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MEETING REPORT

Bioinformatics in Aging Research: A Workshop Report

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Abstract

Evidence is accumulating that the first genuine antiaging interventions (e.g., approved pharmaceutical, nutriceutical, and stem-cell-based therapies) will become available within the next decades. Model organism data, next-generation sequencing, and further advances call for sophisticated large-scale data analysis. To present the state-of-the art and to talk about upcoming tasks and challenges in the bioinformatics and systems biology of aging-related data, a workshop on Bioinformatics in Ageing Research convened leading experts from Europe on May 4–5, 2010, in Rostock/Warnemünde. This meeting report summarizes talks and gives some outlook into future developments.

Introduction

Genuine antiaging interventions, and research into these, may become a significant part of the routine work in a Medical Department within the next 10–20 years. In 1990, a biostatistical analysis by Olshansky et al.[1] revealed that eradicating heart disease, diabetes, and cancer would extend the life expectancy of a 50-year old American female by a mere 16 years. This is a surprisingly low return on investment, and there is some likelihood that this woman, then 96 years old, may suffer from dementia, and upon eradication of dementia, that she may suffer from severe kidney disease. In 1990, there was, however, not much hope to come up with genuine antiaging interventions anytime soon. This prospect may be about to change dramatically. One approach centers around caloric restriction, dietary restriction without malnutrition.[2] Studies have shown that calorie restriction delays disease and mortality in rhesus monkeys,[3] and it may rely on common molecular pathways that are well conserved in many metazoans,[4] thus enabling valid model organism research. These pathways may be summarized as a general response to periods of starvation, during which maintenance is enhanced and aging slowed down. Finally, preliminary studies indicate that one may even be able to trigger this starvation response by small-molecule compounds.[5,6] However, pharmaceutical research is fraught with setbacks, and it is certainly impossible at this time to give any estimates whether and when a genuine slowdown of aging may become possible.

The workshop "Bioinformatics in Ageing Research" was designed to discuss a wide array of mathematical and computational approaches to the analysis of aging-related data, supplemented by some overview talks on the subject given by biogerontologists. Another fairly general approach toward the extension of health span, that is, stem cell therapies and research into these, was also discussed at the meeting, thereby focusing on the interrelationship of stem cells and aging.

Databases, Networks, and Pathways Relevant for Aging Research

Biomedical research, including the biology of aging, is becoming increasingly dependent on informatics, statistics, and mathematics, for example, with the advent of next-generation sequencing.[7] Aging is undisputedly a complex process because it affects the deterioration of most (if not all) aspects of life. Such complex processes cannot be disentangled with

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pencil and paper alone, so computational strategies need to be involved to enhance research work toward a better understanding of the basic processes, the etiology, and the potential points of intervention into aging. The majority of workshop talks (7 out of 19) were concerned with networks of various kinds (interaction, regulation, metabolism), with high-throughput data such as microarray expression data, with aspects of evolutionary bioinformatics and their impact on aging research, as well as with semantics and ontologies as a foundation for a precise description of the data and mechanisms. It became clear that the ultimate goal of integrative data analysis in an all-encompassing context may yield high returns on investment, but it is still a faraway perspective. Nevertheless, the foundations for such integrative analyses may be (and must be) laid today by adopting standards of data interoperability and exchange.

Joao Pedro de Magalhães (University of Liverpool, UK) presented studies of aging-associated protein networks using GenAge (http://genomics.senescence.info/genes/), a database of genes related to aging, an approach that can reveal new candidate aging genes.[8] A meta-analysis of age-related gene expression profiles was also used to identify conserved molecular signatures of aging in mammals.[9] Last, de Magalhaes presented studies on genome evolution to gather new clues about species differences in aging, including recent work on the naked mole rat, an extraordinary long-lived and cancer-resistant rodent.

Bioinformatics tools are essential to support a systems approach to the study of aging. ***Anil Wipat*** (Newcastle University, UK) presented an overview of the range of bioinformatics tools, resources, and approaches that have been developed by the Centre for the Integrated Systems Biology of Ageing and Nutrition (CISBAN) at Newcastle to facilitate a systems approach to aging. In particular, he focussed on research into data and network integration that is underway at the center, presenting a functional interaction network database (CID, the CISBAN Interactomes Database) that spans 12 model organisms used in aging research. He also highlighted ongoing work in the area of semantic data integration.[10]

