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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 socioeconomic, 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.

Keywords

biomarker; aging; mortality; longitudinal data; stochastic process model; dynamics; risk factor

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

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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 section to providing references to selected review papers where representative publications about specific biomarkers can be found.

Crimmins et al. (2008) extensively reviewed some of the most commonly used biomarkers in population aging research, including the markers of the cardiovascular system, metabolic processes, inflammation, hypothalamic-pituitary axis, nervous system, organ functioning, and genetic markers, as well as detailed interrelationships between these markers, where possible. The authors also addressed associations between individual markers and mortality. Crimmins and Vasunilashorn (2011) discussed links between the biomarkers and mortality in large population surveys oriented toward the general population. More recently Barron et al. (2015) conducted a systematic review of the literature on relation between blood-borne biomarkers and mortality in epidemiological prospective cohort studies. The authors found 20 biomarkers associated with mortality risk. Meta-analyses found most significant associations of all-cause mortality with C-reactive protein (CRP), brain natriuretic peptide, coronary heart disease (CHD) mortality, and white blood cell count (with hazard ratios around 1.5), which indicates that preventing chronic inflammation and heart failure in the elderly might help to increase longevity. All studies included in this review, however, contained only one baseline measurement of the biomarkers.

Despite a growing availability of biomarkers in longitudinal data, studies utilizing repeated measurements of biomarkers are considerably less numerous than those using a single measurement or cross-sectional data. Engelfriet et al. (2013) surveyed the literature with the aim of identifying promising new biochemical markers of aging focusing on their use in longitudinal studies of aging with repeated measurements of biomarkers from easily obtainable material such as blood samples. They concluded that "…longitudinal studies with repeated measurements of relevant biomarkers could greatly contribute to unraveling the complex web of aging and disease processes in humans." Below we summarize recent works evaluating the dynamic relationships between mortality and physiological indices from data on repeated measures of respective variables available in longitudinal studies. Most evidence on relationships between dynamics of biomarkers and mortality risk comes from epidemiological studies, many of which, although not nationally representative, have long follow-ups and collected reach and diverse data, including extensive genetic data, that can provide valuable insights in specific subgroups (for example, elderly people, families with exceptional longevity, etc.).

Glei et al. (2011) investigated age-related changes in a set of biomarkers using longitudinal data from a population-based Taiwanese study. They also summarized prior longitudinal studies on changes in biomarkers concluding that most of such studies are limited because of small samples or by design (clinical or convenience samples) and just a few studies have a relatively large sample (>500) but none of such studies is nationally representative. Glei et al. (2014) provided a review of prior works which examined individual biomarkers drawn from multiple systems as predictors of all-cause mortality as well as multi-system summary scores. They also analyzed data on participants of the nationally representative Taiwanese sample who had measurements of biomarkers in two exams to investigate whether inclusion of additional information on a change in biomarkers can help better predict mortality. They found that incorporating changes in biomarkers between two waves yields a small improvement in mortality prediction compared to a single measurement of biomarkers which still warrants longitudinal collection of biomarkers for long-term predictions of

mortality (e.g., for a period distant from the time of biomarker collection, an updated set of biomarker values can substantially enhance prediction).

Studies with two (or a few) longitudinal observations provided an important step forward compared to studies with a single observation because they allowed for investigating the effects of changes in biomarkers on outcomes of interest. One particular focus in the literature was on investigating the impact of changes in weight or BMI on mortality. The literature on this topic is extensive and we present just a few of those papers (with studies performed in different countries) in this mini-review.

In a cohort study of 2,628 elderly males and females examined over ten years starting in 1970s in Sweden, Dey and co-authors made an observation that weight loss greater than 10% between ages 70 and 75 significantly increases risk for subsequent 5 and 10 year mortality in both sexes compared to the weight stability at the same ages (Dey et al., 2001). In line with this, a three-year longitudinal study of community-living aged subjects in Hong Kong found that at ages 70 and older weight loss occurs even in the absence of disease and is associated with greater mortality (Woo et al., 2001). More recent research supported these observations (Cao, 2015; Myrskyla and Chang, 2009). A study of a nationally representative Health and Retirement Study sample of 13,104 individuals followed-up between 1992 and 2006 found that weight loss rather than a gain was associated with excess mortality among normal to mildly obese middle- and older-aged adults (Myrskyla and Chang, 2009). The excess risk increased for larger losses and lower initial BMI in their study, thus suggesting that the potential benefits of a lower BMI may be offset by the negative effects associated with weight loss in non-severe obese people (with initial BMI less than 35). The rapid weight loss in the elderly could potentially be a marker of accelerated physical senescence leading to an earlier onset of physical frailty, often associated with a higher mortality risk in the old (Jotheeswaran et al., 2015).

Longitudinal studies collecting multiple observations for the same individual provide better opportunity to investigate dynamic aspects of relationships between physiological variables and health-related outcomes compared with studies with just a few observations. This is especially true for biomarkers that change non-monotonically with age, or are known to fluctuate substantially over the life course (for example, weight or BMI). Variations in age trajectories of physiological indices between individuals may also reflect underlying differences in the physiological state for these individuals, which may indicate varying levels of physiological dysregulation. Therefore, such variations can be expected to be predictive of future health deterioration and mortality.

Arnold et al. (2010) used longitudinal data on weight measurements in participants of the Cardiovascular Health Study (CHS) who had at least five weight measurements at annual clinic visits between 1992 and 1999 and constructed different characteristics of weight dynamics such as mean weight, variability about the mean, average weight change per year, and episodes of weight cycling or instability (gain/loss). Such measures were used to estimate the associations of weight dynamics with physical functioning and mortality in older adults (aged 65+ at enrollment) using seven-year follow up data. They found that a lower weight, weight loss, higher variability, and weight cycling were risk factors for

mortality, after adjustment for demographic risk factors, height, self-report health status, and comorbidities. This was the first study which evaluated simultaneously all these four dynamic measures capturing unique aspects of the weight trajectory. Substantially, these findings suggest that inability to maintain a stable weight at older ages may reflect difficulties in maintaining homeostasis which result in increased risk for physical disability or mortality (Arnold et al., 2010).

