THE BIOLOGY OF LIFE SPAN

A Quantitative Approach

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constructed of irreplaceable aging elements! For example, in the case when the lifetimes of the elements follow a uniform distribution ($F(x) = x$), a system consisting of an infinite number of such aging elements connected in series will not age (Barlow and Proschan, 1975). The same statement is true in the case:

$$F(x) = 2\Phi(x) - 1, \tag{70}$$

where $\Phi(x)$ is the standard normal distribution function (Galambos, 1978). A system made up of such aging elements connected in series has an exponential life distribution, i.e. it does not age (Galambos, 1978). It is clear that wonders of this kind, contradicting common sense, are only possible for imaginary systems with an infinite number of elements. These conclusions do not apply to real systems consisting of a finite number of elements.

In conclusion, it must be noted that the potentiality of the statistics of extremes for modelling the survival of organisms is at present far from being exhausted. However, this approach has definite limitations which must be known before it can be correctly applied.

6.4. The model of the avalanche-like destruction of an organism in natural aging

For want of a nail
the shoe was lost,
For want of a shoe
the horse was lost,
For want of a horse
the rider was lost,
For want of a rider
the battle was lost,
For want of a battle
the kingdom was lost,
And all for the want
of a horseshoe nail.

(English nursery rhyme)

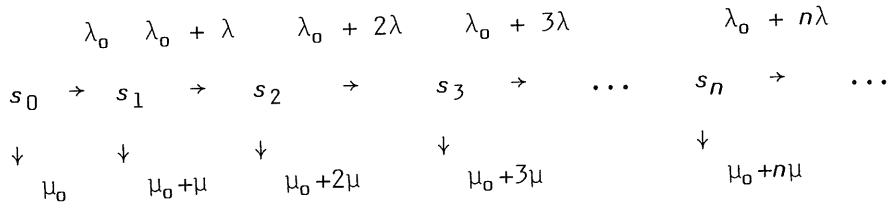
In 1978, we proposed the hypothesis that the aging of organisms is caused by a "cascade of dependent failures"

which occurs when one of the organism's systems randomly fails (Gavrilov, 1978; Gavrilov et al., 1978). This idea that an avalanche-like mechanism is involved in the breakdown of an organism during natural aging is worth further development. In fact, it is well-known that defects in an organism have a tendency to multiply following an avalanche-like mechanism: for example, if there are n cancer cells in the organism, each of which is capable of division, the rate at which the organism is transformed into a state with $n + 1$ cancer cells increases with the growth of the number of cancer cells (n) already accumulated. Infections of the organism follow similar regularities. The positive feedback between the degree and the rate of an organism's breakdown also follows from the fact that when parts of the structure fail, the load on the remaining structures increases, accelerating the wearing-out. A clear example of this cascade-like destruction of the organism is the development of uncompensated diabetes mellitus: prolonged hyperglycaemia resulting from a relative insulin insufficiency leads to the total exhaustion of the insulin-producing capability of the islet of Langerhans in the pancreas and the conversion of the relative insulin insufficiency into an absolute one. This in its turn leads to renal insufficiency (diabetic glomerulosclerosis) and lesions of the cardiovascular system (diabetic angiopathy). Induced renal failure in its turn induces hypertension, while hypertension may precipitate a fatal stroke. The list of examples of this kind could be continued. It seems that aging is caused by precisely such cascades of dependent failures developing over long periods in a hidden, preclinical form. Therefore mathematical models of the avalanche-like destruction of the organism are of particular interest.

We shall now examine the simplest model of the avalanche-like destruction of the organism. Let s_0, s_1, s_2, ..., s_n ... denote the states of an organism with 0, 1, 2, ..., n ... defects. Let λ_0 be the background rate at which defects accumulate (the background rate of destruction), independent of the stage of destruction which the organism has reached. Correspondingly, let μ_0 be the background force of mortality. In the simplest case, both these quantities arise from random harmful effects of the external environment. In tandem, there is also an induced rate of destruction and an induced force of mortality which grow as the number of defects increases. At a first approximation, it can be assumed that both the induced rate of destruction and the induced force of mortality are directly proportional to the number of defects, so that for an organism with n

defects the induced rate of destruction is equal to $n\lambda$, and the induced force of mortality is $n\mu$.

With these assumptions, we can diagram the avalanche-like destruction of the organism as follows:



This diagram corresponds to a system of differential equations:

$$\frac{ds_0}{dx} = -(\lambda_0 + \mu_0)s_0 \qquad (71)$$

$$\frac{ds_1}{dx} = \lambda_0 s_0 - (\lambda_0 + \mu_0 + \lambda + \mu)s_1$$

.....

$$\frac{ds_n}{dx} = [\lambda_0 + (n-1)\lambda]s_{n-1} - [\lambda_0 + \mu_0 + n(\lambda + \mu)]s_n$$

.....

A similar system of equations (not taking into account the background force of mortality) was obtained and solved in a mathematical model linking the survival of organisms with chromosome damage (Le Bras, 1976).

