making by indicating the *degree of frailty*, and thus the likelihood of an adverse outcome.
Individual Frailty Trajectories: Stochastic Patterns

On average, health tends to decline with age, but in individuals, including older adults, health status can improve. In confirmation of such behavior, we have found that the individual values of frailty index do not monotonically increase over time; their changes are highly dynamic such that individuals may show significant change from a higher frailty index value (higher number of deficits) to a lower value reflecting a possibility of health improvement [14, 16]. This is illustrated in figure 1A, where individual courses typically show highly irregular patterns, including a few cases of ‘big jumps’ against a background of relatively small changes. Individual trajectories showing irregular behavior mark a stochastic process of changes in frailty states in relation to aging. Although highly irregular at the level of individuals, the process is nevertheless summarizable at a group level (fig. 1B). To reflect the complex nature of these changes, we introduced a stochastic model of health transitions between two fixed time points [16].

According to that model, the probability of transition from $n$ to $k$ deficits for the fixed time interval can be approximated by the following equation [16]:

$$P_{nk} = \frac{\rho_n^k}{k!} \exp(-\rho_n) (1 - P_{nd}).$$

(1)

**Fig. 1.** A Examples of individual trajectories of the deficit count in 12 randomly selected participants of the NPHS. Individual trajectories are represented by dots connected by dashed lines. The age-specific deficit count (the average cross-sectional trajectory) is shown by the dashed line. Of note, the values of the individual numbers of deficits were changed to satisfy Statistics Canada privacy requirements, but the patterns have been preserved. From Mitnitski et al. [30]. B The probability of transition (y-axis) from a given deficit state $n$ (shown in each subplot cell) to $k$ deficits (x-axis). Circles represent observed transitions between two consecutive cycles. The lines show the model’s fit according to equation 1. The solid line is for 2-year transitions. The data are truncated at 12 deficits for presentation; fewer than 5% of people show 12 or more deficits. From Mitnitski et al. [31].
where \( P_{nd} \) is the probability of death and \( \rho_n \) is the Poisson mean which is state, \( n \), dependent. It is usually well represented by the linear function on \( n \): \( \rho_n = \beta_0 + \beta_1 n \), and the probability of death is well represented by the logistic function, \( \text{logit}(P_{nd}) = \alpha_0 + \alpha_1 n \).

In many settings and with many different measures, this model fits the observed data with very high precision as can also be seen in figure 1B, with the goodness of fit typically accounting for more than 90% of ‘explained’ variability. The major results are: (a) the model allows changes in health to be represented in all directions (including worsening and improvement) and at any degree (both gradual and in ‘jumps’); (b) the model considers these changes and death simultaneously as competing events; (c) the model has a few interpretable parameters that depend on baseline conditions (i.e. the number of deficits at baseline); (d) the model is applicable not only to general health status (represented by the number of deficits) but also to other functions such as cognition. Note that the model illustrates dynamic aspects of how aging occurs through the accumulation of deficits; dynamics arise because of the possibility of repair and recuperation. Note that there is often fluctuation, and that changes in frailty status occur in both directions, i.e. even though, on average, decline predominates, an important proportion of people experience other trajectories.

As noted, an individual’s likelihood of changing his/her health status is largely conditioned by his/her health at baseline (i.e. at the current evaluation). Most transitions, in either direction, are gradual, so that going from having no deficits to having many deficits, for example, is not common (and same for vice versa). From both clinical and public health standpoints, it is important to note two factors. First, this is a probabilistic model: for any individual, the model shows the chance of a series of outcomes, not simply the relative risk of a given outcome. Second, and relatedly, the model allows for the possibility of the real world phenomenon and clinical/public health goal of improvement. In other words, the model shows not just deficit accumulation, but deficit diminution (i.e. improvement).

