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Have the Oldest Old Adults Ever Been Frail in the Past? A Hypothesis That Explains Modern Trends in Survival

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Three important results concerning the shape and the trends of the human mortality rate were discussed recently in demographic and epidemiological literature. These are the deceleration of the mortality rate at old ages, the tendency to rectangularization of the survival curve, and the decline of the old age mortality observed in the second part of the 20th century. In this paper we show that all these results can be explained by using a model with a new type of heterogeneity associated with individual differences in adaptive capacity. We first illustrate the idea of such a model by considering survival in a mixture of two subpopulations of individuals (called "labile" and "stable"). These subpopulations are characterized by different Gompertz mortality patterns, such that their mortality rates cross over. The survival chances of individuals in these subpopulations have different sensitivities to changes in environmental conditions. Then we develop a more comprehensive model in which the mortality rate is related to the adaptive capacity of an organism. We show that the trends in survival patterns experienced by a mixture of such individuals resemble those obtained in an analysis of empirical data on survival in developed countries. Lastly, we present evidence of the existence of subpopulations of phenotypes in both humans and experimental organisms, which were used as prototypes in our models. The existence of such phenotypes provides the possibility that at least part of today's centenarians originated from an initially frail part of the cohort.

RECENT demographic studies of aging and survival reveal three important features characterizing mortality rates and survival dynamics in populations of developed parts of the world. The first feature is the deceleration of the age-specific mortality rate at old ages (1). The second feature deals with the age pattern of mortality and survival improvement (2,3). The third characterizes changes in such a pattern during the 20th century. Figure 1 shows two main patterns of change in survival of Swedish females in the 20th century.

One can see from this figure that the distinct rectangularization pattern of survival improvement observed in the first part of the 20th century was replaced by a near-parallel shift of survival curves to the right with an increase in old-age survival. The unprecedented growth in the proportion of centenarians in developed countries is a good illustration of the latter changes (4). Our analysis shows that trends in survival improvement in the United States, Canada, France, Italy, England and Wales, and Japan are similar to those observed in Sweden.

An explanation of the mortality-deceleration effect was given by Vaupel and colleagues (1) in terms of a frailty model. Long debates about the compression of morbidity (2,5,6) resulted in an admission of the fact that both the effect of rectangularization of the survival curve and the lengthening of the tail of survival distribution do take place in modern survival patterns. In this paper we show that the rectangularization trend in survival improvement that dominated in the first part of the 20th century was replaced by a near-parallel shift of the survival curve to the right in the second part. We also show that the deceleration of old-age mortality, the rectangularization trend, and observed changes in survival patterns with years can be explained by dynamic properties of mortality and survival in a heterogeneous pop-

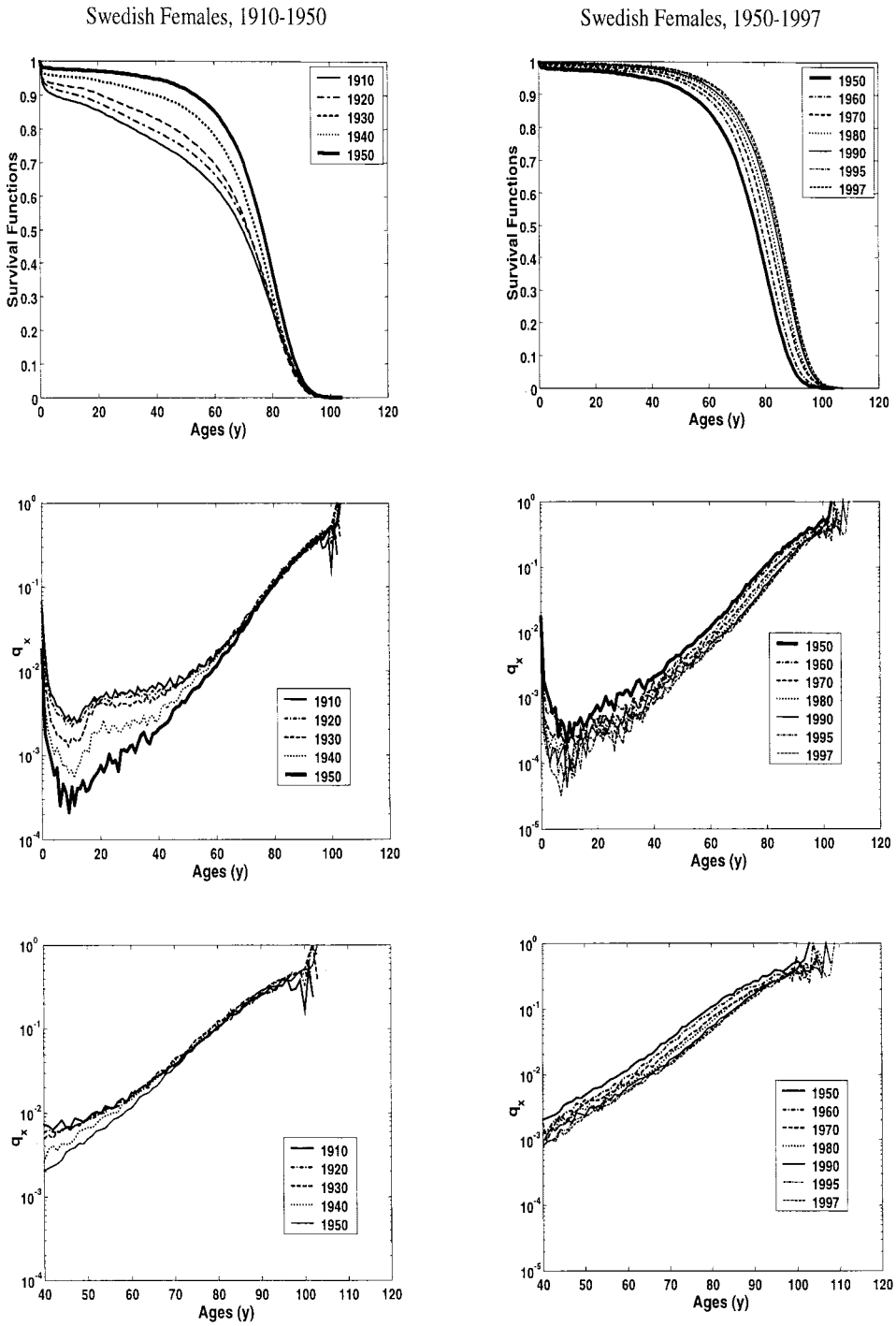

Figure 1. The change in the pattern of survival (top panels) and mortality (middle and bottom panels) improvement in Sweden. The bottom panels show the changes in the logarithm of age-specific mortality after the age of 40 years.