Because a wealth of data regarding the biology of aging at the molecular, cellular, and organismic level has already been assembled by the scientific community, ***Aubrey de Grey*** (SENS foundation, UK) proposed creation of a specialized biogerontological and regenerative medicine knowledge base (SEPIA). This integrative system is composed in a way to bring forward efficient means in solving the tricky problem of extending the length of healthy life.[11] Primary objectives of SEPIA are to: (1) Organize the current biogerontological literature for speed and clarity of use in regenerative medicine and ageing research, (2) model the causal relationships that are inherent in human aging to turn back time by directed interventions, and (3) identify weak links in proposed research strategies with respect to present funding schemes.[12] It is anticipated that translational research could be greatly enhanced by SEPIA by provision of detailed advice about the type of therapy to be applied for the prevention or cure of a given pathology. Moreover, SEPIA shall also highlight a regimen of efficient cues by which the body could be continuously overhauled at the molecular and cellular level to systematically combat the disabilities and illnesses associated with ageing.

Georg Fuellen (University of Rostock, Germany) outlined the benefit of the "personalized preventome," which will become affordable for patients in the near future as the compendium of biological information regarding their genome, organ/tissue-specific epigenomes and transcriptomes, distinct metabolomes, etc., to be incorporated in medical diagnostics and therapy. Integration of data sets of such complexity and subsequent meaningful comparative bioinformatics analyses will obviously rely on information from a multitude of public databases and on an appropriate network analysis, arguing for a large-scale community project. To begin with, specific computational tools have to be designed today, which ease the examination of merged, interdependent, and multilayered biological data. For example, relevant data on gene–protein interaction and regulation may be assembled into a network scheme. Then, differential data (young vs. aged, aged vs. aged under a calorie restriction scheme) may be analyzed in the context of the network,[13] revealing hypotheses for mechanisms involved in aging or calorie restriction. Finally, in a multispecies setting, mechanisms may be effectively structured according to an ontological classification to identify specific evolutionary novelties and to single out those mechanisms that are amenable for medical treatment. In his talk, Fuellen described some first analyses using a network based on the genes of the NetAge database (see next paragraph), and microarray data taken from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus.

Whereas most genetic studies on longevity focus on individual genes and their products, ***Robi Tacutu*** (Ben-Gurion University of the Negev, Israel) attempts to integrate the accumulating data toward a more holistic perspective on ageing and longevity.[14] His network-based analysis revealed that a large number of genes from the human longevity network are also involved in at least one age-related disease, with many being essential for development and growth, thus displaying features of antagonistic pleiotropy. This suggests the possibility of initiating longevity-promoting interventions in adult life, in particular, by using RNA interference, as many of the common essential genes could be pro-longevity targets.[15]

Given that balancing metabolic fluxes is enhancing cellular and organismic robustness, ***Stefan Schuster*** (University of Jena, Germany) set out to first decompose the unmanageable biochemical network of an entire organism to its smallest functional entities.[16] Giving special regard to the nature of the chemical reactions with respect to reversibility and stoichiometry, metabolic networks can then be displayed and evaluated if they are represented as hypergraphs, which allows determination of elementary flux modes of specific metabolic pathways such as nicotine adenine dinculeotide (NAD) synthesis, and to compute the shortest elementary flux modes in genome-scale metabolic networks.[17] Then, metabolic pathways containing futile cycles can be identified on a genome-wide scale. Such pathways are potentially relevant to cellular aging, and they can be kinetically modeled and studied further.

Julio Vera (University of Rostock, Germany) described recent experimental results suggesting that cancer progression and aging could be linked through signaling pathways that modulate cell cycle progression and apoptosis, including p53-regulated signaling and the p16-pRB pathway. He

discussed the elements of a systems biology approach to investigate the fine-tuning of those signaling pathways under tumor and aging progression scenarios, and illustrated this notion with some recently published results concerning the mechanisms underlying 14-3-3ω-mediated cell cycle control in cancer and cell senescence.[18]

In Silico Approaches Initiated by the GerontoSys Initiative

The German Ministry for Education and Research (BMBF) has long recognized the importance of computational analyses in the life sciences, supporting a wide array of bioinformatics and systems biology initiatives. Recently, the BMBF started to fund projects within the initiative "Systems Biology for Health in Old Age–GerontoSys" (www.fz-juelich.de/ptj/gerontosys), giving Germany a prominent role in studies discussed here. At the workshop, all three currently funded GerontoSys research groups were represented by their project leaders (or by the bioinformatics specialist involved). Notably, a project proposed by a group in Rostock, coordinated by R. Köhling, O. Wolkenhauer, and G. Fuellen, received a "recommendation for funding" for the next round of the GerontoSys initiative.