**Health Changes in the Fittest (The Zero State of Frailty)**

The stochastic transition model considered above has an interesting characteristic that has potential in describing population health. Among the four parameters in equation 1, two (\( \alpha_0 \) and \( \beta_0 \)) characterize those people who had no deficits at baseline. People with no baseline deficits are said to be in the ‘zero state’, \( n = 0 \). People can be in the zero state at any age, although the older they are, the less likely this is to be the case. An example of how people transit from a baseline state \( (n) \) to any follow-up state \( (k) \) is illustrated in figure 1B, where cell (a) represents transitions from the zero state. We have evaluated the outcomes of people in the zero state at baseline in relation to their so-called social vulnerability index. Even in Canada, with a universal health care system and average Western indices of economic inequality, the 5-year mortality of
those with the highest social vulnerability was more than twice that of those with the lowest social vulnerability [17]. The transitions of the fittest (i.e. the average number of deficits that they accumulate) are quantitative estimates of these background effects, and thereby appear to be a means of quantifying the health hazard of a given environment.

The Origin of Deficit Accumulation – A Stochastic Framework

Characterizing aging as a process of deficit accumulation gives us an opportunity to represent aging in an individual by the changes in the number of deficits this individual has. If so, the question can be posed: what is the cause of such accumulation? We will show that the origin of deficit accumulation can be understood by considering a very general process of interaction of the environment, which causes damage, and the ability of the organism to sustain/repair the damage. This can be considered under the framework of stochastic processes. To illustrate this, we assume that the process of environmental challenges imposing stresses on the organism can be considered as a stochastic process, with average intensity (rate) $\lambda$. The average time interval between the consecutive stresses is thus $1/\lambda$. Such challenges will be of many different sorts, arising from individual exposures to perturbations in the weather, solar activity, pollution, stressful social events, disease outbreaks, etc. The interval between the challenges ($1/\lambda$) varies from minutes to months; most cannot be measured. Let $R$ be the average time of recovery from such environmental stresses in people of the same chronological age. The ability of the organism to recover depends on the individual’s genetic profile [18], health status, living conditions, and access to modern health care [19]. Most importantly, the time of recovery is age dependent, presumably reflecting subclinical (even microscopic) tissue, cellular and subcellular damage [4].

Queuing Theory and Little’s Law

There is a structural similarity between the process described above and the processes governing the formation of a queue described in stochastic queuing theory. Queuing theory is a mathematical discipline that aims to explain how the length of a queue is related to the intensity of the stream of arrivals to the system, and to the service and waiting times [20], e.g. how long it takes to service the people in the queue. Queuing theory is widely employed across multiple applications in communications, computer architecture, operation management, etc. The statistical mechanics of the queuing system can be complex, and even in simplest cases is described by the Kolmogorov differential equations. Although the specific details of these equations depend on the assumptions of the model (e.g. single server or a network of servers; stationary or non-stationary arrivals, different priory schedules, etc.), as outlined above, there is a gen-
eral and simple relationship between the average number of items in a queuing system (N), the average arrival rate (λ) and the average waiting time of an item in the system, R, known as Little’s Law [21] (here we use the different notation from the original [21]):

$$N = \lambda R$$  \hspace{1cm} (2)

By exact analogy, we suggest that the average number of deficits present in an individual (N) equals the rate of environmental stresses λ (the amount of damage arriving to the queue), multiplied by the average recovery time R (analogous to waiting time) [22].

Damage occurs at the different levels of the organism, including DNA, epigenetics, cells, and organ tissues: each of these levels has its own repair mechanism; the latter are not isolated from each other but organized in complex networks, so the elimination of damage does not go through one isolated system with a queue but through many such subsystems. In some circumstances, repeated damage may happen at the same place and create a ‘local’ queue. It could also be some other reasons for the queue. Independent of the detailed mechanisms of these processes, equation 2 imposes fundamental constraint on them.

