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Meeting Report

Bridging Physics and Aging Biology: Insights from the First Physics in Aging Biology Workshop

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Research in aging has often been descriptive, with few quantitative laws to explain how organisms change with age. However, physicists often build quantitative models to explain observed phenomena and how they change with time. We believe that merging physics with aging biology will help us to develop a deeper understanding of the biology of aging. The Physics in Aging Biology Workshop brought together a diverse group of aging biologists and physicists to exchange ideas on how theoretical physics and complexity science approaches could lead to a better understanding of the aging process.

Introduction

The Physics in Aging Biology Workshop was a first-of-its-kind gathering in Copenhagen on 27 August 2024 during the Aging Research and Drug Discovery Meeting. The objective of the workshop was to showcase and explore how theoretical physics and complexity science can improve our understanding of aging biology. The first part of the workshop showcased prepared presentations of current applications of theoretical physics to various branches of aging biology. The second part of the workshop involved impromptu whiteboard sessions, allowing participants to propose topics they would like to discuss, model, and brainstorm on. The key takeaways of the workshop are summarized in **Box 1**.

Concepts from Theoretical Physics and Complexity Science Applied to Model Phenomena of Aging Biology

In classic physics fashion, Prof. Uri Alon from the Weizmann Institute started out with a chalk talk describing the saturating-removal model of aging and age-related disease[1].

The model assumes a damage x that drives aging but remains agnostic about the nature of x—and thus the model can be applied across organisms. It was calibrated by model selection on longitudinal dynamics of senescent cells in mice and on longitudinal damage in E. coli. The model is a stochastic equation in which damage production rises linearly with age and removal saturates at high damage. It explains the exponential increase in mortality and its slowdown at old age. It also explains data on human age-related disease incidence and the shapes of survival curves shifted by longevity interventions in model organisms. By quantitatively linking damage dynamics to lifespan, the model provides a physics-based framework to explain aging and the impact of interventions.

As a local representative and chair of the Niels Bohr Institute, Prof. Mogens Jensen from the University of Copenhagen presented his group's work on Condensate Formation and DNA repair in Cell Signaling[2]. Their research employs a physics-based model to describe how oscillations in p53 optimize DNA repair by regulating the formation and dissolution of repair foci through droplet condensation. Using differential equations and stochastic simulations, they demonstrate that p53 oscillations suppress Ostwald ripening, ensuring efficient spatial–temporal distribution of repair proteins, a prediction validated experimentally. This work

Box 1. Key takeaways from the workshop.

1. Various physics-based models have been developed over the past decade to investigate the mechanisms underlying aging, drawing on theoretical approaches such as stochastic modeling, network theory, and dynamical systems.
2. These models extend beyond human data, incorporating validation and calibration from animal studies. Network topology, temporal scaling, and the steepness of survival curves have provided novel insights into aging processes and the efficacy of interventions targeting aging.
3. Mathematical frameworks are adopted to explain complex biological phenomena, such as cell differentiation and death, demonstrating the effectiveness of simplified mathematical representations validated across multiple biological contexts.
4. The workshop highlighted the importance of interdisciplinary collaboration in aging research, showing how integrating physics, biology, and epidemiology opens new avenues for understanding aging and underscores the need for sustained cross-disciplinary partnerships.

highlights the interplay between phase transitions and gene regulation, offering new insights into the role of dynamical systems in cellular repair mechanisms.

Dr. Omer Karin, Lecturer in the Biomathematics group at Imperial College London, discussed the physics of cell identity and reprogramming, exploring how stable gene expression patterns define cell identity and how differentiation progresses through multilineage priming and fate restriction[3]. He highlighted efforts to develop simple mathematical models that can capture, predict, and control the large-scale dynamics of cell identity during differentiation and reprogramming. By integrating theoretical approaches with experimental data, these models aim to uncover universal principles governing cell fate transitions, with implications for stem cell biology and regenerative medicine.

A pioneer in network science, Prof. Albert-László Barabási presented his work on Network Medicine of Aging, exploring how protein–protein interaction networks can be used to identify disease modules—clusters of functionally related genes implicated in disease[4]. He proposed that aging itself could be understood as a network-level breakdown of function, where each hallmark of aging corresponds to its own disease module, some of which are highly interconnected while others, like epigenetics and telomere maintenance, are more isolated. His team is developing a drug repurposing pipeline to target multiple hallmarks simultaneously and investigating the Foodome project, which aims to identify dietary molecules that modulate aging. In addition, he discussed how network dynamics can help understand the impact of somatic mutations and epigenetic damage on aging resilience, revealing that highly mutated genes tend to be randomly distributed, while protected genes cluster within functional pathways[5].