ulation. The goal of this paper is not to fit model to the data, but to show that all three features can be explained by using the model of population heterogeneity in which the logarithms of mortality rates in subpopulations cross over. We also provide evidence that such populations exist in nature.

For simplicity, we consider the mixture of two such subpopulations, which we call "labile" and "stable." We also assume that survival in these two groups has different responses to environmental changes. An improvement in living standards increases the proportion of initially frail (labile) individuals in such a mixture in the old part of the population. This is an interesting property, because it shows that today's centenarians might not be among the longest-lived individuals if they were born two centuries ago. We

discuss the plausibility of the latter model, in the light of recent findings about the aging process in humans and laboratory animals and of the wide data on genetics and physiology of extremely old individuals (centenarians). We discuss empirical evidence of the presence of subpopulations of individuals with different slopes of the mortality curve, and we describe possible mechanisms by which an initially frail organism may become robust (or vise versa) later in life. These mechanisms include the following: (i) the antagonistic gene action; (ii) slower aging, which may be associated with not optimal health parameters in some ages; and (iii) the antagonistic change in stress resistance during an individual life.

Finally, we develop a mathematical model of mortality and aging, which illustrates one possible mechanism of antagonistic change in relative risk in the course of an individual's life. This model explains the possibility of a centenarian's origin from an initially frail part of a cohort. It describes survival of two kinds of individuals, which originally have different sensitivities to changes in environmental conditions and different abilities to adapt to these changes. The model establishes interrelations between these characteristics and survival. We show that the trends in survival patterns experienced by a mixture of such individuals resemble those observed in humans during the previous century.

The Model

To explain observed trends in human survival, we hypothesize that each cohort in a human population is a mixture of two subcohorts of individuals—the labile and the stable. The mortality rate in the population of labile individuals is initially higher, but its rate of increase with an increase of age is slower than that of stable individuals. Because of this difference in mortality rates, labile individuals are also referred to as initially frail individuals. In this case, frailty defined as the ratio of mortality rate in labile populations to the respective rate in stable populations (relative risk) declines with age.

Antagonistically Changing Frailty in the Process of an Individual's Life

Let us assume that the human population is a mixture of two subpopulations of individuals, both with Gompertz mortality rates, but with different slopes of a logarithm of mortality. At the beginning of the century the mortality rate for one subpopulation with lower slope is higher than that of the other. The intersection of such curves happens at an age that is beyond the observed range of the human life span (say, at 130 years, or more). The improvements in the standards of living produce a significant reduction of the mortality rate for the first (labile) subpopulation, and less significant changes in the survival chances in the second (stable) subpopulation (see Figure 2).

As a result, the middle-century mortality rate for the first population crosses the mortality curve for the second one at the age of ~85 years. After this time the two curves evolve together (shift to the right) with almost the same speed (Figure 3).

Such an evolution produces the pattern of changes similar to those shown in Figure 1. The overcrossing of mortality curves for two subpopulations around the age of 85 years manifests antagonistically changing relative risk (frailty) in two respective subpopulations. Individuals from the first (labile) subpopulation are originally frailer than individuals from the second one. (Their mortality rate is initially higher than that of the second subpopulation, but its rate of increase is slower.) After intersection (in our example, at age 85 years), the proportion of labile individuals starts to increase. This is because at old ages they become more robust than individuals from the stable population. This intersection indicates that because of significant mortality reduction in the population of labile individuals, some portion of today's centenarians may originate from an initially frail part of the population. It also shows that at least part of today's centenarians would not be among the longest-lived individuals if the progress in mortality reduction had stopped approximately a century ago.

Figure 4 shows how survival function corresponding to Swedish females in 1861 can be approximated as a mixture of two survival functions. The lower survival function corresponds to labile individuals; the higher survival function represents stable individuals. Figure 5 shows how the survival function for Swedish females in 1995 can be approximated as a mixture of survival functions for labile and stable individuals with the same properties. In this figure the survival function for labile individuals intersects that of stable individuals around age 70 years. This intersection happens as a result of faster progress in the mortality reduction in the labile subpopulation.

In the next section we describe a model that incorporates physiological and environmental changes. These changes produce two different survival responses in two subpopulations.

Model of Difference in Stress Response That Produces an Intersection of Mortality Rates

We suggest a model of physiological aging and survival in which adaptation to the stresses of life has a metabolic cost. The model shows that today's centenarians may originate from an initially frail part of a cohort. The model describes survival of two kinds of individuals, the labile and stable. These individuals have different sensitivities to changes in environmental conditions, and so different amplitudes of the response to stress. The model establishes interrelations between amplitude and survival. The low amplitude of the response to stress corresponds to stable individuals; the higher amplitude corresponds to labile ones. The mathematical development is reported in the Appendix; here a qualitative description is given.