Consideration of the analytic approaches is important in analyses of dynamic variables in relation to mortality or other outcomes in longitudinal studies. As the example of BMI dynamics and mortality in the Framingham Heart Study (FHS) in He (2011) shows, the use of different traditional analytic methods may lead to different conclusions depending on study designs and this may also be true for other studies and for other variables. Application of advanced methods can also provide additional insights on dynamics of longitudinal variables compared to standard approaches. Several recent publications applied different techniques to evaluate distinct trajectories of biomarkers and investigated their relation with mortality and other health-related outcomes. Zheng et al. (2013) applied the latent class trajectory models to BMI data in the HRS with the objective to capture heterogeneity in the entire BMI trajectory and to examine mortality related to these trajectories. They identified six distinct latent trajectories (normal weight downward, normal weight upward, overweight stable, overweight obesity, class I obese upward, and class II/III obese upward) and found that the overweight stable trajectory group had the lowest mortality risk. They also observed that associations of the BMI trajectory with mortality are stronger than the associations of the initial BMI status alone. This highlights the importance of studying dynamic characteristics of trajectories in relation to mortality. Zajacova and Ailshire (2014), having the similar goals (to investigate heterogeneity in body weight trajectories among older adults and their association with mortality risks), performed analyses of BMI data in the HRS using the joint growth mixture-discrete time survival model which allows one to identify distinct classes of trajectories and determine differences in mortality risk among the trajectory classes. They identified three distinct classes of BMI trajectories: stable overweight, obese gaining, and obese losing and found that the stable overweight group has the lowest mortality similar to results of Zheng et al. (2013). These results also show that making conclusions about mortality risk based on a single observation can be misleading (e.g., an overweight individual could be from the stable overweight or obese losing groups with different risks). It should be noted that similar or other data-driven approaches to identify types of trajectories and their impact on mortality at older ages in other datasets such as the FHS can shed additional light on the dynamic relationship between the trajectories of BMI (as well as other biomarkers) and mortality at these ages (Yashin et al., 2006; Yashin et al., 2010a).

The works cited in the above paragraph deal with the US-based data. Murayama et al. (2015) is the first study evaluating the heterogeneity of BMI trajectories and its relationship with mortality at old ages in an Asian (Japanese) population using data from the National Survey of the Japanese Elderly. The study found different patterns of changes in BMI than those in Western populations: the majority of older Japanese had downward trajectories at the border between normal weight and underweight subgroups and just a minor group (5%) that followed the stable overweight trajectory. Despite this difference, this small proportion

of older Japanese in the stable overweight group had the lowest risk of death, which is similar to the observations in the Western populations described above. These consistent findings (i.e., the lower mortality risk in the overweight group) are in line with the point of view that "extra body weight, including lean tissue mass and fat mass, may provide protection against nutritional and energy deficiencies, metabolic stresses, the development of wasting and frailty, and loss of muscle and bone density caused by chronic diseases such as heart failure" (Zheng et al., 2013).

High levels of BMI (obesity) have been linked with elevated levels of inflammatory mediators such as C-reactive protein (CRP) (Rodriguez-Hernandez et al., 2013), which, in turn, are associated with increased risk of mortality and cardiovascular disease (CVD) (Currie et al., 2008; Kaptoge et al., 2010). O'Doherty et al. (2014) used the CHANCES consortium data from four European countries which had repeated measures of CRP and BMI to examine the relationship between BMI and CRP with all-cause mortality and first fatal/nonfatal CVD event. They found that CRP, independent of BMI, is positively associated with both mortality and CVD risk and concluded that, if inflammation links CRP and BMI, then they may participate in distinct or independent inflammatory pathways.

There is considerable recent interest in the literature for longitudinal analyses of visit-to-visit variability (VVV) of blood pressure (BP) in relation to CVD and mortality in both clinical settings and in general populations. Diaz et al. (2014) conducted a systematic review and meta-analysis to examine the association between VVV of BP and CVD and all-cause mortality. Although limited by a small number of studies available for the meta-analysis, the review confirmed that modest associations between VVV of BP and CVD and all-cause mortality have been found in the published research. Of note, these studies utilized many different measures of VVV such as standard deviation (SD), coefficient of variation (CV), and SD about regression line with BP regressed across visits, among others. Most studies investigated VVV of BP in select populations such as secondary analyses of randomized controlled trials or patients with or at high risk for vascular diseases in clinical settings. There are still several studies which analyzed VVV of BP in relation to CVD and mortality in general population. The earliest of those dates back to 1983 (Hofman et al., 1983) but the other are more recent.

Muntner et al. (2011) investigated the relationship between VVV of BP and all-cause mortality using data on US adults from the Third National Health and Nutrition Examination Survey. The variability of BP (defined as SD and CV across visits in this study) was assessed from three consecutive blood pressure readings during three separate visits from 1988 to 1994. The authors found that higher levels of short-term VVV of systolic (SBP) but not diastolic (DBP) blood pressure were associated with increased all-cause mortality. The authors discussed several hypotheses for mechanisms underlying higher levels of VVV of SBP (e.g., that arterial stiffness may be one factor leading to higher blood pressure variability) but argued that additional research is needed to identify possible mechanisms involved in the observed association of VVV of SBP with mortality.

Suchy-Dicey et al. (2013) evaluated whether the variability in SBP is associated with all-cause mortality, incident myocardial infarction (MI), and incident stroke, independent of

mean SBP or trends in SBP levels over time using data from the Cardiovascular Health Study (CHS) of elderly (aged 65+) individuals. They computed intra-individual mean as the mean of the five SBP measures from the first five annual clinical visits and defined the intra-individual change over time ("slope") as the beta coefficient for the linear regression of these individual SBP measures. Then intra-individual variability (the primary variable of interest) was calculated as the square root of the variance from the residuals from the participant-specific regressions. They found that intra-individual SBP variability in older adults was significantly associated with increased risk of total mortality and of incident MI but was not associated with the risk of stroke (which may be caused by specifics of the variability measure and the study design). The authors also discussed potential biological mechanisms by which the long-term variability in BP may affect risks of mortality or CVD. For example, the chronic large fluctuations of BP may accelerate wear and tear of the vascular tissue, and thus contribute to the development (or severity) of atherosclerosis. Oppositely, the chronic fluctuations of BP may reflect the underlying pathological process manifested in vessel sclerosis and increased stiffness (Karwowski et al., 2012). The existence of many hypotheses on the mechanisms by which SBP variability may increase all-cause mortality indicates that more research is needed to elucidate exact etiologic pathways of the observed associations before proposing clinical implications for individual patients. In addition, it is important to conduct more studies with non-Western populations to find out how or whether these observations can be generalized. For example, Yinon et al. (2013) was the first study analyzing the variability of BP in a South-Asian (rural Bangladeshi) population and they found that the variability of BP over time (measured as the SD using all available longitudinal measures) was significantly related to the risk of CVDs but not to all-cause mortality. This inconsistency with Western studies can be due to substantial differences between participants of this study and Western studies in the levels of biomarkers (e.g., much lower BP and BMI levels in the Bangladeshi than in the US samples), as well as in environmental exposures or other possible factors which need to be explored.

