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Dynamics of biomarkers in relation to aging and mortality

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ABSTRACT

Contemporary longitudinal studies collect repeated measurements of biomarkers allowing one to analyze their dynamics in relation to mortality, morbidity, or other health-related outcomes. Rich and diverse data collected in such studies provide opportunities to investigate how various socio-economic, demographic, behavioral and other variables can interact with biological and genetic factors to produce differential rates of aging in individuals. In this paper, we review some recent publications investigating dynamics of biomarkers in relation to mortality, which use single biomarkers as well as cumulative measures combining information from multiple biomarkers. We also discuss the analytical approach, the stochastic process models, which conceptualizes several aging-related mechanisms in the structure of the model and allows evaluating "hidden" characteristics of aging-related changes indirectly from available longitudinal data on biomarkers and follow-up on mortality or onset of diseases taking into account other relevant factors (both genetic and non-genetic). We also discuss an extension of the approach, which considers ranges of "optimal values" of biomarkers rather than a single optimal value as in the original model. We discuss practical applications of the approach to single biomarkers and cumulative measures highlighting that the potential of applications to cumulative measures is still largely underused.

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Abbreviations: AD, Alzheimer's disease; AL, allostatic load; APOE, apolipoprotein E; AUC, the area under the receiver operating characteristic curve; BA, biological age; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CSF, cerebrospinal fluid; CV, coefficient of variation; CVD, cardiovascular disease; dbGaP, the database of Genotypes and Phenotypes; DBP, diastolic blood pressure; DI, deficit index; DM, statistical (Mahalanobis) distance; FHS, Framingham Heart Study; FI, frailty index; FI-B, biomarker-based FI; FI-LAB, laboratory FI; GWAS, genome-wide association study; HDL, high-density lipoprotein; HPA, hypothalamic–pituitary–adrenal; HRS, Health and Retirement Study; LDL, low-density lipoprotein; MI, myocardial infarction; MRI, magnetic resonance imaging; PA, physical activity; PD, Parkinson's disease; PRS, polygenic risk scores; SBP, systolic blood pressure; SD, standard deviation; SNP, single nucleotide polymorphisms; SPM, stochastic process model; TC, total cholesterol; VVV, visit-to-visit variability.

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1. Introduction

Death is the end point of aging, certain diseases and accidents, and analysis of mortality data alone has a limited utility in investigation of the process of biological aging in individuals. Inclusion of additional information on the dynamics of relevant biomarkers can help get insights into aging as a biological process and how this process results in the increased chances of death with age. The current physiological state of an organism is characterized by a combination of values of different physiological indices. This instantaneous profile is useful per se, as it provides valuable information about the current aging status (a.k.a. biological age) of the body and its capacity to respond to stresses or damages, which is important for understanding the individual vulnerability to diseases and death at any given moment in the life. However, such "snapshot" of the physiological state does not help in understanding how exactly the organism arrived to this particular state. For example, if some person has a "younger" profile of biomarkers in the age of 80, compared to age peers, it is unclear from this information alone if such outcome is due to better values of respective biomarkers early in life, or due to their slower change with age, or both. Besides, different biomarkers do not necessary change with age in the same direction (e.g., beneficial or detrimental for health) in an individual. The physiological state at a given age is a result of the dynamic interplay of different processes in aging body and cumulative effects of various exposures to internal and external factors ("stressors") interacting with individual genotype starting from birth (or earlier) and up to the respective time point. It is imperative to use the information about the dynamic behavior of biomarkers, when available in data, in combination with other relevant variables in predictive models of mortality and health-related outcomes to improve their efficiency.