If at the initial moment in time the number of defects in the organism is equal to zero, the proportion of organisms with 0, 1, 2, ..., n ... defects changes with time according to the following formulae:

$$s_0 = e^{-(\lambda_0+\mu_0)x} \tag{72}$$

$$s_1 = s_0\left[\frac{\lambda - \lambda e^{-(\lambda+\mu)x}}{\lambda + \mu}\right] \cdot \frac{\lambda_0}{\lambda}$$

$$s_2 = \frac{s_0}{2}\left[\frac{\lambda - \lambda e^{-(\lambda+\mu)x}}{\lambda + \mu}\right]^2 \cdot \frac{\lambda_0}{\lambda}\left(\frac{\lambda_0}{\lambda} + 1\right)$$

.....

$$s_n = \frac{s_0}{n!}\left[\frac{\lambda - \lambda e^{-(\lambda+\mu)x}}{\lambda + \mu}\right]^n \cdot \frac{\lambda_0}{\lambda}\left(\frac{\lambda_0}{\lambda} + 1\right)\left(\frac{\lambda_0}{\lambda} + 2\right)\cdots\left(\frac{\lambda_0}{\lambda} + (n-1)\right)$$

.....

If the number of defects is allowed to grow unrestrictedly, the relationship between the number of survivors and age is determined as follows:

$$l(x) = \sum_{n=0}^{\infty} s_n = s_0\left(1 + kz + \frac{k(k+1)}{2!} \cdot z^2 + \frac{k(k+1)(k+2)}{3!} \cdot z^3\right.$$

$$\left. + \ldots\right) = s_0(1 - z)^{-k}, \tag{73}$$

where $k = \frac{\lambda_0}{\lambda}$, and $z = \frac{\lambda - \lambda e^{-(\lambda+\mu)x}}{\lambda + \mu}$.

Returning to the initial variables, we obtain:

$$l(x) = s_0(1 - z)^{-k} = e^{-(\lambda_0+\mu_0)x}\left(\frac{\lambda + \mu}{\mu + \lambda e^{-(\lambda+\mu)x}}\right)^{\frac{\lambda_0}{\lambda}} . \quad (74)$$

The force of mortality is accordingly:

$$\mu(x) = -\frac{dl(x)}{l(x)dx} = \mu_0 + \frac{\mu\lambda_0(1-e^{-(\lambda+\mu)x})}{\mu + \lambda e^{-(\lambda+\mu)x}} . \quad (75)$$

In the particular case when the rate at which defects multiply is significantly greater than the induced force of mortality ($\lambda >> \mu$), the growth in the force of mortality during the initial stage (with low values of x) is described by the Gompertz-Makeham law:

$$\mu(x) \approx \mu_0 + \frac{\mu\lambda_0(1 - e^{-(\lambda+\mu)x})}{\lambda e^{-(\lambda+\mu)x}} \approx A + Re^{\alpha x}, \quad (76)$$

where $A = \mu_0 - \frac{\mu\lambda_0}{\lambda}$; $R = \frac{\mu\lambda_0}{\lambda}$; $\alpha = \lambda + \mu$.

This model of the avalanche-like destruction of the organism not only provides a theoretical justification for the well-known Gompertz-Makeham law, but also explains why the values of parameter A sometimes turn out to be negative. Within the framework of the model, parameter A represents the background force of mortality (μ_0) minus a quantity equal to R (see above). Therefore, if the background force

of mortality μ_0 is small (as for populations in the developed countries and populations of laboratory animals), and the value of parameter R is significant (when the background rate of destruction λ_0 is large), parameter A can be negative.

Another important virtue of the avalanche-like destruction model is that it correctly predicts deviations from the Gompertz-Makeham law towards lesser values of mortality at very old ages. In this extreme age-range, the force of mortality grows according to the formula:

$$\mu(x) \approx \mu_0 + \lambda_0(1 - e^{-(\lambda+\mu)x}). \qquad (77)$$

Thus the model predicts an asymptotic growth in the force of mortality with an upper limit of $\mu_0+\lambda_0$. Putting this conclusion together with data on the survival of long-lived people, it can be determined that for human beings λ_0 is approximately 0.5 - 1.0 $year^{-1}$. The value of λ for human beings is 0.05-0.12 $year^{-1}$ and $\mu = 10^{-6} - 10^{-7}$ $year^{-1}$ (these estimates are based on typical values of R and α for human beings).

Alongside the virtues already listed, the avalanche-like destruction model has one significant weakness: it does not conform to the well-known phenomenon known as the compensation effect of mortality (see section 4.5). Although the model predicts an inverse relationship between the parameters R and α as parameter λ (the rate of multiplication of defects) is varied, this relationship takes a rather different form:

$$\ln R = \ln(\mu\lambda_0) - \ln(\alpha-\mu). \qquad (78)$$

Thus, this particular version of the avalanche-like destruction model unfortunately does not agree quantitatively with the compensation effect of mortality, and consequently needs to be significantly improved. Nevertheless, in our opinion the idea that organisms undergo cascade destruction is one of the most promising ideas in the mathematical modelling of life span.