Poortvliet et al. (2013) used the Leiden 85-plus Study to evaluate the independent contributions of both the trend in SBP and the SBP value at age 90 to the prediction of mortality in nonagenarians. The Leiden 85-plus Study is a prospective population-based study among 85-year-old inhabitants of the city of Leiden (the Netherlands) which collects biomarker data and follow-up information thus providing an opportunity to explore dynamics of biomarkers in relation to mortality in the older ages. The authors defined the "trend" as the regression coefficient in a linear regression of SBP against time using individual data over the five preceding years (85–90 years) for each participant. They found that at the oldest old ages, both decreasing trend in SBP over the previous five years and the current SBP value independently contribute to prediction of all-cause mortality. One interesting and important observation from this study is that a decreasing trend in SBP in the preceding five years in participants with a low SBP at age 90 predicted a more than doubled mortality risk compared to participants with an average five-year trend in SBP and a high SBP at age 90. This suggests that keeping SPB relatively high and stable in advanced years of life may be more important for survival toward extreme ages than reducing risks of particular health conditions such as, e.g., CHD or stroke. Indeed, excessive reduction in SBP at older ages might promote physical frailty, a major risk factor for all-cause mortality in the

very old. We additionally explored the trade-off-like influence of risk factors for major diseases and senescence related causes, such as physical frailty, on all-cause mortality in the elderly in a recent review paper (Ukraintseva et al., 2016).

Dynamics of traditional metabolic risk factors (such as BMI, cholesterol, glucose, blood pressures, triglycerides, albumin, hemoglobin, CRP, 19 risk factors in total) in relation to mortality in elderly (85+) individuals has been investigated in van Vliet et al. (2010) using the Leiden 85-plus Study. These traditional metabolic risk factors and indicators of health and disease were measured annually during a five-year follow-up period (giving up to six measurements per participant). They found that mortality was associated with stronger declines in BMI, total cholesterol (TC) levels, and blood pressures and with weaker increases in HDL cholesterol levels. Similar effects were detected in Yashin et al. (2010a) using different method and data. The second major finding in van Vliet et al. (2010) is that annual changes in these traditional metabolic risk factors cluster together with indicators of health and disease, and such clusters are associated with specific causes of death. The distinct profile identified in such analyses (annual changes in total and LDL cholesterol, albumin, and hemoglobin levels showed the strongest correlation with respective principal component) is suggestive of underlying wasting disease.

A distinct example of epidemiological studies useful for analyses of trajectories of biomarkers and mortality is the FHS (Dawber et al., 1951; Feinleib et al., 1975; Splansky et al., 2007), which, with its unique design (multigenerational study, with follow up as long as more than 60 years in the original cohort) and rich data (up to 30 biannual measurements of some physiological indices in the original cohort, extensive genetic information), provides vast opportunities to explore relationships between dynamics of biomarkers and mortality risk, and the role of other factors such as genetic markers in these relationships. Below we briefly summarize recent results on available empirical evidence on such relationships evaluated from the FHS data.

Several earlier studies from the 1980–1990s used the FHS data to explore associations between changes in selected biomarkers (weight, BMI, lipid levels, BP) and morbidity and mortality risks, considering impact of other factors such as smoking cessation or diet. For example, Higgins et al. (1993) studied dynamics of weight or BMI, and its impact on CVD and total survival, in a sample of 2,500 male and female participants of the FHS original cohort who were between 35 and 54 years old at baseline and followed for 20 years. The authors found that relative risks of death from CVD and all causes combined were significantly greater in participants whose weight or BMI decreased after adjusting for age and other risk factors (Higgins et al., 1993). At the same time, weight loss was associated with improvements in blood pressure and cholesterol levels. These seemingly paradoxical results suggest that maintaining stable trajectories of weight later in life might be especially beneficial for longevity, while having “good” levels of certain risk factors for major diseases may be more beneficial for morbidity reduction earlier in life. Indeed, at the oldest old ages risks of many complex diseases (e.g., CHD, cancer, asthma, diabetes) decline, while mortality risk continues to increase. This indicates that postponed manifestation of physical senescence may be more important for achieving extreme longevity than simply having a lower disease risk. The apparent trade-off between the detrimental impact of weight loss on

mortality rate and its beneficial impact on some risk factors for disease was further explored by Allison et al. (1999) using the FHS data. They found that although the weight loss was associated with an increased mortality rate during eight years of follow-up, thus confirming others' findings, the fat loss was associated with a decreased mortality rate in their study. This indicates that most of the detrimental effect of the weight loss on mortality could come from the muscle loss, which typically accompanies senescence. This is in line with the above consideration that postponed manifestations of physical senescence (such as physical frailty, sarcopenia, muscle atrophy, etc.) may be important for achieving extreme longevity.

Hofman et al. (1983) investigated how changes in BP are related to the occurrence of CVDs and death. They used the FHS data with 26 years of follow-up divided into a 12-year "observational" period for assessing the rate of change in BP in individuals (estimated as the slope obtained from regression of individual measurements of blood pressure on time) and a subsequent period during which follow-up outcomes (incidence and mortality) were determined. They found, in particular, that this dynamic variable (slope) was associated with mortality from all causes so that individuals with larger slopes (i.e., with a faster increase of blood pressure) have higher mortality risks. Kreger et al. (1994) examined individual variability in TC in exams 2 to 7 of the FHS in relation to morbidity and mortality outcomes over the next 24 years. The TC variability was computed as the square root of the mean squared error for observations fitted by a linear function. The results showed a positive association of such TC variability with all-cause mortality in men and cardiovascular and coronary diseases incidence and mortality in both sexes with risk ratios for highest vs. lowest quartiles of TC variability up to 1.75.

These earlier studies using the FHS data were based on shorter follow-up periods than this ongoing study can provide nowadays. The additional follow up period in the FHS allows for investigating the dynamics of biomarkers at wider age ranges including older ages where such individual trajectories may have a more complex shape (e.g., an inverse U-shape, i.e., an increase in middle age followed by a decline at older ages). Several papers considered dynamics of biomarkers in the FHS in relation to mortality and morbidity outcomes using the more extended recent FHS data.

Yashin et al. (2006) further investigated whether shapes of age trajectories of several physiological indices (such as BP, BMI, blood glucose, TC, hematocrit and pulse rate) in middle age (40–60 years) affect the residual life span distribution. The analysis demonstrated that indeed the survival patterns in individuals who survived to age of 65 depended on the behavior of the physiological indices between ages 40 and 60 years.

Individuals with values of biomarkers substantially deviating from "optimal" levels should experience higher mortality risks and tend to die out first. Yashin et al. (2012b) showed that the average trajectories of different biomarkers in individuals dying at earlier ages deviate substantially from the trajectories in long-lived individuals: in the former groups, trajectories for many biomarkers tend to increase to higher levels and/or start declining earlier, sometimes at a faster rate, than the trajectories in long-lived individuals. This indicates that the deviant dynamics of biomarkers with age may result in higher mortality risks.

Yashin et al. (2010a) and Yashin et al. (2012b) investigated how dynamic characteristics of individual age trajectories of biomarkers at some age interval in the middle or old age affect later mortality risk. For biomarkers with almost monotonic age trajectories (e.g., blood glucose and pulse pressure), such characteristics were: an initial value of at age 40, the rate of change at ages 40 to 60, and the variability (i.e., deviations of observed values from those approximated by a linear function at ages 40 to 60). For biomarkers with non-monotonic trajectories (inverse U-shape, such as BMI, TC, SBP, DBP), the dynamic characteristics were: the rate of increase, age at reaching the maximal value, the rate of decline after reaching the maximum, and the variability at biomarker- and sex-specific age intervals. The analyses showed that these dynamic characteristics of trajectories of biomarkers at middle and old ages indeed influence subsequent mortality risk at older ages. Yashin et al. (2010a) considered survival functions in two groups of individuals having values of dynamic characteristics above and below the median of their sex-specific distributions. Yashin et al. (2012b) evaluated survival functions in groups corresponding to tertiles of respective distributions and found both monotonic and U-shaped relationships (with the middle tertile group having the best survival).

