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Aging and Health – A Systems Biology Perspective

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Introduction

Systems biology is a reemerging discipline. Its origins are found in Ludwig von Bertalanffy's general system theory, which eschews reductionism and treats the organism thermodynamically as an open system. A good exposition of this approach is contained in his compendium [1], which is still relevant.

Although general system theory had a significant impact on various disciplines, notably informatics, its consideration in biology, from which it sprung, waned. Systems biology rose again on this substratum around the year 2000. A significant impetus for this was the development of various '-omics', with their capability of generating vast datasets pertaining to cell and organism behavior. The majority of efforts have since been devoted to the generation of networks, and layers of networks, to deduce the multiple interactions of the variables in these datasets.

Another antecedent to the current systems biology is the work of mathematical biologists, whose efforts to model biological processes dynamically feature importantly in some 'strains' of systems biology. Metabolic control analysis comes to mind immediately, as does the literature on the mathematical modeling of the cell cycle. These modeling approaches often incorporate nonlinear functions, and they frequently take into account stochastic elements. These facets are kindred to the consequences of the interaction between components of a system in general system theory. The efforts of both the network systems biologists and the dynamic systems biologists should be juxtaposed to the work of bioinformaticians, who devise methods for manipulating large datasets and cataloging their features.

The systems biology of aging has an even more recent history, although the relevance of the systems approach to aging was already heralded in 1996 [2]. The two sorts of systems biology referred to in the previous paragraph coincide roughly with bottom-up and top-down approaches to the modeling of biological systems. A useful consideration of how these distinct approaches can be profitably integrated has been presented [3]. Most efforts to date attempt to understand the aging process as a determinant of longevity or demise. Little attention has been paid, however, to the emergence of disease and dysfunction as a result of aging, or to the information this emergence has on the biological aging process itself.

The initial idea for this monograph was to explore the frontiers of knowledge connecting aging and health, within a systems biology framework. The crucial importance of this approach lies in the possibility of improving population health by postponing aging or by slowing down individual aging rates. For various reasons, this idea was difficult to realize fully. One reason is that many aspects of the aging process remain unclear and continue to be under intense study, making a discussion of their connections to health perhaps premature. Another reason is that the systems biology of aging is a developing discipline as well, with many new ideas and methods still to appear and to evolve. These factors restricted the scope of this volume and focused it on the foundations and specific aspects of the systems biology of aging, with particular attention to the links between aging changes and diseases of the elderly where corresponding information is available.

The first two chapters introduce the reader to network systems analysis. In the first one by *Tarynn M. Witten*, the author briefly addresses the history of systems biology and introduces the notion of complexity, which manifests itself through nonlinear dynamics, hierarchies and network analysis and can be used to study the intricate and fascinating behaviors of living systems. She suggests treating the biological organism as a network. Then, she explains how network mathematics (graph theory) can provide deeper insight and can even predict potential genes and proteins that are related to the control of organismal life span. The author reviews the history of network analysis at the cellular level and introduces various commonly used network variables. She shows how these variables can be used to predict potential targets for experimental analysis. She also discusses some of the challenges that network methods face.

The second chapter by *Christopher Wimble* and *Tarynn M. Witten* applies the ideas and methods described in the first chapter to concrete examples, using *Saccharomyces cerevisiae* and *Caenorhabditis elegans*. The authors consider possible aging-related changes in a network, which include inactivation of active nodes/activation of inactive nodes (e.g. genes) and loss of connectivity/increase in connectivity. The factors affecting these processes are not considered. The authors show that the network structure determines its vulnerability to possible targeted attacks. Attacks that knock out essential genes disrupt the life span network because the organism dies when an essential gene is knocked out. The authors believe that understanding patterns in network decomposition could lead to early detection of potential neurodegenerative disorders and to potential pharmaceutical intervention at earlier points of disease development.

The third chapter by *Mark Mc Auley* and *Kathleen M. Mooney* focuses on the application of computational systems biology in aging research starting with the rationale for using it for investigating the aging process. The authors discuss alternative theoretical frameworks that can be used to build models of the complex age-related disorders associated with unhealthy aging. The chapter starts with the description of dynamic modeling using differential equations. Then, it incorporates aspects of network analysis and agent-based modeling. Computational modeling is

supposed to be an integral component of systems biology, amalgamating with the other techniques discussed in this book to quantitatively represent and simulate biological systems.