For simplicity, we assume that at any age an organism may be in one of two possible states. One is the state of normal functioning. The other is a state of stress, disease, or other tension (arousal), induced by some external or internal conditions, in which the systems of an organism are functioning with an "overload" (7). A long stay in this state must have a cost for an organism: when it accumulates, the survival chances of an organism decline. The response of an organism to stress is regulated by the parameter λ, called the rate of recovery, or the adaptation rate (see the Appendix). The lability property is associated with small values of λ;

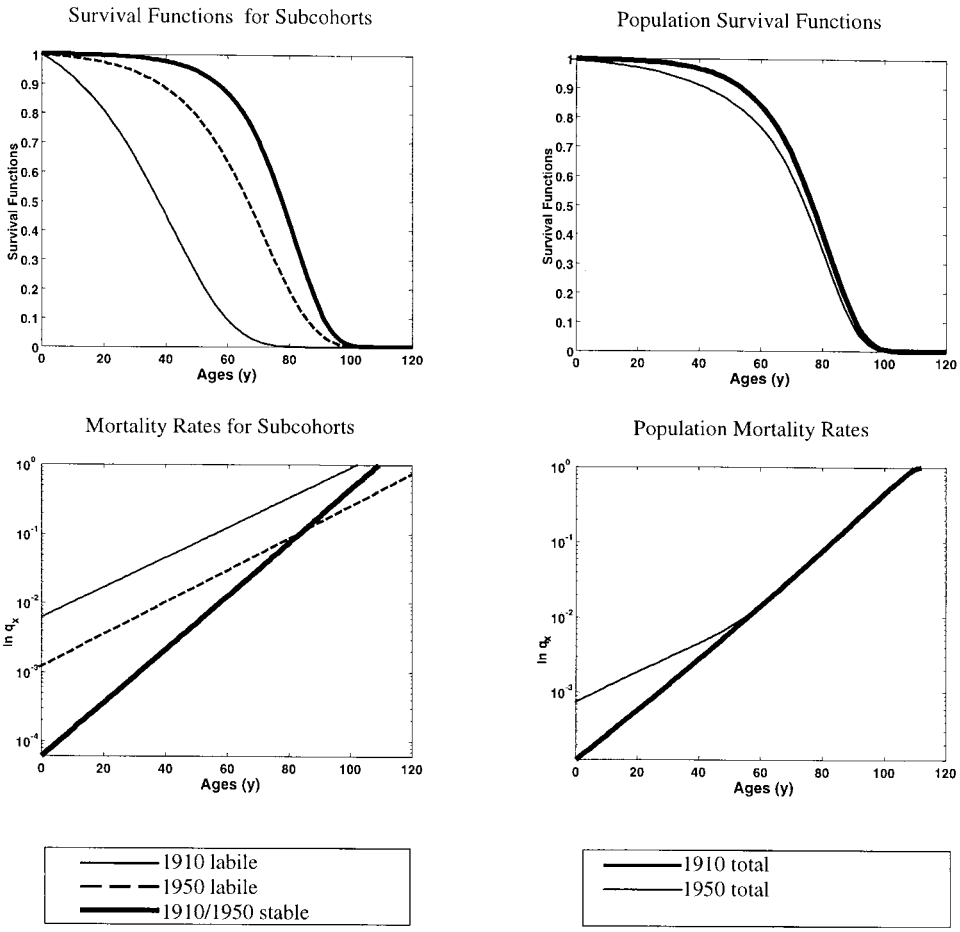

Figure 2. Secular trends in survival calculated in accordance with the model of mortality in a mixture of two subpopulations with different slopes of the Gompertz curve, adjusted to the mortality data on Swedish females for the years 1910 and 1950, respectively.

stability is associated with high ones. Because those who cannot adapt properly die first, the survival function of individuals with a small adaptation rate (i.e., labile individuals) is initially lower than that of individuals with high values of this rate (i.e., *stable* individuals). This means that stable individuals have a survival advantage earlier in life. The model establishes interrelations between the rate of adaptation and the accumulation of damage: a high rate yields a metabolic cost included in the definition of allostatic load; see Equation (3) of the Appendix. Then, at older ages, individuals with smaller values of the adaptation rate may have higher survival chances than those with higher values of λ. That is why the survival curves for these two groups of individuals may intersect. Another important parameter of the model σ characterizes permanently acting environmental disturbances. The higher the σ, the higher the level of disturbances. The life-span distribution in this model is obtained by simulation of individual life spans for a large sample of individuals (see the Appendix). Figure 6 shows survival patterns, generated by the model, in hypothetical populations of labile (small λ) and stable (large λ) individuals, for two values of σ: the two values of σ represent the transition from low standards of living (high value of σ) to improved ones (lower value of σ).

One can see that the survival functions for labile and stable individuals have different shapes. Even for large values of disturbance factor σ, respective survival functions intersect. The age at intersection moves to the left when the level of disturbances declines. Perhaps the most striking result shown by the simulation is that the variation of σ (an increase in living standards) has a small impact on the stable population, whereas it substantially increases the survival of the labile one, which exceeds that of the stable population at older ages.

Figure 7 shows the survival patterns of a mixture of labile and stable individuals (with survival functions shown in Figure 6) before and after an improvement in living standards. One can see from this figure that the resulting survival function shows both features. It became more rectangular, and it has a longer tail than the initial one.

The Genes: Experimental Data

Individual lability–stability could be regarded as a phenotypic trait resulting both from the individual specific environmental history and from the individual specific genetic equipment. However, different genes are expected to affect the trait in different ways, according to their role and effectiveness in stress response. Because centenarians living to-