Availability of genetic information in the FHS allows computations of average age trajectories of biomarkers in carriers of different genotypes or alleles. Arbeev et al. (2012) found that the average age trajectories of TC and DBP in individuals dying at earlier ages markedly deviate from those of the long-lived groups and these patterns differ for carriers and non-carriers of the APOE e4 allele. It was observed that long-lived individuals, compared to short-lived ones, have consistently higher levels and a less steep decline of both TC and DBP at old ages (65+) when such levels naturally go down in aging human organism. This observation is in line with findings in Yashin et al. (2010a) and Yashin et al. (2012b) that individuals with the slowest decline in biomarkers had the best survival.

Recently Zhang and Pincus (2015) showed using data from the FHS that about 10% of variation in future lifespan can be predicted using the common physiological measurements of height, weight, BMI, blood glucose level, and SBP and DBP at ages 28–38. They also found that incorporating information from multiple time points in the “cumulative” measure which sums the past values of physiological measurements increased predictive capacity. These results indicate that harmful effects from the sustained abnormal levels of these variables (e.g., having high blood pressure, high blood glucose, or being overweight) gradually accumulate over time that causes an additional damage in the organism’s systems leading to various pathologies and, eventually, to death.

In addition to emerging studies on dynamics of biomarkers and mortality, substantial efforts have been recently directed towards understanding connections between the dynamics of biomarkers and major diseases, most notably the Alzheimer’s (AD) and Parkinson’s (PD) diseases. For AD, longitudinal changes in cerebrospinal fluid (CSF) and MRI biomarkers, such as CSF proteins (amyloid-β, amyloid precursor protein, tau protein, and other), magnetic resonance imaging brain volume and rate of atrophy, and in cognitive test scores, have been most often targeted. Several studies reported significant longitudinal changes in CSF biomarkers in AD patients, while others did not; some suggested that the shape of the association of AD biomarkers with disease severity can sometimes be nonlinear (e.g.,

sigmoidal or quadratic) and differ between biomarkers (Jack et al., 2013; Mattsson et al., 2012; Mouiha et al., 2012; Wildsmith et al., 2014). Other groups utilized longitudinal imaging measures to estimate temporal trajectories of cortical amyloid deposition before the onset of clinical symptoms to use them as potential predictors of progression to AD (Bilgel et al., 2015). Some CSF biomarkers also changed over time correlating with progression and/or cognitive decline in patients with PD (Hall et al., 2016).

Predicting coronary artery disease risk based on multiple longitudinal biomarkers started to be explored as well (Yang et al., 2016). There have been found associations between habitual physical activity (PA) and changes in PA over time and onset of CHD in 3,320 ambulatory men during a median of 11 years of follow-up, favoring even light PA (Jefferis et al., 2014). Another study assessed the impact of chronic psychological stress in midlife and older Australian women on subjective and objective health markers, and concluded that the frequency and chronicity of stressors increases women's risk of adverse health events (Seib et al., 2014). Also, important research has been done on changes in BMI over time in twin studies demonstrating that long-term (mean follow-up range=6.4 years) BMI discordance between adult monozygotic twins is rare, thus indicating a potentially major role of genotype in stability of age-patterns of BMI (van Dongen et al., 2015).

All these studies highlight the importance of considering the dynamics of biomarkers in relation to mortality, health outcomes, and the processes of aging. Joint influence of different aging-related mechanisms can manifest itself in the observed dynamics of biomarkers and its relation to mortality risk. The approach to indirect evaluation of such "hidden" characteristics of the process of aging from individual age trajectories of biomarkers and follow-up data on mortality is discussed in Section 3. But first we proceed in the next section with a brief overview of several methods to construct cumulative measures based on multiple biomarkers. Such composite indices are appealing as they often are better predictors of mortality than single biomarkers. They may also have rationale from both theoretical (biological) as well as practical (statistical) perspectives.

2.2. Cumulative Measures Based on Multiple Biomarkers and Mortality Risk

The process of aging results in biological changes in different organs and physiological systems in an organism. Such changes can accumulate over time in a complex and non-additive fashion across different regulatory systems and their cumulative effect manifests in increasing physiological dysregulation, development of chronic diseases and death. Summary measures based on combinations of biomarkers from different physiological systems aim at capturing this complex effect of aging on different systems and they are expected to be better predictors of mortality and health-related outcomes than individual biomarkers.

One of such measures which found broad applications to different data is allostatic load (AL). Different operationalizations of AL which are used in the literature represent practical realizations of the theoretical concepts of allostasis and AL (McEwen, 1998; McEwen and Stellar, 1993; McEwen and Wingfield, 2003; Sterling and Eyer, 1988). The concept of allostasis is defined as "maintaining stability through change" (McEwen and Wingfield, 2003), which is "a fundamental process through which organisms actively adjust to both

predictable and unpredictable events" (McEwen and Wingfield, 2003). AL is the "cumulative cost to the body of allostasis" (McEwen and Wingfield, 2003) which accumulates when regulatory systems operate at elevated or reduced levels denoted as "allostatic states" (Koob and Le Moal, 2001; McEwen and Wingfield, 2003). Recently a more comprehensive "reactive scope model" (Romero et al., 2009) has been proposed which is based on the allostasis concept but can be generalized beyond the systems involved in energy balance as in the AL model. Although there are still some refinements and discussions on the concepts of allostasis and AL (McEwen and Wingfield, 2010; Romero et al., 2009), the conceptual idea gained popularity and there is extensive literature on practical implementation of AL in real data.

The original operational definition of AL was based on 10 biomarkers and it counted the "high risk" values of the biomarkers into a summary score of 0 to 10 (Seeman et al., 1997). The biomarkers included in the original definition of AL were: SBP and DBP (represent cardiovascular activity), waist-hip ratio (reflect more long-term levels of metabolism and adipose tissue deposition), serum HDL and total cholesterol levels (indicating long-term atherosclerotic risk); blood plasma levels of total glycosylated hemoglobin (an integrated measure of glucose metabolism during a period of several days); serum dehydroepiandrosterone sulfate (a functional HPA axis antagonist); 12-hour urinary cortisol excretion (an integrated measure of 12-hour HPA axis activity); 12-hour urinary norepinephrine and epinephrine excretion levels (integrated indices of 12-hour sympathetic nervous system activity) (Seeman et al., 1997). Thus, the components of this score reflect parameters of different regulatory systems contributing to wear and tear on the body.