The evolutionary theories of aging of biological systems are widely discussed in the literature [4–11]. These theories claim that because aging is largely a postreproductive phenomenon, it should not evolve by natural selection. *Joshua Mitteldorf* believes that aging could be advantageous for stability of ecosystems and hence can be the result of natural selection. The author pays attention to the fact that animals and plants have biological clocks that help to regulate circadian cycles, seasonal rhythms, growth, development and sexual maturity. He puts forth the hypothesis that evolutionarily evolved aging is also clock driven. He focuses on the epigenetic process of DNA methylation, as a clock mechanism, and its relevance to stem cell aging, in particular, in his chapter. Research on the relationship between methylation and aging is still in an early stage, and it has not yet even been proven that alterations of the methylation state are a cause and not simply a product of aging. The hypothesis that the body's age is stored within the cell nucleus as a methylation pattern suggests a program of research and an anti-aging strategy. If validated, this hypothesis would point to a challenging target for medical intervention. Recent results [12] provide additional information for thinking in this direction.

To what extent can insights derived from the systems biology of aging in animal model systems be applied to human aging? *Michael Rose* and his colleagues argue that systems biology of aging might have a different focus in two types of species. The authors provide evolutionary arguments that aging processes taking place in species with rare sexual recombination are quite different from those in which it is frequent. In the species of first type, the systems biology of aging can focus on large-effect mutants, transgenics, and combinations of such genetic manipulations. In frequently recombining species, the systems biology of aging can examine the genome-wide effects of selection.

Many gerontologists have the strong belief that aging is nonprogrammed and provide arguments supporting this view [13]. Many others provide arguments that aging is likely to be programmed [14–16]. Further studies are needed to resolve the issue. *Bruno Cesar Feltes* and his colleagues treat aging as a programmed process and consider it as a continuation of developmental processes. To overcome environmental challenges, the embryo needs to adapt its metabolism in response to environmental fluctuations. Epigenetic programming is responsive to perturbations or imbalances of intrinsic and/or extrinsic factors experienced in utero. Immune system development and aerobic respiration/glucose metabolism processes are modulated during early development. Small changes in developmental mechanisms and adult trait specification that occur during early development might result in significant morphological alterations during later stages. This can promote an adaptive response and influence gene expression patterns, leading to age-associated diseases, such as cancer, osteoporosis and the decline of the immune system. This concept underpins a net-

work approach to aging that provides a framework for the appearance of diseases of aging.

In the chapter that follows, *Arnold Mitnitski* and *Kenneth Rockwood* describe the use of their frailty or deficit index to characterize the state of an aging human. This is a top-down approach that incorporates age-related disease and dysfunction into its derivation. The authors propose that the frailty index can be used as an indicator of an individual's biological age. This index manifested reproducible properties including nonlinear increase with increasing age, higher values in women, strong association with mortality and other adverse outcomes, as well as other properties. Importantly, the authors employ a stochastic dynamics approach to model how the organism recovers as a function of age.

Aging is associated with immunosenescence, and it is accompanied by a chronic inflammatory state which contributes to development of chronic conditions. The chapter by *Verónica Guarner* and *Maria Esther Rubio-Ruiz* shows how low-grade systemic inflammation may be the basis of multiple dysfunctions that evolve during aging, including metabolic syndrome, diabetes, and their cardiovascular consequences. Cardiovascular diseases and endothelial dysfunction are characterized by a chronic alteration of inflammatory function, markers of inflammation, and the innate immune response. Inflammation may thus serve as the integrating factor that makes the frailty index a global measure of system function.

Pharmacologic interventions are believed by many gerontologists as a possibility for slowing down or postponing individual aging processes. A widely discussed target for such interventions is the mTOR (mammalian target of rapamycin) nutrient response pathway. In multicellular organisms, TOR regulates cell growth and metabolism in response to nutrients, growth factors and cellular energy state. Deregulation of TOR signaling alters whole-body metabolism and causes age-related disease. The life-extending effects of dietary restriction in yeast, worms, flies and mice appear to be due largely to inhibition of TOR signaling. There is evidence that TOR may also control aging via modulation of stress-responsive genes and through autophagy. Inhibition of this pathway extends life span in model organisms and confers protection against a growing list of age-related pathologies. In the next chapter, *Simon Johnson* and his colleagues focus their attention on mTOR signaling. The authors inform that some medical interventions affecting this pathway are already clinically approved, and others are under development. Thus, targeting the mTOR pathway is a promising strategy for slowing down the aging rate and improving health of the elderly.