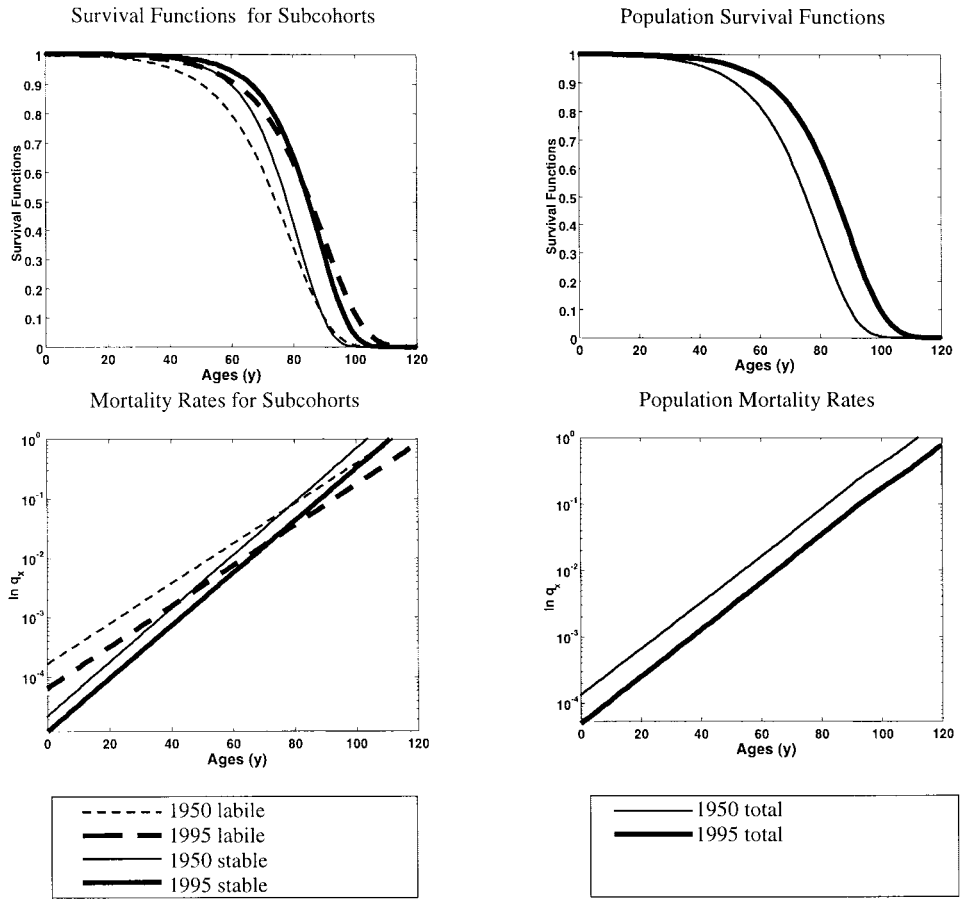

Figure 3. Secular trends in survival calculated in accordance with the model of mortality in a mixture of two subpopulations with different slopes of the Gompertz curve, adjusted to the mortality data on Swedish females for the years 1950 and 1995, respectively.

day experienced dramatic social and cultural changes (from high to low σ values) with respect to those of younger individuals (low σ), the cohort of centenarians should be formed by both labile and stable individuals (Figure 6). The model discussed above can be checked by comparing the levels of genetic homogeneity between centenarians and younger individuals (20–60 years old) extracted from the same population. Let us consider a stress responder gene, with *A* and *a* alleles conferring lability (small values of λ) and stability (high values of λ), respectively. Let us assume that the frequencies of *A* and *a* at the birth of the cohort are $pA = pa$, and that the population is in Hardy–Weinberg equilibrium. When survival selection operates under high σ (thin lines in Figure 4), the allelic pool will tend toward an increase of *a*, with a consequent decrease of heterozygosity. However, as σ decreases (thick lines in Figure 6), *A* will tend to remain in the gene pool, and the level of heterozygosity will increase in the cohort of centenarians. Therefore centenarians are expected to show increasing heterozygosity with respect to youths for stress-responder genes affecting lability–stability. We checked our hypothesis by estimating heterozygosity at 12 autosomal loci in centenarians and younger individuals, after verification of Hardy–Weinberg equilibrium. The results are shown in Table 1.

A trend toward decreasing heterozygosity from youths to centenarians was observed at the loci denoted with numbers from 1 to 8 in Table 1. This result is in line with the negative correlation between population heterozygosity and life span observed by studying neutral polymorphisms (10). In contrast, the level of heterozygosity tended to increase from youths to centenarians for HSP70, THO, INS, and IGF2 loci. It must be noted that THO, INS, and IGF2 loci lie in the same chromosomal region (11p15.5) and that both INS and IGF2 markers are in linkage disequilibrium with THO markers in Table 1 (data not shown). THO and HSP70 are the only stress-responder genes studied until now with respect to human life span. THO is the rate-limiting enzyme in cathecolamine biosynthesis, amino acid-derived molecules that act both as hormone (adrenalin) and neurotransmitters (dopamine and noradrenalin). HSP70 is the stress-responder gene evolutionary conserved from bacteria to humans. The finding that centenarians are less homogeneous than younger subjects at both THO and HSP70 loci supports the model given above.

Discussion

In the following subsections we discuss how both the assumptions from which the model is built up and the results

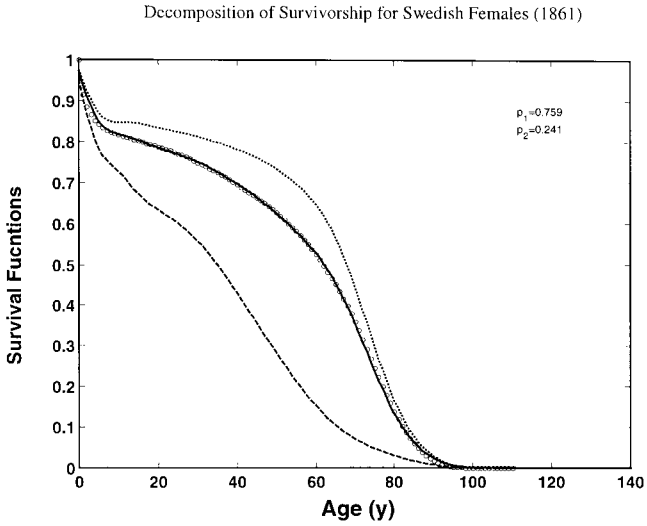

Figure 4. Survival function in Swedish females in the year 1861 (○) approximated by a survival function in a mixture of stable (...) and labile (---) individuals with initial proportions of $p_1 = 0.759$ and $p_2 = 0.241$, respectively. The central line (—) refers to a mixture of two hypothetical cohorts of labile and stable individuals.

provided by it enable us to explain several phenomena observed in human population and experimental studies.