Various modifications of the original operationalization of AL and other approaches to its computation have been suggested in the literature (see detailed discussion in recent review papers by Beckie, 2012; Juster et al., 2010; Leahy and Crews, 2012). The association of AL and mortality has been documented in different studies. For example, Seeman et al. (2001) found that higher baseline AL scores were associated with significantly increased risk for seven-year mortality in the MacArthur Successful Aging Study. These findings supported the concept that AL is a measure of cumulative biological burden that can provide insight into the cumulative risks to health from biological dysregulation across multiple regulatory systems (Seeman et al., 2001).

With a few exceptions, such studies evaluated associations between baseline measurement of AL and subsequent mortality. Several studies explored the association between dynamic changes in AL and mortality. Karlamangla et al. (2006) investigated how initial values and changes in biomarkers were related to mortality in the MacArthur Studies of Successful Aging. They observed that individuals with increased AL score over a 2.5-year period had higher risk of subsequent all-cause mortality compared with participants whose AL decreased over the same period. The fact that both baseline AL and the change in AL were independently and significantly associated with subsequent all-cause mortality suggests that not only the current state of respective biomarkers but also the history of abnormal values of these biomarkers contribute to mortality risk. Hwang et al. (2014) showed similar results to Karlamangla et al. (2006) in a bigger population-based community study in Taiwan. They also found that both static and dynamic measures of AL were related to mortality and a fast

increase in AL was associated with significantly higher mortality risk compared to participants with declining AL. There are also other recent studies exploring the dynamics of AL in longitudinal studies in relation to other outcomes (see, e.g., Merkin et al., 2014; Upchurch et al., 2015). However, in general, the potential of longitudinal studies in this area is largely underexplored and it is recognized in the literature that investigation of AL measured at multiple time points in population-representative longitudinal studies is one of the priorities for future research (Beckie, 2012).

Another popular approach to construct cumulative scores is a frailty index (FI) (Mitnitski et al., 2001), also known as a deficit index (DI) or an index of cumulative deficits (Kulminski et al., 2008). This score was developed to quantify frailty based on accumulation of various health-related deficits. An FI is computed as the number of deficits in an individual divided by the total number of available deficits so that the theoretical range of FI is between 0 and 1 (although in practice the maximal values of FI in different studies are close to 0.7, see, e.g., Rockwood et al. (2015)). The FI (or DI) have been investigated by several research groups in applications to different datasets from different countries and they showed remarkable robustness of results to data collection methods (clinical vs. self-report), study design (cross-sectional vs. longitudinal) and variables used in construction of the index. The FI is a strong predictor of adverse outcomes including death and it outperforms chronological age as a predictor of mortality (see discussion summarizing these topics in Mitnitski and Rockwood, 2015). Section 3.3 discusses applications of FI in the SPM framework which investigated relations between FI, aging-related mechanisms and mortality.

Although various types of deficits can be combined to produce an FI (such as health conditions, symptoms, diseases, etc.), the versions of FI constructed from various biomarkers and standard laboratory tests have recently been suggested in the literature. Howlett et al. (2014) developed an FI based on 21 routine blood tests plus systolic and diastolic blood pressure (the “laboratory FI” or FI-LAB) and showed that FI-LAB can identify older adults at an increased risk of death. This observation was later confirmed by Rockwood et al. (2015) who considered FI-LAB in long-term care settings. Mitnitski et al. (2015) constructed a biomarker-based FI (FIB) using 40 biomarkers of cellular aging, inflammation, hematology, and immunosenescence and found that FI-B was more powerful for mortality prediction than any individual biomarker and it was robust to biomarker substitution. These studies indicated that different biomarkers combined into the FI can be used to predict mortality and the observation that so many biomarkers contribute to mortality prediction reflects the systemic characteristics of aging and mortality which such cumulative measures as the FI can help reveal and which may be masked when individual biomarkers are analyzed (Howlett et al., 2014; Mitnitski et al., 2015).

As such “biomarker-based” FIs are new developments, it is important to consider how such indices compare with more “traditional” ones counting health-related deficits from questionnaires collected in surveys or in clinical settings. Howlett et al. (2014) constructed the “standard” FI from data obtained during the clinical evaluation in the Canadian Study of Health and Aging which were routinely used in analyses before. They found that the distributions of the traditional FI and the FI-LAB were similar with comparable medians (0.24 vs. 0.27) and ranges (0.02–0.72 vs. 0.05–0.63). Mortality rates generally increased as

the indices rose with a more marked effect for the FI-LAB. Both indices also contributed separately in the Cox regression analyses although there was only a moderate increase in AUC for the combined index compared to the separate ones (0.71 for the "traditional" index, 0.72 for the FI-LAB and 0.74 for the combined index). Mitnitski et al. (2015) compared the FI-B with the index computed earlier from 40 clinical variables in the Newcastle 85+ Study and found that those are significantly but weakly correlated and showed different distributions. They observed, for example, that the individuals ranked as "clinically fittest" (i.e., those with 0 or 1 clinical deficit in the "clinical" FI) still had a sizable level of biomarker-based deficits (average FI-B in this group equals 0.33 with 95% confidence interval 0.32–0.34). The highest levels of the two indices were similar (95^{th} percentile 0.48 in the FI-B vs. 0.46 in the other index) but the lowest ones were much higher in the FI-B (5^{th} percentile 0.24 vs. 0.06 in the "clinical" FI). Such observations suggest that the FI-B could be a more sensitive measure of health at lower values of the clinical deficits so that the FI-B may better reflect subclinical deficits accumulation and that "the FI-B could be used as a pre-clinical measure to identify at-risk individuals before changes are apparent on clinical examination" (Mitnitski et al., 2015). The analyses of the combined index (the FI-B plus clinical) revealed the better discriminatory ability of this index (AUC=0.76 vs. 0.68 and 0.71 for its components) indicating that the FI-B complements the clinical FI in this study. As the authors indicate, combining the biomarker-based indices with those based on clinically detectable deficits can help better identify individuals at higher risk of death. It is also important to validate how such biomarker-based indices perform in other studies, their sensitivity to the choice of biomarkers and thresholds used for dichotomization in the construction of biomarker-based indices, as well as to evaluate to what extent such indices can improve prediction of adverse outcomes other than mortality.