**Age-Related Deficit Accumulation Reflects the Increase of Age-Related Time of Recovery**

Equation 2 states that the average recovery time is proportional to the average number of deficits that the individual has. The coefficient of proportionality (λ) which is the intensity of the environmental stresses is an average characteristic of the environment. Let us assume that during the life course this average intensity does not change. As we know, deficits accumulate with age. According to equation 2, this means that the average recovery time changes proportionally to the increase in the number of deficits, i.e. the kinetics of the deficit accumulation with age is the same as the kinetics of recovery time. It has been demonstrated that the kinetics of deficit accumulation can be fitted by an exponential function [7, 9, 22] with the exponent parameter typically close to 0.03. Figure 2A shows age-specific (cross-sectional) average trajectories for the 9 waves of the National Population Health Survey (NPHS) of Canadians aged 20+ years, over 16 years of follow-up, repeated every 2 years. There is about a 3-fold increase in the number of deficits during 3 decades after the age of retirement (65 years) and about an order of magnitude increase from early adulthood to 100 years. Given the exponential increase in the number of deficits with age, according to equation 4 we can say that the *average* recovery time increases exponentially with age, and with the same parameter $k = 0.035$ [22]:

$$\frac{dR}{dt} = kR$$  \hspace{1cm} (3)
Even though the time it takes to recover from illness is age dependent [23, 24], the most severe conditions contribute to a greater extent to the average recovery time than relatively benign conditions.

**Changes in the Distribution of the Number of Deficits Indicates Change in Recovery Potential**

An important limitation of Little’s Law is that it describes relationships only between the average characteristics. The stochastic dynamical model of deficit accumulation is needed to explain the changes in the distributions of the deficit accumulation over time. Note that these distributions change characteristically from being highly asymmetrical in younger people (most of whom have few deficits) to the gamma-like distributions seen in older people [22]. These patterns now can be understood from our model. When the recovery time is low, the damage caused by the environmental stresses is quickly repaired, which explains why most of young people have no or a few deficits. The length of the queue in a system with ‘light traffic’ shows the same highly asymmetrical density distributions as we see in younger people. As can be seen in figure 2B, in younger people (20–35 years old), the distribution of the number of deficits is highly asymmetrical (see a similar figure in Rockwood et al. [25]). The same figure also shows the density distribution of the number of deficits in an older group.
of individuals aged 75–100 years also fitted by the gamma density function typical for ‘heavy traffic’ models [22].

The age-related increase in recovery time can be related to the decreasing vitality first suggested in 1960 by Strehler and Mildvan [26]. The difference is that in their model vitality declines linearly while the rate of recovery changes exponentially. Here, too, increasing the recovery time with age appears also be related to a very general systems biology mechanism of critical slowing [27]. Finally, the origin of these changes can be related to the fact that the organism is not in equilibrium with the environment. The entropy of the organism is lower than the entropy of the environment, so that maintaining and keeping the structure of the organism requires permanent efforts for compensatory adaptation, repair and elimination of damage. The maintenance of such nonequilibrium causes increasing metabolic cost [2].