Paradoxes in Centenarians

The progress in health and living standards experienced by the human population today tends to increase the proportion of originally frail individuals in successive generations (11,12). The proportion of centenarians in human populations of developed countries also increases faster than be-

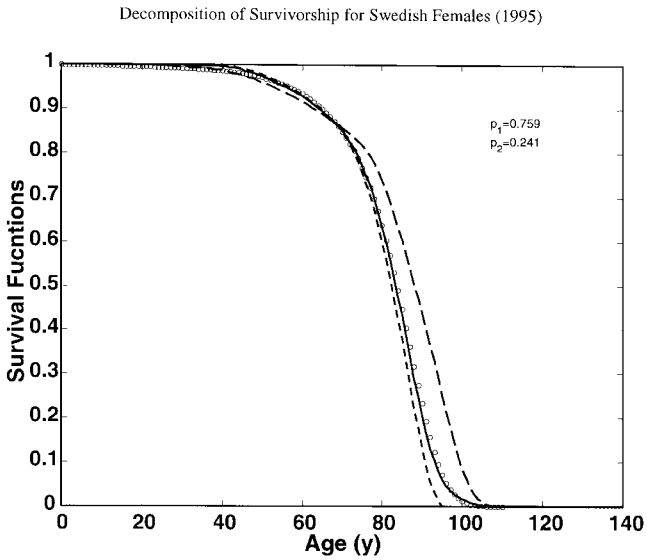

Figure 5. Survival function in Swedish females in the year 1995 (○) approximated by a survival function in a mixture of stable (---) and labile (– – –) individuals with initial proportions of $p_1 = 0.759$ and $p_2 = 0.241$, respectively. The central line (—) refers to a mixture of two hypothetical cohorts of labile and stable individuals.

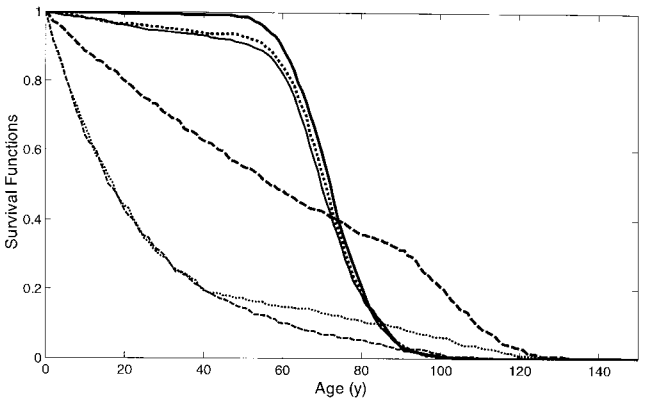

Figure 6. Survival functions in hypothetical subcohorts of labile ($\lambda = 370$, ---, sample size 500) and stable ($\lambda = 550$, —, sample size 1500) individuals before ($\sigma = 6.4$, — and ---) and after ($\sigma = 6.0$, — and ▪▪▪) improvement in living conditions. Dotted lines (... and ▪▪▪, respectively) show changes in respective survival functions, assuming that an improvement in living conditions ($\sigma = 6.4$ was replaced by $\sigma = 6.0$) happened at the age of 40 years in each subcohorts. The data are simulated in accordance with the life history model for labile and stable individuals described in the Appendix.

fore (4). It is clear that both effects may mirror an influence of the increasing standards of living on the mortality curves of homogeneous subcohorts, comprising heterogeneous groups of individuals. This, however, does not explain the observed trends in survival patterns. The explanation would be easier to obtain if we assume that a substantial part of the group of centenarians originates from an initially vulnerable, frail part of a generation, whose deaths at adult age were prevented by the improvements in health and living standards gained by industrial progress. Because industrial progress is likely to increase survival chances for all indi-

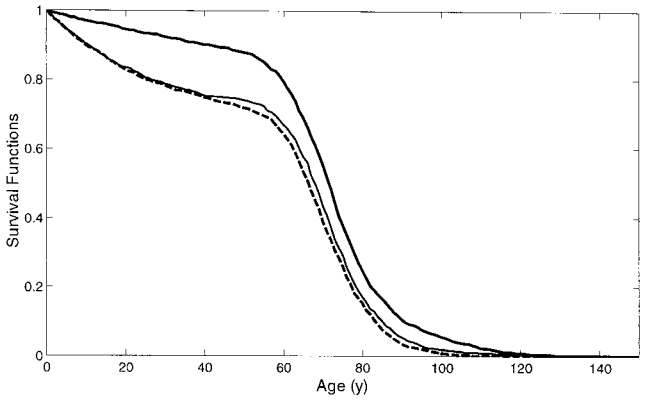

Figure 7. Survival functions in a mixture of hypothetical subcohorts of labile ($\lambda = 370$, sample size 500) and stable ($\lambda = 550$, sample size 1500) individuals before ($\sigma = 6.4$, ---) and after ($\sigma = 6.0$, —) improvement in living conditions. The initial proportion of labile individuals is 0.25. The thin solid line shows changes in survival in a mixed cohort (initial $\sigma = 6.4$) as a result of improvement in living conditions that occurred at an age of 40 years (at this age $\sigma = 6.4$ was replaced by $\sigma = 6.0$). The data are simulated in accordance with the life history model for labile and stable individuals described in the Appendix.