The properties of the FI suggest that it can be considered as an approximation of individual's biological age (BA). The concept of BA evolved in the literature as the approach to merge multiple biomarkers into a single variable with the aim to have a better assessment of an individual's aging process than chronological age. Several methods of BA computations were developed but there is a lack of consensus on what is the most optimal one. Recently, Levine (2013) compared predictive ability of several BA algorithms and found that the Klemera and Doubal (2006) method was the most reliable predictor of mortality performing significantly better than chronological age. The fundamental relationship between the FI and BA was discussed in recent publications by Mitnitski and Rockwood (Mitnitski and Rockwood, 2014, 2015) but there is some disagreement on this (Levine, 2014). Note that BA, computed from cross-sectional data, cannot provide an input on longitudinal changes within a person. Therefore, longitudinal data containing repeated measures of biomarkers are necessary to evaluate the rate (or "pace") of aging within specific individual. In a recent publication, Belsky et al. (2015) suggested such longitudinal measure, the "Pace of Aging." They applied mixed-effects growth models to compute individual slopes using repeated measurements of 18 biomarkers and calculated individual "Pace of Aging" as the sum of these 18 slopes. The Pace of Aging is thus a "dynamic" measure which captures individual longitudinal changes across different physiological systems, and it is different from a "static" BA computed from a single measurement in cross-sectional studies. The authors found that such longitudinal measure allows quantification of the pace of coordinated

physiological deterioration across multiple organ systems (e.g., pulmonary, periodontal, cardiovascular, renal, hepatic, and immune function) and can help assess biological aging in young humans who had not yet developed age-related diseases. These findings highlight the importance of incorporating multiple longitudinal repeated measures of biomarkers tracking changes across different organ systems in studies of aging. It is also important to investigate how this or different dynamic measures can be applied to studies with wider ranges of ages including the oldest old ages where the dynamics of different biomarkers follows non-linear (e.g., an inverse U-shape) patterns (Yashin et al., 2010a).

Another approach to construct a composite measure from multiple biomarkers has been presented in Cohen et al. (2013). They suggested a measure of physiological dysregulation based on statistical distance (specifically, Mahalanobis distance, (De Maesschalck et al., 2000)), DM. This statistical distance is constructed for the joint distribution of multiple biomarkers and it uses the correlation structure of the biomarkers to measure how "aberrant each individual's profile is with respect to the overall average (centroid) of the reference population" (Cohen et al., 2015). This "reference" population is assumed to represent the "normal" physiological state. The biomarkers used for construction of DM in Cohen et al. (2013) were selected from the original list of 63 common blood chemistry markers including blood metabolites, hormones, inflammatory markers, basic blood count measures, micronutrient levels, lipid levels, and ion levels. These blood markers have been separately (or as panels) used in various studies of health. However, they are not typically used in aging studies all together, as a combined set of blood biomarkers. The DM variants constructed from subsets of biomarkers from this original list (from the "positive suite" containing 14 biomarkers with deviances from baseline means positively correlated with age: red blood cell count, hemoglobin, hematocrit, osteocalcin, calcium, sodium, potassium, chloride, total cholesterol, BUN–creatinine ratio, creatinine, albumin, bilirubin (direct), basophils, and from the "negative suite" of 5 biomarkers with deviances from baseline means negatively correlated with age: vitamin D hydroxyl, alkaline phosphatase, vitamin D dihydroxyl, alanine transaminase, ferritin) were suggested as the measure representing multi-systemic physiological dysregulation in aging. The authors showed that such DM correlated positively with age, increased over time in individuals and higher values of DM predicted higher subsequent mortality. The results supported hypotheses of simultaneous dysregulation in multiple systems and showed that DM provides an approach to reduce high-dimensional biomarker space into a single measure which summarizes information about physiological dysregulation in an aging organism.

Several publications about DM appeared in the literature since the original paper by Cohen et al. (2013) which investigated the properties of DM and applied the measure to different datasets. Milot et al. (2014) showed that DM trajectories (specifically, individual slopes of DM) predict mortality, frailty, and chronic diseases (cancer, cardiovascular diseases, and diabetes). The results for mortality were replicated in three longitudinal studies thus confirming the role of dynamics of physiological dysregulation (as represented by DM) as the predictor of mortality in different studies. Cohen et al. (2014) extended the analyses of DM to two additional datasets assessing the stability of the measure across populations and concluded that "statistical distance as a measure of physiological dysregulation is stable across populations in Europe and North America." Cohen et al. (2015) investigated the

sensitivity of DM to the number and choice of biomarkers. Analyses with measures calculated using different subsets of biomarkers showed that the effect of physiological dysregulation increases as the number of biomarkers increase but with a "saturation" effect, i.e., the value of additional variables diminishes as more biomarkers are added. They observed that, if a substantial number of biomarkers are included, the specific choice of biomarkers has little effect on the resulting measure. This provides a parallel with another measure, FI, which is constructed differently (counting the number of deficits) but it also shows minimal sensitivity to the choice of deficits. Thus investigation of relationships between both measures seems interesting but it is yet to be done (Cohen et al., 2015).

Cohen et al. (2015) also investigated the sensitivity of DM to the definition of the reference population. They found a moderate effect of a choice of reference population: as appears intuitively clear, "younger and healthier" reference populations generally performed better, as well as those "demographically similar to the study population."

The concept of "norm" is present either explicitly (as the average of biomarker values in the reference population in DM) or implicitly (e.g., "highest risk" quartiles of biomarkers are used in AL operationalization (Seeman et al., 1997), "empirical cut off points" define the absence/presence of deficits in FI-B (Mitnitski et al., 2015)) in such composite measures. The question how to define such a "norm" is, however, not trivial. The "norm" can be defined as the value of a biomarker which minimizes risk of death (as a function of that biomarker). As shown in recent studies, such a "norm" can depend on age, sex, genetic and other factors (Arbeev et al., 2012; Yashin et al., 2010b; Yashin et al., 2012b; Yashin et al., 2009). These studies evaluate the "norm" and other aging-related characteristics in the framework of the stochastic process model which is discussed in the next section.

3. Stochastic Process Model: Unifying Framework for Analyses of Trajectories of Biomarkers in Relation to Processes of Aging and Mortality

3.1. Concepts and Ideas Behind the Model's Structure: Statistician's and Biologist's Perspectives

From a statistician's point of view, we have longitudinal measurements (biomarkers) which need to be analyzed jointly with time-to-event outcome (mortality). There is variety of methods appropriate for such analyses (see, e.g., Arbeev et al., 2014a) with different underlying assumptions, levels of complexity and a history of applications to different research areas. In many cases such assumptions are aimed at "statistician's convenience," e.g., they may provide analytical tractability or other properties useful in theoretical developments or practical implementations. In many cases, this may be sufficient to generate useful and interpretable results. However, in some areas these same models can be viewed as rather too simplistic, especially if they do not take into account different theoretical concepts accumulated in the field. Thus, such approaches may have a limited usability in these cases because they cannot provide results interpretable from, for example, a biologist's point of view.

The SPM methodology provides an example where both statisticians and biologists may find some useful characteristics from their perspectives. First of all, why does the model need to be “stochastic”? The stochastic component (or “chance”) is an important feature of the process of aging (Finch and Kirkwood, 2000). Therefore, it is not surprising to see the word “stochastic” in the name of the model related to aging as this stochasticity represents the natural phenomenon which needs to be accounted for in the model. Then, which stochastic process can or should be used to represent this stochasticity in the model of aging? Among the variety of stochastic processes, there is one class, so-called “mean-reverting” processes (such as the Ornstein-Uhlenbeck process (Uhlenbeck and Ornstein, 1930) and its generalizations), which has appealing properties relevant for modeling biological processes in a living organism (e.g., modeling age dynamics of biomarkers). Specifically, in the long run, such a process tends to drift towards its equilibrium state (long-term mean) which has a natural biological interpretation in terms of homeostatic regulation. Thus, such processes provide the possibility to represent homeostatic regulation, the fundamental property of a living organism, in the structure of the model.