### Estimating Biological Age

Although an important and desirable goal, the characterization of biological ageing has proven to be difficult, and for a long time was unsuccessful in tackling interindividual variability [1]. By long convention, the assessment of biological aging has translated into an often controversial search for biomarkers of aging – i.e. a search for specific nondisease traits which change over a life span. According to the usual terms of engagement in the debate, any biomarker should predict the outcome of a wide range of age-sensitive tests in multiple physiological domains in an age-coherent way, and do so better than chronological age. The many candidates considered as biomarkers of ageing have particularly included endocrine system/immune responses, those associated with caloric restriction, and cell membrane viscosity, the concentration of prostacyclin in fibroblasts, alterations of DNA methylation, compliance of the cardiovascular system and a host of several others. The chief challenge in finding any single biomarker is how to integrate across organ systems in a unified way so as to allow the estimation of biological age at the level of the whole organism. A standard response to this challenge is to evaluate many biomarkers using some form of multivariate regression analysis. Although common, this approach strikes us as deeply flawed. That is because as discussed above, candidate variables in such analyses, although held to be independent on statistical grounds can hardly be considered to be so: in biological systems, exactly the opposite generally holds. That is why results from any multivariate model typically do not prove to be generalizable; the output of these statistical exercises is contingent on the particular samples from which they are drawn. What should be evident, however, is that their application in other datasets will require recalculation of the weights which they employ; this level of precision is unlikely to be generalizable. Unless the model shows stable parameter estimates across databases, any theoretical understanding of biological age will be restricted.
The consistency of the relationship between the frailty index, age and health outcomes made it possible to suggest that it can be used as a basis for approximation of personal biological age [14, 28]. As an illustrative example (fig. 2A), consider 2 people, A and B, of the same chronologic age, for example, 65 years with their frailty index values deviated from the average. At 65 years, the mean value of the frailty index is 0.12. Person A has a frailty index value of 0.24, which is 0.12 higher than the mean value of the frailty index at 65 years (0.12), and rather corresponds to the mean value of the frailty index at age 80 years. In essence, person A has the health of an 85-years-old: although chronologically 65 years old, person A can be considered to be biologically 20 years older than chronologically. By contrast, person B has a frailty index value of 0.07, which is 0.05 lower than the mean frailty index value at age 50 years. In essence, person B has the health of a 50-year-old: although chronologically 65 years old, person B can be considered to be biologically 50 years old, i.e. 15 years younger than chronologically.

In other words, we used the relationships between the average frailty index and age as a calibration curve (fig. 2A).

\[
\ln(\hat{FI}) = a + b \cdot CA
\]

Where \(\hat{FI}\) is the mean frailty index estimated as a function of age from the equation above that we can call a *calibration equation*. CA is the chronological age and \(a\) and \(b\) are empirical parameters that can be estimated from the data, using for example a least squares regression technique. Note that in general, the slope parameter \(b\) has been estimated in several databases to be about 0.03 [7]. For example, the most recent estimates obtained from the NPHS for people aged 15–105 years gave the estimates of \(a = -4.16 \pm 0.08\) and \(b = 0.035 \pm 0.001\) [22].

The biological age of an individual can be estimated from inverting equation 4, given the value of the FI of the individual:

\[
BA = \left[\ln(FI) - a\right]/b
\]

It can be seen that the difference between biological age and chronological age can be found from the following equation:

\[
BA - CA = \ln \left(FI/\hat{FI}\right)/b
\]

In other words, biological age could be equal, greater or lower than chronological age. This approach therefore gives a ready metric for estimating by how many years an individual is younger or older than the average person of his/her chronological age in a given population. In that specific sense, people can be considered as biologically older compared to those who are in a better health who can be considered as biologically younger compared to those who are in worse health.

Equation 6 contains only one parameter, slope \(b\), which has a narrow range of values [14]. For those individuals who had no reported deficits (i.e. the fittest people) biological age can be calculated by substituting \(FI = 0\) by its next minimal value, which
corresponds to one deficit present. The corresponding FI could be calculated accordingly: e.g. where 40 deficits are being considered, FI = 0.025, with 100 deficits FI = 0.01, etc.

Note too that the theoretical limit to BA (when FI = 1) is \(-a/b\). For the NPHS data, max BA = 126 years. As maximally observed empirical limit of the FI = 0.7, the limit to BA according to equation 5 is 116 years, which is close to max life span observed in human.

The frailty index is fundamental to this method of calculating biological age; it is based on a simple count of deficits that are broadly defined, but biologically/clinically meaningful. The outcomes using predictive models based on this approach are highly generalizable – they typically show superior performance of the frailty index compared to chronological age [7, 11]. Biological age calculated based on the frailty index can become a useful means of assessing and monitoring health status in individuals.