Table 1. Heterozygosity in Centenarians and Younger Subjects

Autosomal Loci	Gene	Marker	*Allele No.	Sample Size	Young Subjects (20–60 y)	Sample Size	Centenarians
1	REN	$(acag)_n$STR	5 (4)	218	0.429 (0.383–0.472)	157	0.352 (0.286–0.411)
2	SOD2	$C/T_{(401)}$	2 (2)	187	0.492 (0.474–0.499)	167	0.488 (0.467–0.498)
3	PARP	$(gt)_n$STR	7 (6)	171	0.528 (0.464–0.582)	147	0.482 (0.415–0.543)
4	APOB	3′VNTR†	3 (3)	658	0.558 (0.536–0.575)	260	0.549 (0.511–0.582)
5	APOA1	MspI-RFLP	2 (2)	575	0.391 (0.364–0.413)	194	0.336 (0.292–0.378)
6	APOC3	SstI-RFLP	2 (2)	575	0.179 (0.153–0.205)	197	0.153 (0.105–0.198)
7	APOA4	HincII-RFLP	2 (2)	575	0.243 (0.206–0.260)	193	0.238 (0.190–0.287)
8	APOE	ε2/ε3/ε4	3 (3)	179	0.297 (0.237–0.357)	210	0.181 (0.131–0.227)
9	THO	$(acag)_n$STR‡	2 (2)	358	0.482 (0.470–0.488)	217	0.495 (0.485–0.505)
10	INS	Fok!-RFLP	2 (2)	257	0.268 (0.224–0.316)	217	0.301 (0.251–0.345)
11	IGF2	AvaII-RFLP	2 (2)	257	0.439 (0.408–0.464)	217	0.454 (0.425–0.477)
12	HSP70	A/C (promoter)	2 (2)	227	0.445 (0.411–0.461)	198	0.480 (0.459–0.494)

Note: 95% confidence intervals calculated by bootstrap are reported in parentheses for young and centenarian subjects.
*The number of alleles in centenarians is reported in parentheses.
†Alleles recoded as small, medium, or large (8).
‡Alleles recoded as small and large (9).

viduals in the population, one should find a good reason why some originally frail individuals get survival advantages at old age. Several examples discussed below provide compelling evidence about the possibility of the original frailty of today's centenarians.

Recent genetic studies in centenarians pointed out some unexpected findings, as the presence of genetic risk factors in their gene pool (13). For example, several alleles, known to be associated with increased cardiovascular risk in middle age, are present in centenarians at the same frequency as in younger individuals (14–17). In some cases, such risk factors occur even more frequently in centenarians than in younger individuals (18–22). Such counterintuitive accumulation of originally harmful alleles may be easier to understand if the biological and physiological role of respective alleles in survival is taken into account.

For example, let us consider the guanine insertion/deletion polymorphism 4G/5G in the promoter of the plasminogen activator inhibitor 1 (PAI-1) gene, a predictor of the risk of atherothrombotic disease. The 4G4G genotype is associated with a high plasma level of plasminogen activator inhibitor and therefore with an increased risk of atherothrombosis and myocardial infarction in adulthood (19). Unexpectedly, the frequency of the 4G4G genotype is higher in centenarians than in younger individuals (20). Our model can explain this apparent paradox on the basis of the physiological role of the PAI-1 hemostatic protein. The improvement in medical care and living conditions in early and in middle ages (e.g., by saving lives and preventing deaths of those who would otherwise die) promotes an increase in the proportion of individuals carrying the harmful genotype. However, this genotype, which is a risk genotype at middle age, may turn out to be advantageous at older ages, when the rate of metabolic processes decelerates, and many processes including a recovery from injury go slower. In such ages, a higher rate of blood coagulation may be beneficial for faster recovery (e.g., for stopping bleeding). Thus individuals with potentially harmful alleles, who yet survived under the pressure of selection and reached old age, may get an advantage from the same alleles later in life.

Centenarians may also be those individuals whose development (and aging) processes go slower than those in other individuals of the same generation. Such individuals may have a higher risk of death earlier in life because their health parameters at young and adult ages may substantially deviate from those "optimized" by the evolution. This is confirmed by the fact that the risk of death at a given age regarded as a function of physiological parameters can often be approximated by a U-shaped curve (23). For example, being both underweight and overweight is associated with an increased risk of mortality. A person who grows old slower may have a body mass index as well as other physiological parameters (such as metabolic rate) that are not optimal for survival at early and adult life. But if such a person survives this period, he or she may have a survival advantage at older ages because of a slower aging phenotype (see Figure 8). Progress in medicine and health care together with improvements in living standards increases survival of such

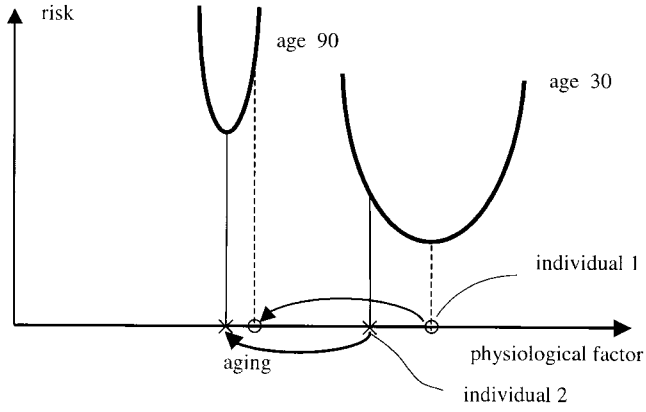

Figure 8. Risk as a quadratic function of hypothetical risk factor at ages of 30 and 90 years. Individual 1 has minimum risk at age 30 but an increased risk at age 90. Individual 2 has an increased risk at age 30 but a minimum risk at age 90. This happens because both the value of the physiological risk factor and the parameters of risk function change with age.

individuals earlier in life. This yields an increase in the proportion of such individuals in old ages, where they get survival advantages, and it contributes to the increase in the proportion of centenarians in a population.

