# Application of heterogeneity modeling in aging and risk assessment

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## Abstract

Heterogeneity is considered in application to measurement of aging, determined in demographic meaning as increase of mortality with age. Influence of heterogeneity is discussed and inclusion of heterogeneity in risk assessment models is presented.

## 1 Aging process

Aging is the result of mutual action of different biochemical processes in living systems, which leads to development of debilitation processes leading to death [6]. Attempts at understanding the causes of aging are limited by the complexity of the problem. Aging is manifested from the molecular to the organismic level, it is affected by environmental factors and often secondary effects mask the primary mechanisms. In the result there are no precisely defined and easily measured biological markers of aging. In humans aging is associated with loss of bone tissue, reduction in muscle mass, reduction respiratory function, decline in cognitive function, rise in blood pressure and so on. In result humans demonstrate at advanced age the progressive decrease in physiological capacity and the reduced ability to respond to environmental stresses, which lead to increased susceptibility to disease, may predispose to chronic disabling conditions and, consequently, all causes mortality increases with aging.

Aging in demographic meaning can be measured by changes of mortality rate at different age groups. In case of non aging population mortality does not depend on age as in the case of technical systems at the period of exploitation. At the same time even technical systems demonstrate increase in failure rate after long operation time – parametric failure, which reflects development of degenerative processes. This is a clear analogy with aging in living organisms. Generative processes lead to reduction of life protective forces and increase of mortality rate.

The main advantage of the demographic definition of aging is that it can be estimated on the data from longevity records in big groups and populations. These data can be in form of individual life span records or counts of death cases in specific age groups. The main disadvantage of the demographic definition of aging is that it describes changes in population surviving but not individual one. The individual mortality can differ from mortality observed in population because of changing structure of survivors. The clear example gives deceleration of cause-specific mortality at advanced ages, established at the second half of XX century, when the number of old survivors became significantly large to make the statistical estimates [5]. Up to age 80 years old mortality increased almost exponentially but then demonstrated leveling off, which can be interpreted as a sign of robustness increasing at old ages. The possible alternative explanation of mortality leveling off is natural selection, when only 'robust' people with low susceptibility to disease survive till the advanced ages [7].

## 2 Heterogeneity modeling

Estimation of mortality at the individual level is impossible because of probabilistic nature of the longevity process. One can measure only number of death in a given group of individuals or in a population. Proportion of survived people is observed but the chance of dying during one year is of primary interest. These chances influence the numbers of survivors and are used in calculation and projection of the life expectancy and the population age structure. In this meaning estimation of mortality using population data is an inverse problem: to estimate the "cause effect" (individual mortality) by observation the "result effect" (number of age-specific deaths in population).

To produce estimation of mortality on individual level one is to incorporate the link between individual mortality and mortality in population. The notions of frailty and population heterogeneity are convenient for construction of such mathematical models. The most popular are frailty models with proportional hazard $\mu(x,z) = z\mu_0(x)$ where z is a 'frailty index'-random variable, which is fixed in time but takes different values for different people [3]. The extension is 'dynamic frailty' when z is stochastic process [9]. It is shown that observed in heterogeneous population mortality at age x $\bar{\mu}(x)$ can be presented as conditional expectation for individual mortality among survivors till age x

$$\bar{\mu}(x) = E(\mu(x,z)\,|X > x).$$

The survival function in such population is given by expression

$$\bar{S}(x) = \exp\left(-\int_0^x \bar{\mu}(t)\,dt\right).$$

The most advanced results are obtained in several specific cases. Some of these cases are:
1) frailty is gamma-distributed with scale $\theta$ and shape $k$

$$\bar{\mu}(x) = \frac{k\theta}{1+\theta\int_0^x \mu_0(t)\,dt}\mu_0(x);$$

2) frailty is square of normal variable with mean $m_0$ and variance $\sigma_0^2$

$$\bar{\mu}(x) = \left(m^2(x) + \sigma^2(x)\right)\mu_0(x),$$

where $m(x)$ and $\sigma^2(x)$ satisfy to a set of two differential equations

$$\begin{array}{l} \frac{d}{dt}m(t) = -2m(t)\,\sigma^2(t)\,\mu_0(t) \\ \frac{d}{dt}\sigma^2(t) = -2\sigma^4(t)\,\mu_0(t)\ . \end{array}$$

3) frailty is a random variable with inverse Gaussian distribution

$$\bar{\mu}(x) = \frac{1}{\sqrt{1+2\gamma\int_0^x \mu_0(t)\,dt}}\mu_0(x)$$

These and more sophisticated models with stochastically changing frailty were applied to analyze health statistics data, in risk factors analyses, in econometrics.