Prof. Andrew Rutenberg from Dalhousie University discussed a minimal model[6] that can be parameterized using longitudinal data to empirically explore the stability of complex aging health dynamics. His team employs a linear dynamical model that includes a constant "W" interaction matrix to capture how biological variables influence each other over time. He reports that the least stable modes and the modes with drifting fixed points with age are most often associated with poor individual outcomes. Aging-related decline arises from the drifting modes, which his group calls "mallostasis." The model provides a quantitative but interpretable approach to identifying early-warning signals of aging and predicting health outcomes from complex health data. Prof. Rutenberg emphasized that the same model can be used at other organismal scales, such as to assess the complex interactions of multiple aging clocks[7].

Prof. Jan Gruber (National University of Singapore) presented a framework for understanding aging-related mortality through the lens of stochastic dynamical systems and first-passage dynamics. In this view, aging reflects a gradual destabilization of the organism's physiological state, modeled as a high-dimensional Langevin process centered around a dynamic homeostatic setpoint[8]. This model describes aging as movement through a feature space shaped by a potential landscape, where curvature along specific directions (eigenmodes) reflects physiological resilience. As these physiological potentials along specific directions in feature space decline with age, the likelihood of stochastic excursions beyond the basin of health increases exponentially. These rare but catastrophic events correspond to first-passage failures: transitions to disease or death. Based on this view, mortality clocks can be constructed—data-driven models that predict future mortality based on clinical or -omics data[9]. He also emphasized the role of critical slowing and rising autocorrelation in longitudinal data as early-warning signals, suggesting that aging follows predictable dynamical patterns that may guide targeted interventions.

In his talk "How Ovarian Aging Can Modify Chronological Aging," Prof. Joshua Johnson from the University of Colorado School of Medicine considered how ovarian aging is likely to influence overall chronological aging. Collaborative work from his group has produced simulations of the behavior of the ovarian primordial follicle "reserve" and shows how follicle growth and survival dictate the timing of menopause such that it occurs between ages 40 and 62 with a median age 51[10]. Because later age at menopause in women correlates with longer overall lifespans[11], slowing ovarian follicle loss holds the promise of improving overall healthspan and longevity. Johnson and colleagues' models have been modified to assess the potential impact of such interventions on reproductive lifespan. Understanding the mechanisms that regulate follicle depletion may allow for targeted strategies to delay menopause, improve long-term health outcomes, and potentially extend the lifespan.

Dr. Yifan Yang from the Weizmann Institute of Science presented research on damage dynamics in E. coli cell deaths and their implications for aging universality. Using stochastic modeling and membrane damage markers, his work demonstrates that aging-related mortality in bacteria follows the Gompertz law, similar to patterns observed in mammals[12]. With Uri Alon, he developed a stochastic model named the membrane-potential saturating-removal model[13], showing that damage accumulates due to a balance between rising production and saturating-removal rates, a process potentially universal across different organisms. The model's predictions align with human frailty indices and blood biomarker data, suggesting a shared underlying mechanism of aging across species.

Prof. Nick Stroustrup, Group Leader at the Centre for Genomic Regulation in Barcelona, presented his research on temporal scaling in *C. elegans* aging, demonstrating that lifespan variations follow a scaling law where the standard deviation and mean lifespan remain proportional[14]. Using an interdependency network model, he showed that organismal aging results from cascading failures of interconnected biological nodes, rather than a single central aging regulator. His findings suggest that both weakening and strengthening subsets of these nodes lead to predictable

temporal scaling of survival, identifying a novel state variable, r(t), that governs the risk of death. This supports the idea that diverse molecular and environmental interventions influence lifespan by altering a single effective rate constant of aging, highlighting the need for a systems-level understanding of aging mechanisms.

A Whiteboard Session: Exploring and Modeling Impromptu Ideas for Aging Research

For many participants the discussions during the whiteboard sessions, facilitated by Prof. Uri Alon—with a guitar and encouraging words and songs—were a highlight of the workshop. The impromptu and interactive format allowed any workshop participant to suggest a topic they would like to discuss for 15 min and model on the whiteboard with inputs from the audience.