In the light of the theory of allostasis (McEwen and Wingfield, 2003), such a state which an organism is forced to follow by regulatory systems operating at “non-optimal” (i.e., reduced or elevated) levels is termed the allostatic state. The construction of the model allows representing the “mean allostatic state” which is another example how statistical properties of stochastic processes used in SPM have biologically relevant interpretation for research on aging. Another term in the stochastic process, the “negative feedback coefficient,” also can be associated with aging-related processes. This term regulates how fast the trajectory returns to the mean (i.e., to the mean allostatic state if interpreted in the context of research on aging) and thus it modulates the rate of adaptive response of an organism to the conditions (or “stressors”) which cause the trajectories of biomarkers to deviate from this state. The SPM permits flexible specifications of all components so that these two characteristics (the mean allostatic state and the rate of adaptive response) can be modeled as functions of age. For example, one can investigate whether the adaptive response of an organism to deviations of biomarkers worsens with age so that more time is needed for the values of biomarkers to go back to the mean allostatic state at older ages compared to the time needed at younger ages. This effect (referred to as “aging-related decline in adaptive capacity”) has been evaluated in applications of SPM to data on age trajectories of physiological variables and follow-up data on mortality or aging-related diseases collected in longitudinal studies (Arbeev et al., 2011; Yashin et al., 2012b). The SPM also permits modeling these aging-related characteristics as functions of genetic and non-genetic covariates to investigate how genetic, socio-demographic and other factors can be related to these processes (Arbeev et al., 2009; Yashin et al., 2012a). This allows utilizing a largely underused potential of modern longitudinal studies collecting a wide array of genetic data, follow-up information on mortality and health-related events and repeated measurements of biomarkers.

The random process representing the stochastic dynamics of biomarkers or other variables in SPM does not run indefinitely long but rather it is stopped at some random moment (i.e., time of death or onset of some health-related event). Therefore, the second part of the model is related to specification of respective hazard rate (i.e., mortality or incidence rate) as a

function of this random process. Respective statistical theory of random hazards or survival functions induced by stochastic covariates is developed decades ago (Myers, 1981; Woodbury and Manton, 1977; Yashin et al., 1989) although it did not receive much attention in the mainstream biostatistical literature, see, e.g., comments in Aalen and Gjessing (2004) and Aalen et al. (2008), chapter 1. This theory is applicable to the basic SPM (Yashin et al., 2007a) and its more recent developments.

Specification of the shape of the hazard rate as a function of the stochastic covariates (e.g., biomarkers) is an important step in model description. The SPM uses the quadratic form of the hazard, hence its alternative name, the quadratic hazard model. We emphasize again that this quadratic form is a function of the stochastic covariates (not age). The coefficient of this form can depend on age. This form of the hazard turns out to be a convenient and useful choice as it has nice statistical properties (Yashin, 1985; Yashin et al., 1989; Yashin et al., 1985) and also it is based on many observations in epidemiological studies that the hazard rate as a function of various risk factors has a U- or J-shape (see, e.g., Allison et al., 1997; Boutitie et al., 2002; Kuzuya et al., 2008; Okumiya et al., 1999; Protogerou et al., 2007; van Uffelen et al., 2010) which this quadratic form captures.

Age is an important predictor of mortality or onset of diseases so the hazard rate in SPM also has to be a function of age. In addition to the quadratic term, it also has the baseline hazard which can hypothetically be any function of age and this form dictates the general shape of the hazard as a function of age (i.e., for any given fixed value of a stochastic covariate). In applications to mortality, the choice for the baseline hazard is usually Gompertz (exponential) or gamma-Gompertz (logistic) corresponding to observations of mortality rates in human populations (Vaupel et al., 1998).

Another specific feature of SPM is that it allows estimating physiological or biological “norms”, i.e., the values of biomarkers corresponding to minimal hazard rate at a given age (Yashin et al., 2010b; Yashin et al., 2009). The problem of evaluating such “norms” from available data is not straightforward. One cannot, for example, use the average values of biomarkers at different ages for this purpose because if the biomarkers affect mortality risk then those having deviant dynamics of biomarkers will tend to die out first and individuals dying at different ages may have different shapes of trajectories of biomarkers (Yashin et al., 2010b; Yashin et al., 2012b; Yashin et al., 2009). Focusing on a subset of long-lived individuals and computing average values in this group can be a possible solution (Arbeev et al., 2012; Yashin et al., 2012b) but such data for large samples are rare and also this approach does not take into account the contribution of other factors (e.g., socio-demographic, behavioral) which can also affect the “optimal” values. The SPM can estimate such “norms” explicitly because the quadratic part contains the difference between the value of a biomarker and some parametric function which plays the role of the “norm”: if a value of a biomarker equals that function then the quadratic part is zero and any other values of biomarker result in a non-zero quadratic part and, hence, a larger hazard rate. The “norms” or “optimal states” can be functions of age and various genetic and non-genetic factors which can be analyzed in the model (Arbeev et al., 2009; Yashin et al., 2012a). It is also worth noting that such “optimal” trajectory minimizing the risk of death can be different from the “mean allostatic state.” The difference between these two trajectories indicates that

an organism cannot return to the "optimal state" and its regulatory systems function at non-optimal levels and, as a result of such functioning, there is a "price" in terms of increased risk of death. This introduces the concept of AL in the SPM approach. However, this operationalization is different from those used in other approaches as it is specifically tailored to the SPM structure.

The width of a U-shape (or a J-shape) of mortality as a function of a biomarker can be interpreted in the context of stress resistance (Yashin et al., 2015; Yashin et al., 2012a) or in alternative terms of "vulnerability" (Arbeev et al., 2011). The width of the U-shape can be used to characterize the "robustness", or "vulnerability," component of stress resistance. If the U-shape narrows (e.g., as the individual ages), an organism becomes more vulnerable to deviations of respective biomarkers from the "normal" values: if the U-shape is narrower then the same magnitude of deviation from the "optimal" value which minimizes hazard results in a larger increase in the risk of death. The SPM allows characterizing this important component of the process of aging (i.e., decline in stress resistance) from available data on longitudinal dynamics of biomarkers and investigate various genetic and non-genetic factors that can affect this decline (Yashin et al., 2015).