Jürgen Sühnel (Leibniz Institute for Age Research–Fritz Lipmann Institute, Jena, Germany) presented the Jena Centre for Systems Biology of Ageing–JenAge (www.jenage.de). This newly established center sets out to specifically investigate whether mild stress can promote healthy aging, adopting a multispecies approach. This aim is based on previous work of JenAge member groups.[19,20] The center's setup is supported by a 5-year grant from the German Ministry for Education and Research (BMBF).

Niels Grabe (University of Heidelberg, Germany) introduced the BMBF-funded consortium "GerontoSys: Stromal Ageing," which focuses on the role of aging fibroblasts in human skin aging. The long-term age-associated changes of isolated fibroblast cell strains, as well as their potentially altered capability to react to dynamic short-term pertubations, are determined on a genome-scale level. Multiple experimental and computational techniques on the genomic and proteomic level are applied. The results are validated in native tissue and organotypic *in vitro* tissue cultures. Research groups from the Universities Heidelberg, Freiburg, Munich, and Düsseldorf are involved here.

Axel Kowald (Humboldt University, Berlin, Germany) started with a description of the constant worldwide increase of human life expectancy over the last 150 years. However, the underlying biochemical mechanisms are, despite this enormous success, still unclear. During aging, changes appear at the organismic, cellular, and subcellular levels, leading to a network of complicated interactions and phenotypes. This situation makes it difficult to study the aging process experimentally, but also makes it a prime candidate for systems biological modeling. "GerontoMitoSys" is a BMBF project that started in 2010 with the aim of modeling mitochondrial pathways involved in aging and life-span control. Kowald's talk gave an overview of the planned experiments and models. He also discussed the differences between quantitative and qualitative models and argued that both modeling approaches are valuable tools for the investigation of the aging process.

Mathematical and Animal Models and Diseases Relevant to the Study of Aging

Modeling human aging in model organisms is of high relevance because it can be assumed that many of the underlying mechanisms are conserved.[4,9] Computational work features prominently here because finding similarities and dissimilarities across species on a large scale require automated approaches. In particular, the talks by de Magalhaes and Wipat, discussed above, described work on model organism data. Three more talks concerning model organism research and two talks about disease and aging in human were delivered. The relationship between disease and aging is a complex one, but it is clear that many computational analyses (such as cardiovascular risk prediction and intervention strategies as well as text mining research into neurodegeneration) can effortlessly be envisioned to be applied directly to the study of molecular ageing processes.

Daniel Levitis (Max Planck Institute for Demographic Research, Rostock, Germany) presented a simple model suggesting that the specificity of mutational action is affected not only by age-specific selection pressures, but also by the age-specific probability density of *de novo* mutations. Analyzing expression data from fruit flies, he suggested that most *de novo* mutations will cause increased mortality early in life and very few will cause mortality late in life. This may have profound implications for our understanding of the health challenges that can be expected at the extreme old ages.

Andreas Hoeflich (Leibniz-Institute of Farm Animal Biology, Dummerstorf/Germany) discussed the negative interrelationship between growth and life expectancy. He makes use of unique outbred mouse models (*Dummerstorfer* selection lines) characterized by extreme body mass and severely reduced life span. By crossbreeding strategies combining the *Dummerstorfer* outbred lines with transgenic or knockout mouse models, he is currently performing quantitative functional genome analysis with a particular focus on life span control for the major genes involved in growth, aging, and metabolism.

Greg Tyrelle (DNage B.V., Rotterdam, The Netherlands) outlined how he introduces DNA repair defects both *in vitro* and *in vivo* to study the effects of DNA damage accumulation (originating from either endogenous or exogenous sources) on the aging process in mouse. Such mouse models of accelerated aging may be used to find compounds that can intervene in aging-related pathology and biomarkers that can predict the onset and progression of aging symptoms. He described how the numerous high-throughput datasets, obtained by techniques such as microarrays, proteomics, glycomics, and metabolomics, may be integrated by a systems biology approach to elucidate the defects in the signaling mechanisms between DNA repair mutations and premature aging phenotypes. By using computational models of key pathways that are differentially regulated due to mutations in the DNA repair pathways, he intends to find new targets and biomarkers in the fields of osteoporosis, neurodegeneration, and premature aging syndromes.

Michael Greeff (German Research Center for Environmental Health, Neuherberg, Germany) presented a semantic text mining approach to analysis of data on neurodegenerative diseases like Alzheimer disease or Parkinson disease. These are a group of highly complex neurological disorders

that are difficult to model partly because classical data integration technologies cannot account for the aberrant protein-binding behaviors. Semantic text mining technologies can address both the complexity and the unique protein–protein interactions of neurodegenerative diseases by using high-quality data described in research articles,[21,22] and it allows the creation of qualitative representations of the disorders. Using *Excerbt*, a semantic text mining tool developed at the MIPS (Helmholtz Zentrum Munich) that relies on natural language processing, Greeff created a general overview of Parkinson disease, filtered a set of hippocampal Alzheimer genes, and identified their regulation by microRNAs.