There is extensive literature on the relationship between various biomarkers and mortality (see e.g., Crimmins et al., 2008; Crimmins and Vasunilashorn, 2011). Most of such studies use a single measurement of a biomarker (e.g., at baseline). However, if a biomarker is measured only once, then this measurement does not contain information on its dynamics and the process of aging in an individual. It is necessary to have repeated measurements of essential biomarkers in the data to infer about the dynamics of physiological dysregulation, which, in a long run, eventually leads to death. The feasibility of respective analyses is supported by the growing availability of data on biomarkers in contemporary longitudinal studies collecting information on various biomarkers measured in aging humans at different time points (exams). Examples include the Framingham Heart Study (with the original cohort collecting measurements of some basic physiological indices such as blood pressure in as many as 30 exams in over 60 years), the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, the Atherosclerosis Risk in Communities Study, among others. The Health and Retirement Study (HRS) is another example of a longitudinal survey of a representative U.S. sample of approximately 20,000 Americans over the age of 50, and it currently has two waves of measurements of many biomarkers. The Long Life Family Study, a unique international study in three US cites and Denmark is now in the process of collecting data from Visit 2, which will provide a second measurement of various biomarkers in the large collection of families selected based on clustering for exceptional survival. All these studies also contain extensive genetic data, which have been made available for the research community through the database of Genotypes and Phenotypes (dbGaP) website. Such rich data allow for analyzing the effects of interaction of various socio-economic, demographic, behavioral and psychological variables with biological and genetic factors, to result in differential rates of aging and health deterioration in individuals.

In this mini-review, we will first summarize some recent publications investigating dynamics of biomarkers in relation to mortality (Section 2.1). Aging is an extremely complex process and interrelated biological changes can happen in multiple systems leading to physiological dysregulation, health deterioration and death. Deviations in multiple biomarkers can produce non-additive effect on mortality. Also, changes in specific biomarkers can be small but the cumulative effect of such changes across different domains of regulatory systems can be substantial and better predict mortality than individual variables. Several approaches to construct different summary measures from multiple biomarkers appeared in the literature based on biological theory, clinical evidence and statistical considerations. We will review several such approaches in Section 2.2.

Although the number of studies providing data on various biomarkers is increasing, there is no single study which would collect information on all biomarkers representing different aspects of the process of aging in its entirety. Therefore, approaches conceptualizing some mechanisms of aging-related changes known in the literature and evaluating them "indirectly" from available data are needed if one wishes to investigate such mechanisms in relation to various factors (e.g., socio-economic, demographic, genetic) and outcomes (e.g., mortality, morbidity). One such approach developed recently in the biodemographic literature, the stochastic process model (SPM), sometimes also known as the quadratic hazard model, incorporates such "hidden" mechanisms of aging in the structure of the model and it works with follow-up data on mortality (or other time-to-event outcome such as onset of a disease) and age trajectories of biomarkers which are collected in longitudinal studies, with addition of other information (socio-demographic, genetic, etc.), if available and necessary. Although a review of SPM has been published recently (Yashin et al., 2012a), this review was aimed at the audience with mathematical or statistical background. Here (Section 3) we provide a less technical presentation of the approach focusing on conceptual ideas, provide graphical illustration and discuss practical implementations of the methodology. We also describe (conceptually) an extension of the SPM which considers age-specific "ranges" of optimal values rather than a single optimal trajectory as in the classical SPM (technical details can be found in Supplementary material). Section 4 contains concluding remarks.

2. Static and dynamic measures of biomarkers in relation to mortality risk

In this section we overview some recent publications summarizing effects of various "static" and "dynamic" measures of biomarkers in relation to mortality risk. By "static" we mean the analyses in which the evidence comes from a single (e.g., baseline) measurement of respective biomarkers, and "dynamic" refers to analyses using repeated measurements of biomarkers over time in the same individual. We start with the studies investigating effects of a single biomarker and continue with discussion of some summary or cumulative measures based on multiple biomarkers. We note that there are many such composite measures which may be based on biomarkers only or on combination of information from biomarkers and other variables (e.g., socio-demographic, behavioral, comorbidity measures, etc.). Comprehensive discussion on all such measures is beyond the scope of this mini-review and we focused on a few approaches relevant for subsequent discussion.

2.1. Individual biomarkers and mortality risk

The literature on "static" biomarkers and their relation to mortality is enormous. We therefore restricted the first part of this