3.2. SPM with "Optimal Ranges"

The model in Yashin et al. (2007a) and its generalizations presented in the literature assume that the "norm," i.e., the "optimal state" minimizing the risk of death, is a single value of a biomarker (but see Appendix in Arbeev et al., 2011). It may be a function of age and different genetic and non-genetic factors but still it is assumed that any deviation from that single value of a biomarker (keeping all other factors fixed) increases the risk of death. It may be argued though that there is a range of values of a biomarker such that if the regulatory system of an organism maintains the level of a biomarker within that "optimal range" then there is no increase in the baseline mortality level. If the trajectory of a biomarker falls outside this range then there is a corresponding increase in the mortality risk compared to the baseline level. The magnitude of the increase can, in general, be different in case of deviations to smaller and to larger values of a biomarker. The "optimal range" may be hypothesized to narrow with age as a manifestation of aging. It may also be different in carriers of some alleles or genotypes. Different other non-genetic factors (socio-economic indicators, stressful life events, onset of diseases, etc.) may influence the width of the "optimal range." The hypotheses on the effects of such measured and partly measured covariates on the "optimal range" can be tested in this modification of SPM similarly to the original SPM with single "norms" (Arbeev et al., 2009; Yashin et al., 2011; Yashin et al., 2012a). The hypothesis on whether there is such a range or rather there is a single optimal value can also be tested (see Appendix in Arbeev et al., 2011). Supplementary Material contains technical details on specifications of the model as well as formulations of some null hypotheses in terms of parameters and components of the model.

Supplementary Fig. 1 illustrates the mortality rate as a function of age and a hypothetical biomarker as well as other components of the model (see more technical details in Supplementary Material). Panel (A) shows the total mortality rate, which is the sum of the baseline mortality and the additional (quadratic) term. We show the case when the "optimal

range" (shown as black lines) narrows with age and there is a non-symmetric and narrowing quadratic shape outside this range. We modeled the baseline mortality (see panel (B)) as Gompertz (exponential) function of age in this example (note that it does not depend on the value of a biomarker by definition). Panel (C) presents the additional term in mortality which is added to the baseline mortality when the biomarker deviates from the "optimal range" (i.e., the zero level here corresponds to the baseline mortality at respective age). Panel (D) shows this additional quadratic term in mortality (for visibility, here we display 100 levels as contour lines) together with the hypothetical "mean allostatic state" (blue line) and a trajectory of a biomarker (shown in red). At younger ages, the regulatory system is typically able to maintain the biomarker levels within the "optimal range" (note the "mean allostatic state" lies within that range at younger ages so that the trajectories tend to stay within the "optimal range") but at older ages, this regulatory capacity diminishes so that the "mean allostatic state" deviates from the "optimal range." Thus, the trajectory of a biomarker tends to spend more time outside the "optimal range" which leads to an increased risk of death compared to the baseline level at respective age corresponding to the values of the biomarker within the "optimal range."

Of course, the scheme shown in this figure represents a very simplistic model and we use it here just for illustration. The reality is much more complicated and multi-dimensional. All these characteristics may depend on different factors (both genetic and non-genetic) and the relationships between those can be non-linear and dynamic.

3.3. Practical Applications of SPM: Individual Biomarkers and Cumulative Measures

Summaries of recent developments in SPM and its applications can be found in our recent papers (Arbeev et al., 2014a; Arbeev et al., 2014b; Yashin et al., 2012a). Most applications of Yashin et al. (2007a) and its subsequent generalizations dealt with a one-dimensional model applying the approach to each biomarker separately. Summary measures constructed from multiple biomarkers (such as FI-LAB, FI-B and DM) or various health deficits (FI or DI) provide an opportunity to work with cumulative effect of multiple variables (biomarkers or deficits) in a one-dimensional setting. This has advantages from both computational and substantial points of view. Application of such measures helps avoid heavy computational burden and possible technical difficulties related to the use of multidimensional models. It also allows investigating systemic effects of health deterioration and physiological dysregulation captured by such measures in their relation to different aging-related mechanisms implemented in SPM and, ultimately, to mortality risk.

Currently, applications of SPM to cumulative measures are scarce. Yashin et al. (2007c) implemented FI in the SPM framework confirming earlier observations on relations between FI, aging-related mechanisms and mortality found in the model with different specification of hazard rate (Yashin et al., 2007b). Yashin et al. (2008) considered a two-dimensional SPM in application to FI and medical costs. Recently we applied DM in the context of SPM using data on several biomarkers with repeated measurements available in Framingham data (Arbeev et al., 2016). This short list indicates that the potential of applications of SPM to cumulative measures is largely underused, given the large and growing number of longitudinal studies collecting repeated measurements of biomarkers along with extensive

data on socio-demographic, behavioral, and other covariates, follow-up data on mortality and onset of diseases as well as genetic markers.

Genetic information available in modern longitudinal studies may include data on millions of single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS). The SPM (especially its continuous-time version) is computationally intensive so the most effective use of this approach with genetic data is to apply it to a set of candidate SNPs or to polygenic risk scores (PRS). PRS are widely applied in recent years as they are useful for detecting shared genetic aetiology among different traits and also can help reveal a genetic signal in underpowered studies. PRS can be used as an additional covariate and analyzed in SPM in a usual way in relation to various aging-related characteristics and mortality. The score can also be dichotomized (e.g., above/below median) and used similarly to any other dichotomous trait in the framework of “Genetic SPM” (Arbeev et al., 2009; Arbeev et al., 2015) which allows combining data from genotyped and non-genotyped participants of longitudinal study to increase the power compared to analyses of genotyped subsample alone.

Another potential area of applications of SPM with implemented summary measures and genetic scores is their use in forecasting of mortality and health. The SPM can connect trajectories of summary measures constructed from multiple biomarkers, PRS constructed from multiple SNPs, data on health status and mortality and estimate parameters interpretable in terms relevant to studies on aging (see more discussion on this topic in Arbeev et al., 2014a; Arbeev et al., 2014b).

Current versions of SPM used in the papers cited above were realized in MATLAB and SAS (codes are available from the developers of this methodology at Duke University). An R-package “stpm” is currently being developed and its version implementing several SPM variants (including, for example, the one-dimensional model by Yashin et al. (2007a)) is available online (https://cran.r-project.org/web/packages/stpm/index.html; http://github.com/izhbannikov/spm).

4. Concluding Remarks

Contemporary longitudinal studies collecting repeated measurements of biomarkers allow for analyzing 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 reviewed recent publications on the dynamics of physiological markers in relation to mortality, which use single biomarkers, as well as cumulative measures combining information from multiple biomarkers. Such cumulative measures are often better predictors of mortality than single biomarkers, and they also have theoretical rationale and useful empirical properties. We also discussed the stochastic process models which conceptualize several aging-related mechanisms in the structure of the model and allow 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 introduced an extension of the approach which considers ranges of “optimal values” of biomarkers rather than a single optimal value as in the classical SPM. We discussed practical applications of SPM to single biomarkers and cumulative measures highlighting that the potential of applications of SPM to cumulative measures is still largely underused.

In conclusion, longitudinal studies collecting repeated measurements of biomarkers coupled with appropriate analytical methods can help improve our understanding how age dynamics of biomarkers can be related to different aging-related processes leading to health deterioration and death and what role other (genetic and non-genetic) factors can play in these processes and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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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Highlights

- Dynamics of biomarkers is related to mortality and process of aging
- Composite measures based on multiple biomarkers can often better predict mortality
- Math models can help relate dynamics of biomarkers, process of aging and mortality
- Potential of applications of such models to composite measures is underused