In the following chapter, *Rüdiger Hardeland* discusses melatonin as a systemic integrating agent that interfaces with the environment. A number of studies support the anti-aging properties of melatonin [17, 18]. Melatonin is a derivative of the amino acid tryptophan and widely distributed in food sources, such as milk, almonds, bananas, beets, cucumbers, mustard, and tomatoes. In humans, melatonin is primarily synthesized by the pineal gland, but it is also produced in the gastrointestinal tract and retina. Melatonin and its metabolites are potent antioxidants with anti-inflammatory,

hypotensive, cell communication-enhancing, cancer-fighting, brown fat-activating, and blood lipid-lowering effects, and thereby protecting tissues from a variety of insults. Melatonin has been shown to support circadian rhythm, hormone balance, reproductive health, cognition, mood, blood sugar regulation, and bone metabolism, while improving overall antioxidant status and lowering blood pressure. Melatonin may assist in preventing diabetic complications, and improving treatment outcomes in patients with cardiovascular disease and certain types of cancer. Consuming melatonin neutralizes oxidative damage and delays the neurodegenerative process of aging [19]. *Hardeland* here shows that this chronobiotic impinges on multiple physiologic systems with implications for health and disease during aging. The chapter discusses the associations of the loss of melatonin secretion and rhythm amplitudes with aging and development of age-related diseases.

It is well known that a diet rich in plant-based foods has many advantages in relation to the health and well-being of an individual. Much less known is the large contribution of the gut microbiota to this effect. *Denise B. Lynch* and her colleagues expand the discussion of aging, health, and disease to encompass the gut microbiome and its mutual relationship with the host. This relationship goes beyond an uneasy symbiosis implicated in immune-related disorders because the host genome and the microbial ecosystem constitute a supergenome. Thus, this is more than an interaction of the host with the environment with significant consequences for healthy aging.

The penultimate chapter by *Anuradha Chauhan* and colleagues serves as a coda. The authors reprise the history of the systems biology of aging and the different methodological approaches it encompasses. They provide the rationale for using the methods of systems biology in the analyses of the aging of biological systems. They outline the main features of the methodology emphasizing that the structure and functions of the biological systems are investigated by analyzing experimental data through the use of sophisticated mathematical and computational tools, including advanced statistics, data mining, and mathematical modeling. The methodology also includes formulation of working hypotheses, designing new experiments able to prove these hypotheses, and developing computational tools with predictive ability in a biomedical environment. The authors provide several examples that make direct use of the system motifs introduced in previous chapters, and they point to the importance of expanding upon the rudimentary achievements of the systems biology of aging at the present time if we are to intervene in the appearance and progression of age-related disease. The authors believe that the optimal design of biomedical strategies to counteract aging-associated pathologies will require the use of tools and strategies adapted from engineering.

The final chapter by *Vladimir N. Anisimov* addresses the issue of interventions raised again by *Chauhan* and colleagues. He describes experimental studies evaluating effects of biguanides and rapamycin on survival and carcinogenesis in mice paying attention to similarity in the majority of effects of these drugs on patterns of changes observed during normal aging and in the process of carcinogenesis. Anisi-

mov considers whether an antiaging drug is in hand, one that combats age-related disease. The conclusion is that promising leads may already be available.

This book is bound to leave the reader unsatiated. The systems biology of aging is a new field. Although it is based on established methodologies, their application has been relatively limited to date. Furthermore, aging presents problems that are peculiar to it. Some of these peculiarities derive from the forces underlying its evolution. Others are the result of its fundamentally stochastic nature and its heterogeneity among individuals. Its presentation as a set of multiple morbidities and comorbidities only adds to the difficulty. We expect that future research will make use of new concepts and new tools to allow these aspects of aging to be adequately treated. Furthermore, we trust that this volume will stimulate such endeavors.

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