Stress Resistance and Longevity: Labile–Stable Individuals

A positive correlation between stress resistance and longevity has been confirmed by many experimental studies in model organisms (24–27) and has been hypothesized in human longevity too (18,28,29). Stress resistance means faster response of the organism to destabilizing factors, and quicker stabilization of homeostatic equilibrium. However, the high level of stability has a metabolic cost, and the price must be paid by an organism, if not at the adult age then at the late ages. Thus, high stress resistance may be profitable for the survival of an organism at young and adult ages but have deleterious consequences later in life. For instance, some individuals may be more resistant to fluctuations of temperature and atmospheric pressure than others, who are more susceptible to environmental changes. Such vulnerable individuals have fluctuations of their vascular state in parallel with the waves of ambient temperature and atmospheric pressure. In contrast, the first-type individuals are more robust when they are at adult ages, having better health and lower chances of death than the vulnerable individuals. For many years of life, their cardiovascular system has had less variability in parameters. As a result, this system may be trained much less than that of vulnerable individuals. However, if the latter manage to survive to adult ages, they may get a survival advantage later on, because of a better-trained vascular system. In this scenario, some heavy stresses at old ages are likely to be more lethal for the robust individuals than for the originally vulnerable ones. Thus, an originally more vulnerable (and primarily more labile) organism may improve the quality of its own response to stress compared with an originally more robust (and primarily more stable) organism. Such change in the resistance to stress may give a survival advantage at older ages to the originally more vulnerable organisms. Because more such organisms got the chance to survive their adulthood during the past decades, they may be more present in the population of the oldest old, that is, centenarians, today. The increase of heterozygosity at stress-responder loci with respect to younger controls (Table 1) is in line with the above considerations.

The same considerations can be applied to model organisms. Stress experiments with nematode worms *Caenorhabditis elegans* reveal an intersection of survival curve in the population exposed to 4 hours of heat shock with that in the control group (30). The survival curves corresponding to a population of some long-lived mutants of *C. elegans* intersect those of wild-type worms under normal conditions (31).

Experiments with rodents give one more confirmation of the existence of the labile phenotype. In aging studies on rodents, rats and mice exposed to high doses (0.5 mg/rat) of pineal gland preparation epithalamin (known as geroprotector) show lower survival earlier in life and better survival later in life than those in the control group (Figure 9). These rodents also manifested both increased maximal life span and postponed aging (32–34). That is, treated rodents lived

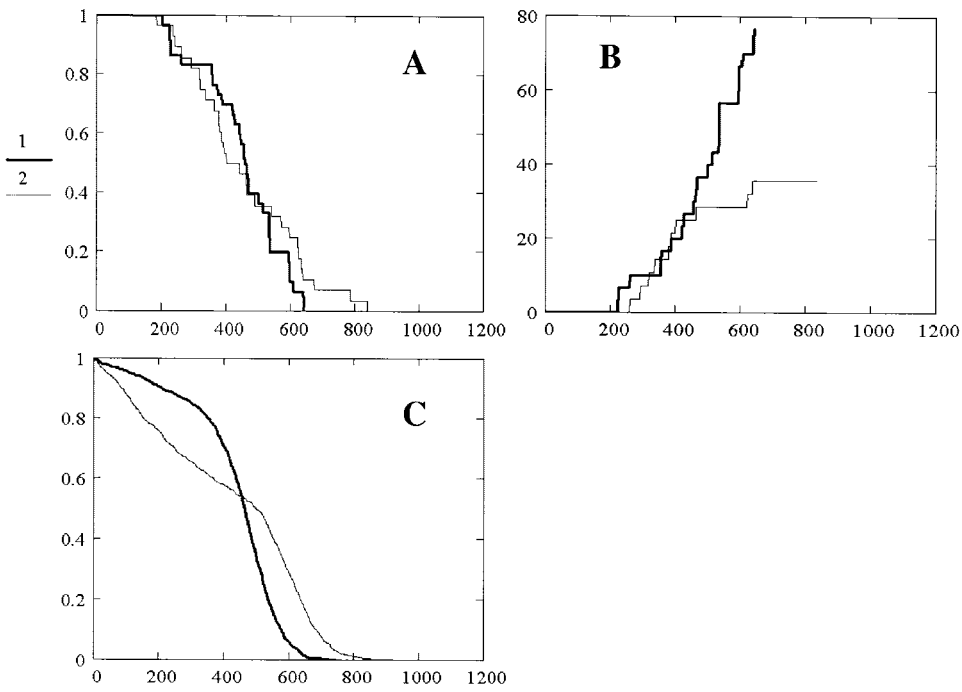

Figure 9. Effect of succinic acid on survival and tumor incidence of female C3H/Sn mice (adapted from Anisimov and Konrashova, 1979). **A**, survival curves; **B**, fatal tumor yield curves; **C**, simulated survival curves; 1, control; 2, treated with succinic acid. The treatment with succinic acid prolonged an average and maximum life span and decreased spontaneous mammary adenocarcinoma development. The survival curve for the treated group has a crossing at early age with the survival curve for the control group.

longer and aged slower (by a number of physiological parameters). At the same time, they are frailer at their young and adult ages, and they are more robust at old ages than rodents in the control group. Furthermore, in populations with lower survival earlier in life and higher survival later in life, tumorigenesis is going slower (32). This observation is expected in the population of labile individuals, in which the accumulation of damage associated with the excess of metabolic activity is slower than in the stable individuals. A similar antagonistic change of survival in adult and in old ages was observed in some experiments on rodents exposed to caloric restriction, a treatment known to increase longevity and postpone aging (35).

Experimental studies show that labile and stable phenotypes may be the result of gene–environment interactions (36). It means that individuals who are stable in one set of environmental conditions may manifest a labile phenotype in case of another set of conditions and vice versa. In any case, all the above data agree with the existence of labile and stable individuals assumed in our model.

Evolutionary Adaptation May Produce an Intersection of Mortality Curves

The intersection of survival curves may have evolutionary reasons. The evolutionary theories suggest that genes that would enhance fitness earlier in life may be selected for, even if they produce detrimental effects later in life (37). Because the notion of fitness involves fertility as well as mortality, one may assume that mortality rates for genotypes may have a spectrum of possible shapes (the average fertility rates for the populations of these genotypes must also be different). These theories link the life span with the quality of maintenance and repair systems in the cells of an organism. However, they do not provide an explicit description of possible mechanisms, which relate characteristics of physiological and biological aging with demographic survival curves. The idea of disposable soma suggested by Kirkwood (38) looks promising; however, it requires additional specification of resource-allocation strategies that may depend on environmental conditions. In addition, none of the theories explains why some individuals in a population are more sensitive to industrial progress than the others.