Attila Altiner (University of Rostock, Germany) focused his remarks on cardiovascular disease and its treatment. In primary care, cardiovascular prevention relies greatly on the principles of drug-induced blood pressure lowering and the prescription of statins. These interventions, however, do not prevent cardiovascular events, they just make them less likely, thus setting back the age-related risk of a treated patient to that of an identical younger untreated person. A possible interpretation is that we are already applying "antiaging" medicine without understanding the mechanisms, but with evidence for the effects.

Stem Cells and Aging: Mechanisms, Networks, and Cell State Models

A strong connection is proposed between (insufficient) maintenance of stem cell reservoirs and (acceleration of the) aging process.[23] Antagonistic pleiotropy may partially explain such insufficient maintenance, given that early in life (until the usual end of the reproductive phase) it is more important to minimize the risk of cancer by a very strict control of proliferation. Three talks at the workshop focused on stem cell aging from various perspectives, giving an overview on mesenchymal stem cells (MSCs) and some informatics aspects concerning the analysis of stem cell data in relation to aging. The latter encompasses analyses of transcriptomic data, but high-level simulation analyses of cell state and cell fate in populations of stem cells were also presented.

Günter Lepperdinger from the Austrian Institute for Biomedical Ageing Research (Innsbruck/Austria) reported on aging studies with MSCs, a showcase for tissue-specific (or adult) stem cells. The clinical use of MSCs is an emerging field, and thus a prominent part of future regenerative medicine is assigned to this particular cell type. Early in life, most, if not all, uncommitted MSCs exhibit multipotential differentiation capacity, and their developmental fate is tightly controlled.[24] An important question concerns the general fitness of primary MSCs from individuals of different age and life history, as well as consequences of challenges such as hypoxia, which are affecting their basic stem cell properties.[25] Results presented at the workshop, and unpublished at that time, further argue that the basic properties of MSCs become altered *in vivo* by an inflammatory milieu. A continuous chronic stimulus appears to lead to a decline in proliferation potential and dysregulation of differentiation capacity, thus being causative for the diminished regenerative vigor in older age.[26]

Alexandra Stolzing (Fraunhofer Institute for Cell Therapy and Immunology, Leipzig/Germany) and ***Jörg Galle*** (Interdisciplinary Centre for Bioinformatics, Leipzig/Germany) reported on a combined modeling/experimental study of MSCs. MSC clones from the same donor often differ in their *in vitro* properties. This kind of heterogeneity has been suggested to originate from an individual decline in MSC function called stem cell aging. To explain these observations, an individual cell-based computer model of aging MSC populations was introduced. In this model, cells undergo permanent fluctuations in their state of differentiation. The amplitudes of these fluctuations are set by the environment. Aging is mimicked by assuming that each cell division increases the amplitude of stem cell state fluctuations, destabilizing these states in the daughter cells. Galle demonstrated that the model consistently describes experimental findings on MSCs.[27]

James Adjaye (Max Planck Institute for Molecular Genetics, Berlin/Germany) hypothesized that the metabolic stability of regulatory networks, that is, the ability of cells to maintain stable concentrations of reactive oxygen species (ROS) and other critical metabolites, is the prime determinant of life span. In a systems biology approach, the age-dependence of transcriptional changes of genes involved in insulin signaling, glutathione metabolism, immune responses (stabilizing networks), and oxidative phosphorylation (dissipative networks) in young and aged mouse tissues and human bone marrow–derived MSCs was investigated. The studies delineate age- and tissue-specific patterns of transcriptional changes that are consistent with the metabolic stability–longevity principle.[28] It was also highlighted that human induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), although not identical, share similar mitochondrial properties and, in particular, are better at modulating ROS levels in comparison to somatic cells.[29] This implies that cellular reprogramming can modulate the mitochondrial/oxidative stress pathway, thus inducing a rejuvenated state capable of escaping cellular senescence.

Conclusions and Outlook

At the end of the meeting, various issues of data integration were discussed. Creation of a central repository and analysis website was not considered realistic in the short or medium term. However, as technological advances in semantic web technology,[10] collaborative resource maintenance,[30] and ontologies[31] enable collaborative, structured, and content-guided data integration and versioning, establishment of a central community resource is of prime importance. Links between databases, database interoperability, and sharing of tools for maintenance and analysis are possible today, however, and part of the German "GerontoSys" effort is the establishment of best practices toward this goal.

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