**Aging, Health, Wealth and Life Expectancy Worldwide**

The numerous indicators of population health include health risk factors, disabilities, chronic disease and conditions, maternal and infant health, social determinants of health, etc. The deficit accumulation approach was evaluated in relation to national income and healthcare spending as well as their relationship with mortality. By assessing over 35,000 people from 15 European countries who participated in the Survey of Health Aging and Retirement in Europe (SHARE), we demonstrated that the frailty index constructed from 70 deficits showed significant inverse relationships with gross domestic product, health expenditures and mortality. Survival of frail people was higher in higher-income countries: the higher level of the frailty index generally corresponds to the lower level of gross domestic product [19]. Perhaps higher health expenditures in more developed countries can contribute to recovery from major illnesses and decrease the average recovery time. Similarly, the decrease in the intensity of the environmental stresses in countries with more developed social policies would also accord with our model with decreasing \(\lambda\) in equation 2. This is another large area of inquiry where the use of deficit accumulation approach can be promising.

**Conclusions and Perspectives**

Aging can be conceptualized as a process of the accumulation of deficits, taking place in different individuals in different ways, with a variety of rates for different organ systems. Deficit accumulation depends on the interplay of intrinsic and extrinsic factors. Deficits are indicators of physiological deregulation and therefore,
by counting them, it is possible to quantify the level of such deregulation. This approach offers a simple and justifiable way of assessing health in individuals and populations.

Note that this approach to health deficits is silent on the nature of the deficit (e.g. disease, disability, symptoms, sign, laboratory or imaging or electrodiagnostic abnormality). The point merits further comments. First, it has proven to be surprisingly controversial, especially in the clinical literature. This is understandable for two reasons. Clinical training traditionally emphasizes diagnostic parsimony. A single cause for a large number of abnormalities is more likely to be correct than is an explanation that invokes multiple causes. (It is certainly more psychologically satisfying to the person who recognizes it.) Clinical training also emphasizes diagnostic precision: what works for condition A might be harmful for similarly looking condition B. (Confusion in a diabetic is a trivial example: giving insulin will help the patient whose confusion is due to blood sugar being too high, but be harmful to the diabetic in whom confusion reflects blood sugar being too low.) The disciple of precision and parsimony is not readily overcome, for good reason. Even so, it is less well suited to the reality of the nature of ageing, especially as the number of deficits increases. Attempts to ‘disentangle disability and comorbidity for frailty’ are rooted in this approach.

A second reason that the nature of the deficit being less important than the number of deficits has proven controversial is that at first glance it seems counter-intuitive. How can a skin problem and a heart attack be equivalent, in the sense of each simply being a single deficit? But the truth is that they can be. Not every heart attack is fatal. Not every rash is benign. To the extent that they impair function or induce a spiral of other diagnoses, they will add to the deficit count, and in that way the frailty index will capture their unequal nature in relation to prognosis.

Considering deficits in relation to age and not just diseases – i.e. adopting more a systems perspective – also appear to have implications for understanding the epidemiology of late life illness. An interesting report in this regard was published in *Neurology* in 2011, in the same issue as two other papers that reported ‘novel risk factors for Alzheimer’s disease’ [29]. Instead, the third paper combined 19 so-called ‘non-traditional dementia risk factors’ in an index variable. The index variable (composed of items such as a history of diarrhea, dentures or foot problems) was a stronger risk for predicting all causes of late-life cognitive decline than was any traditional risk factor. The perspective offered here, that deficit accumulation reflects impaired recovery time, and that age-related recovery processes in the brain will not be unrelated to those in other parts of the body gives some broad insight into why deficits are so powerful, even if they are not known to be specific risk factors for the disease in question. Recent work by our group has replicated this observation in another cohort, and for both heart disease and osteoporosis.

To advance our understanding of age-related, multiply determined illnesses, the development of the statistical mechanics of deficit accumulations involving interac-
tion between different subsystems of the human organism is the next natural step, and one that we are pursuing. This will allow better understanding of the processes of deficit accumulation, and their relationships with long- and short-term changes in the environment. This approach fits comfortably into overall agenda of extending the healthy life span.

References


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