Conclusions

Mortality decline in the human population forms a survival pattern, which shows signs of both the rectangularization of the survival curve and the lengthening of the tails of survival distributions (5,39,40). In this paper we propose a mixed stochastic–deterministic mathematical model of survival, which incorporates parameters directly related to qualitative features such as adaptive capacity and sensitivity to environmental changes of an individual. The qualitative analysis and the simulation experiments show that the observed pattern of mortality as well as trends in human survival can be explained in terms of a mixture of two subpopulations. An important feature of these subpopulations is that their mortality rates intersect, thus giving a solid interpretation to the intersection of mortality curves often observed in the studies of aging and survival, including human and nonhuman subjects.

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Appendix

The Model

We introduce five main dynamic components of the processes of aging and mortality, denoted by X, N, ν, μ, and A. The first, $X = (X_t)_{t \geq 0}$, characterizes the rate of metabolic processes. It may be regarded as a difference between metabolic rates in the state of normal functioning and in the arousal state. The dynamics of this process reflects changes in metabolic characteristics during the adaptation to the new state of an organism induced by external or internal conditions. For simplicity, we assume that there are only two possible states—"0" and "1." State 0 is characterized by the absence of stress, disease, or other conditions that require substantial adaptational efforts. State 1 is an arousal state. It is characterized by elevated metabolic activity (as in the case of stress, disease, etc.). The process $N = (N_t)_{t \geq 0}$ describes random changes between these states. The process ν_t characterizes the intensity of transitions (incidence of disease, stress hits) resulting in an arousal state

$$\nu_t = e^{\delta A_t} \tag{1}$$

where δ is a nonnegative parameter. This process depends on A_t, the fifth process contributing to aging, which we associate with the price for staying in the arousal state. The process μ_t describes the rate of recovery from the arousal state. We assume that

$$\mu_t = m \exp(bX_t - A_t) \tag{2}$$

Here m and b are nonnegative parameters. The process $A = (A_t)_{t \geq 0}$ describes the accumulation of damage, that is, a cost paid by an organism associated with its stay in the arousal state (e.g., an allostatic load; 7,41,42). It seems reasonable to assume that $A = (A_t)_{t \geq 0}$ depends on the history of the process X up to time t, for example,

$$A_t = a\lambda \int_0^t X_u du \tag{3}$$

where a and λ are nonnegative parameters. We also assume that the process X is related to process N by the equation

$$dX_t = -\lambda(X_t - N_t)dt + \sigma dW_t, \quad X_0 = 0. \tag{4}$$

Here $W = (W_t)_{t \geq 0}$ is the standard Wiener process, and parameters λ and $\sigma > 0$ are fixed for all genetically identical individuals. This equation contains deterministic and stochastic components. The deterministic part represents the homeostatic feedback mechanism by which process X adapts to the level of N. The stochastic component characterizes permanently acting disturbances, for example, oxidative stress or immunological stress, which disturbs homeostasis. It is important to note that parameter λ influences both the X process and the A process. In the first case it characterizes the rate of adaptation of an organism to changes in the state. The higher the value of λ, the faster the organism adapts. The variance of fluctuations of the process X_t is $\sigma^2/2\lambda$; that is, it is inversely proportional to parameter λ. Thus the weaker the adaptive capacity of an organism, the higher the fluctuations of X. The high rate of adaptation is, however, not for free. It has a metabolic cost included in the definition of allostatic load (7,41). Note that according to Fries (3), even for the same trajectories of X the allostatic load will be accumulated faster for an individual with larger values of λ. Thus any jump of N_t from 0 to 1 induces an increase of an average level of X. An increase in X_t causes faster accumulation of allostatic load A_t and finally results in a reduction of a stress resistance μ_t and in an increase of intensity of diseases ν_t.

Three possible causes of death were considered in this model. The first is associated with a decrease of vital characteristics below the admissible level (in the example given below, $X_t < -1$). The second arises when the recovery rate falls below its admissible level (in the example given below, $\mu_t < 0.01$). The third arises when X exceeds the admissible level (in the example given below, $X_t > 2$).

Simulation of the Modern Pattern of Survival

We simulated life-span data by using a computer experiment with our model and calculated survival functions for different sets of parameter values. The control set (F1) of the parameters is $\lambda = 370$, $\lambda = 550$, $\sigma_1 = 6.4$, $\sigma_2 = 6.0$ $a = 0.00066$, $\delta = 0.2$, $b = 0.5$, and $m = 10$. The statistics is based on 2000 independent random realizations consisting of two cohorts: 25% (500 individuals) with

$\lambda = 370$ and 75% with $\lambda = 550$ (1500 individuals); $T^* = 40$ years. The sample size of simulated data is 2000 individuals.

The parameter λ in this model is supposed to be genetically determined and fixed for all individuals in a given birth cohort. As it defines the rate of adaptation and is inversely proportional to the variance of X_t, an increase in λ leads to an increase in survival probability for the younger ages, where the allostatic load is small and most of the deaths occur because of fluctuations of X_t. Because the allostatic load increases faster with age for such individuals, the survival curve for them goes steeper to zero. Thus we can simulate the phenomenon of the intersection of the survival curves by assigning different values of parameter λ to respective populations of individuals. Note that the old-age survival probability is significantly higher for the organisms with a lower level of feedback rigidity (with smaller λ). The main cause of the mortality among individuals with strong feedback (large values of λ) is the fast decrease in the recovery rate caused by accumulation of damage (allostatic load). The individuals with low feedback (weak homeostatic mechanisms, small values of λ) die mostly because of crossing the admissible boundary by the process X_t.

Thus individuals with the large values of λ usually do not die from the fluctuations of X_t, because they are small. However, the accumulation of allostatic load for them is going faster. Individuals with small λ have higher levels of fluctuations in X_t (are more labile). Thus they die more often at the beginning of life. However, the allostatic load in these individuals increases at a slower rate, which gives them better survival chances later in life compared with more stable individuals.