The whiteboard session started out with Taylor Thompson, Hoskinson Health and Wellness Clinic's exercise physiologist, focusing on the topic of stress and recovery cycles to build resilience. Physiological oscillations, particularly in inflammatory and mitochondrial dynamics, play a key role in optimizing training timing and adaptation to improve healthspan and lifespan[15]. Tracking resting heart rate, perceived fatigue, inflammatory markers, and oxidative stress helps to determine the optimal frequency of hormetic stressors to maximize performance[16,17]. The initial stress response within a hormetic framework is exemplified in **Figure 1A**, which shows increased creatine kinase and immune cytokines following musculoskeletal stress[17]. Proper recovery returns these levels to near baseline before another stress stimulus is applied, to optimize adaptation. These hormetic effects apply to other stressors as well, such as temperature and pressure. Approaching health and training as a dynamic system with periodic inputs, the discussion aimed to identify the ideal schedule for balancing stress and recovery to achieve peak function.

Prof. Nick Stoustrup took the opportunity to present ideas from his course on probability theory and statistical inference, emphasizing how integral linear regression is to both statistics and machine learning. Using an example of how ethanol levels relate to liver enzymes, he demonstrated what makes a good regression model, highlighted the importance of residuals, and explained how the best-fit line minimizes and flattens them.

Dr. Veronika Kedlian presented on the dynamics of thymic cells during involution, aiming to understand how the thymus ages and

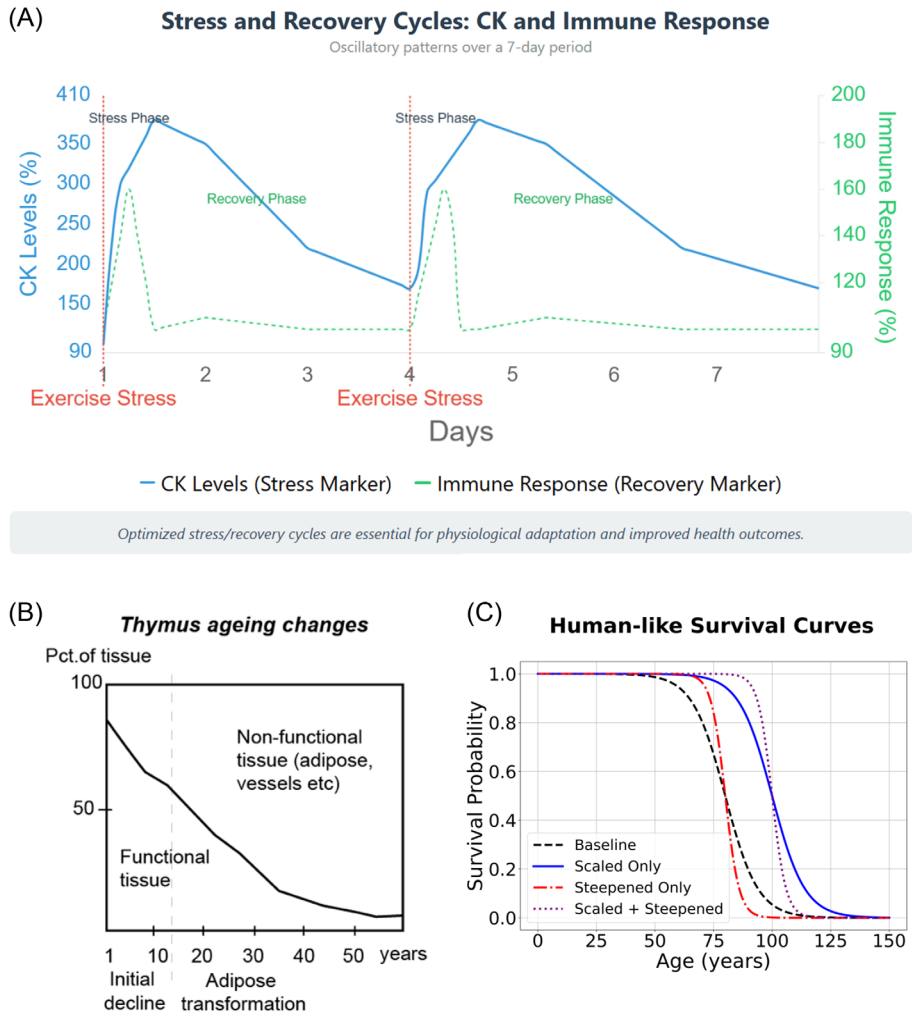

Figure 1. Graphs that were drawn and explored on the whiteboard session. (A) Example of stress and recovery dynamics showing increased creatine kinase (CK) and immune cytokines following musculoskeletal stress within a hormetic framework. **(B)** Age-related thymic involution, showing early and rapid decline in thymic cellularity and transition to adipose tissue. **(C)** Conceptual survival curves illustrating baseline, temporal scaling, steepening, and combined scaling + steepening in response to longevity interventions.

its impact on immune function. The thymus is the primary immune organ and the main site for the production of naïve T cells. Unlike most other organs, which exhibit a gradual decline in function that accelerates with age, the thymus shows an early and rapid decrease in cellularity beginning shortly after the age of one (**Fig. 1B**). This process transitions into adipose transformation during puberty, culminating in approximately a 50% loss of functional tissue by early adulthood, after which the rate of involution slows down[18,19]. She also highlighted the importance of interaction between the thymus and bone marrow, where T-cell progenitors originate, for thymus aging modeling.