## 3 Risk assessment models

Heterogeneity notion is important in estimation of risk for health from different external influence such as radiation and chemical pollutants. The analysis of data on radiation risks in population, exposed to radiation in a result of the industrial factors action or technogenic disasters, as well as in the workers of atomic industry, is of large scientific and practical interest. The obtained results are widely discussed in the scientific publications [1], [8]. At present it is widely accepted that for study of radiation risks, particularly in the domain of low doses, it is insufficient to consider only accumulated dose, but it is necessary to take into account the age and medical conditions of the population under investigation, the character and mode of irradiation, other random factors [2]. In practice, such information at the individual level is inaccessible and should be considered as presence of nuisance factors. The effect of such influence can be captured by introduction of unobserved heterogeneity factor as it is done in mortality modeling.

It is accepted that the radiation risk means the effect of the morbidity increase in result of radiation action. The increase is measure by comparison with the morbidity without the radiation, which is called spontaneous morbidity. Quantitatively, the radiation risk is estimated by a value of the additional morbidity related to a value of the obtained dose. In radiology the morbidity at the age $x$as a result of the radiation action at the age $y$is presented the model of the proportional risk in form

$$\lambda(x,y) = (1 + ERR \times d)\,\lambda_0(y),$$

where $\lambda_0(y)$ denotes spontaneous morbidity at age $y$, $ERR$ denotes the excessive relative risk, $d$is the absorbed dose. The individual excessive relative risk $ERR$ is the value, which is considered to be responsible for heterogeneity in population. To write the model, introduce frailty $z$, which describes distribution of the relative risk in population. The individual morbidity takes form

$$\lambda(x,y|z) = (1 + z \times Err \times d)\,\lambda_0(y).$$

The observed in population morbidity among people of age $x$, exposed to radiation at age $y$ equals

$$\hat{\lambda}(x,y) = (1 + E_{xy}(z) \times Err \times d)\,\lambda_0(y),$$

where $Err$ is a "nominal" relative risk normalized to set mean value of frailty equal one. $E_{xy}(.)$ denotes averaging among people, irradiated by at age $y$ and still healthy at age $x$. In the case of gamma-distributed frailty $z$ the averaging is made analytically in the form

$$\hat{\lambda}(x,y) = \frac{1 + Err \times d}{1 + \sigma^2 (1 + Err \times d)(x-y)\lambda_0(y)}\lambda_0(y),$$

where $\sigma^2$ denotes variance of the frailty $z$. In the presence of latent period $\Delta$ for effect of radiation action observed morbidity takes form

$$\tilde{\hat{\lambda}}(x,y) = \begin{cases} \lambda_0(y), & x - y \le \Delta, \\ \frac{(1+Err\times d)\lambda_0(y)}{1+\sigma^2(1+Err\times d)(x-y-\Delta)\lambda_0(y)}, & x - y > \Delta. \end{cases}$$

This is for example the case of radiation induced solid tumor morbidity, when latent period is estimated to be 10 years in length.

In construction of log likelihood function for model identification one is to take into account specificity of the real data. The presented expression takes into account limited period of observation - right censoring. In addition includes probability for cases, which were diagnosed only after death - left censoring. The resulting formula is

$$\ln L = \sum_{i \in S_1} \ln\left(\tilde{\lambda}(x_i,y_i)\right) + \sum_{i \in S_2} \ln\left(1 - \exp\left(-\tilde{H}(x_i,y_i)\right)\right) - \sum_{i \in S_3} \tilde{H}(x_i,y_i) \quad .$$

The first term sums members of the population who sick during investigation period - the set of indices $S1$. The second term sums the persons who died with the diagnosis that was not revealed in life - the set of indices $S2$. The third term sums all persons, apart from those who are taken into account in the second term – the set of indices $S3$.

The approach described was used in investigation of radiation risk of "solid cancers" among the persons participated in the liquidation of consequences of the accident at the Chernobyl Nuclear Power Plant in the years 1986–1991. It is shown that the heterogeneity disregard leads to understated estimates of the radiation risk of the origin of radiation-induced solid cancers [4].

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