The Director of the Center for Healthy Longevity at the National University of Singapore, Prof. Brian Kennedy, discussed a puzzle that he has been thinking about for a long time, inspired by and related to Nick Stroustrup's research on the scaling of *C. elegans* lifespan curves[14]. The discussion explored whether longevity interventions in humans will primarily rectangularize survival curves—increasing median lifespan without extending maximum lifespan—or whether they could scale lifespan and shift the upper limit (**Fig. 1C**). Model organisms show both behaviors, with yeast studies demonstrating how mutations affecting replicative aging alter survival curve steepness and variance. Dr. Max Unfried suggested that earlier interventions and repeated true rejuvenation could reshape survival curves to extend lifespan, while Prof. Collin Ewald proposed testing this in *C. elegans* by activating daf-2 repeatedly late in life to extend lifespan beyond natural limits, as activating daf-2 when 75% of worms are already dead extends the lifespan of the remaining worms by 50%.

Dr. Mirre Simons from the University of Sheffield discussed that trade-offs between physiological domains, including reproduction and aging, are central to the evolutionary biology of aging[20]. Between-species trade-offs explain many aspects of morphology and physiology, including aging[21]. Within species, however, trade-offs have less evidence and may not provide the assumed evolutionary constraint[22]. Furthermore, trade-offs can appear from stochastic effects alone, meaning we possibly overestimate the dominance of trade-offs in determining aging-related physiology[23]. These considerations are important, as they suggest side effects from antiaging treatments are not a given, and thus healthy aging without any physiological downsides could be more probable than current theory predicts.

On the whiteboard, Dr. Yifan Yang circled back to the topic of lifespan distribution and survival curves. He explored longevity intervention studies, which typically report median lifespan but often overlook the full information contained in survival curves[24]. A proposed metric for survival curve steepness allows for a more nuanced assessment of interventions, as demonstrated using data from the NIA ITP program. The discussion highlighted that different mechanisms of action map to distinct regions in the lifespan-steepness space, with the most promising interventions being those that both extend lifespan and increase steepness, potentially compressing sickspan and improving late-life health.

Dr. Weilan Wang from the National University of Singapore discussed the challenges of quantifying resilience, damage, and repair in the context of biological age modeling throughout the lifespan. The discussion highlighted limitations of existing biological clocks trained on datasets usually only covering a relatively narrow age range, also with their reliance on chronological age and mortality risk, which may not fully capture quality of life and resilience factors, emphasizing the need for improved models through collaborative efforts.

The last impromptu whiteboard talk was given by Prof. Joshua Johnson on causality and aging, building on his earlier presentation by exploring whether transplanting young ovarian tissue into older ovaries could extend lifespan in women. Since ovaries are among the first organs to fail, the idea involves cryopreserving ovarian tissue from healthy women and reimplanting it before menopause to delay its onset. Given that later natural menopause correlates with longer lifespan, while surgical menopause shortens it, the discussion focused on how to model and predict the potential impact of ovarian interventions on longevity.

Conclusion

The packed attendance and strong enthusiasm at this workshop underscore the growing interest in applying physics-based approaches to aging biology and signal an opportunity for more physicists to contribute their modeling and analytical expertise. Recurring themes included connecting molecular and population dynamics, oscillations in biological systems, temporal scaling of lifespan curves, and the importance of considering curve steepness alongside mean, median, and maximum lifespan. Discussions also emphasized linearization approaches leading to Langevin equations and the role of network dynamics, which can be manipulated to explore aging mechanisms. Many open questions remain, highlighting the need for continued interdisciplinary collaboration.

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Author Contributions

M.U. organized and facilitated the workshop and wrote the original draft. U.A. facilitated the whiteboard sessions. U.A., J.G., M.J., J.J., O.K., V.R.K., B.K., A.R., M.J.P.S., T.T., W.W., and Y.Y. presented their work and modified the draft. D.B., A.Z., and M.S.-K. are the main organizers of the ARDD conference that enabled the workshop and modified the draft.

Conflicts of Interest

The authors declare that they have no competing interests.

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