

References and Notes

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Redundancy and Biological Aging

Abstract. *The relationship between aging and organizational redundancy in biological systems was investigated from the standpoint of information theory. A mortality rate function derived for a randomly deteriorating redundant system approximates observed mortality rates more closely than does the Gompertz function and indicates that variations in redundancy among various mammalian species could account for their widely different rates of aging.*

From the standpoint of information theory, all organization in a system can be lumped together and quantified as information. With the passage of time, in any living system there is a progressive loss of organization and an irreversible accumulation of informational entropy. Some degree of compensation for this process can be afforded by the incorporation of redundant information, or spare parts, so to speak, into the system, a principle analogous to the use of redundancy in messages carried over noisy communications channels, or the use of parallel systems to improve reliability of control systems. That such protective adaptation would have a positive survival value and might therefore be of fundamental importance in living systems was pointed out by Dancoff and Quastler (1) over 10 years ago.

Detailed application of this abstract notion to a living organism is a complex problem, since essential information, redundant in part, is manifest at all organizational levels from molecular structure to gross anatomy. The importance of redundancy at the organ level is well known. Over 75 percent of mammalian renal tissue, for example, seems to be redundant, since over three-fourths of the kidney tissue of a healthy mammal must be removed to produce renal failure. Much has been written on the information content of macro-

molecules (2), and Ehret (3) has estimated the information requirement at the cell organelle level, but just what part of this information is redundant is not known.

It is much easier, though less descriptive, to consider the pooled information from all levels of organization. Effective pooled redundancy can be estimated to some extent by measuring the reserve capacity of a complex function requiring intact information at many levels. The studies by Shock and collaborators (4) of basal metabolic rate, work rate, cardiac output, pulmonary function, nerve conduction velocity, and renal function have shown that losses of 20 to 60 percent of function during aging are still compatible with life, indicating overall redundancies of at least 20 to 60 percent for these complex functions.

In this investigation of the effect of redundancy upon aging, biological age will be expressed as the probability, at time t , of death within a given time interval. This probability, equivalent to the age specific mortality rate or the q_x of actuarial tables, can be written

$$-\frac{1}{S} \frac{dS}{dt} \equiv -\frac{S'}{S} = f(t)$$

where S is the number of survivors at time t . Throughout the last two-thirds of life this is generally considered to be a simple exponential function as originally proposed by Gompertz (5). In most mortality studies, however, the rise of $-S'/S$ is somewhat less than exponential. This has been emphasized by Strehler (6) in the case of *Drosophila*, by Lindop (7) in the case of mice, and by Auerbach (8) in the case of human mortality statistics.

Considering the living organism as a collection of information, the present problem is to examine the mortality rate curve (S'/S versus t) of a randomly decaying ensemble of message-laden, redundant information.

A large part of the total information of an organism is expendable, being either unnecessary or readily replaced. There is, however, a body of information which is replaced with difficulty or not at all. Errors which accumulate here are perpetuated throughout the life of the individual. This vital information is held to some degree in larger structures but chiefly in certain irreplaceable cells of nonproliferating cell populations and in the progenitive cells of renewal cell populations. Within these cells the main repository of information is in the structure of nucleic

acids, by which all protein synthesis is directed.

A certain minimum of this vital information is necessary for life. This minimal or essential message is carried in a minimal ensemble of structural elements, ω in number, which will be assumed in the following model to be largely independent. Since various types of structural units carry various amounts of information, it will be necessary to use a mean value of b bits of information per structural element. The informational unit of the nucleic acids, the nucleotide pair, carries two bits of information, so that the overall mean of information per structural unit throughout the entire organism should be of this order. The essential message is then equal to $b\omega$ bits.

The repetition of structure throughout the organism gives redundancy to the complement of irreplaceable information. Since the variation of redundancy among various parts of the essential message is unknown, the simplest case, that in which redundancy of all elements is the same, will be used as a model. Redundancy is customarily given as a percentage, but it will be convenient here to define a redundancy number, n , such that

$$\% \text{ redundancy} = 100 (1 - 1/n)$$

where n is the number of times an informational structural element appears within the organism at the time of maximal redundancy. This is analogous to the "hitness" number in target theory. If $b\omega$ bits of information carry the essential message, then the full complement of information is

$$H_{\max} = nb\omega$$

This can be conveniently represented as a matrix of ωn elements:

$$\begin{array}{cccccccc} A_1 & A_2 & A_3 & \dots & A_n \\ B_1 & B_2 & B_3 & \dots & B_n \\ C_1 & C_2 & C_3 & \dots & C_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \omega_1 & \omega_2 & \omega_3 & \dots & \omega_n \end{array}$$

Each element is an independent, structural unit carrying b bits of information; all members of class A carry identical pieces of information; and the essential message reads downward from any A to any ω . At least one element of each class must be present to retain the essential message.

Now let structural elements decay with time in the manner of a first-order chemical reaction. Errors will accumulate in the matrix in a random fashion. If the mean probability of an

error occurring within a period of time is m , then at time t the probability of any particular element's being free of error is e^{-mt} , and the probability of survival of at least one complete essential message in a matrix is

$$S = [1 - (1 - e^{-mt})^n] \omega$$

This expression is similar to one used by Szilard (9) for an aging model in which ω was not large, being the number of chromosome pairs, and in which $n = 2$.

The age specific rate of loss of essential messages, or individuals, from a population is

$$-\frac{S'}{S} = mn\omega(1 - e^{-mt})^{n-1} \times [1 - (1 - e^{-mt})^n]^{-1} e^{-mt} \quad (1)$$

It now remains to determine the values of the constants in Eq. 1. Exact values are not available, but approximations of reasonable orders of magnitude will serve to illustrate the effects of redundancy upon the mortality rate function, $-S'/S$. In general terms, m , the error rate, will be small because of the great stability of the information-rich macromolecules, particularly the nucleic acids; ω must be very large because of the vast amount of information inherent in a living organism, and the magnitude of n is unknown.

The redundancy of the individual increases by cell division throughout the growth period and is minimal at the one-cell stage of development. Since information is in its most concise form at this time, the total information content of the zygote should closely approximate the essential message, ωb . If, at this stage, the storage material for information is DNA, then the actual quantity of DNA present in the zygote will set an upper limit for ωb . Diploid mammalian nuclei contain about 5×10^{12} g of DNA with very little interspecies variation (10). A nucleotide pair has a mass of about $1000/N$ or 1.7×10^{-21} g, placing the number of base pairs at 3×10^9 , and allowing for the storage of 6×10^9 bits of information. The actual value of ω will be less, depending upon the value of b and upon the redundancy and the efficiency of the DNA informational storage system. In the following illustration $\omega = 10^9$, although, as can be seen in Fig. 1, tenfold variations in ω have little effect upon the shapes of the mortality curves.

The value of m can probably be approximated closely enough for the present purposes. Expressing t in days,

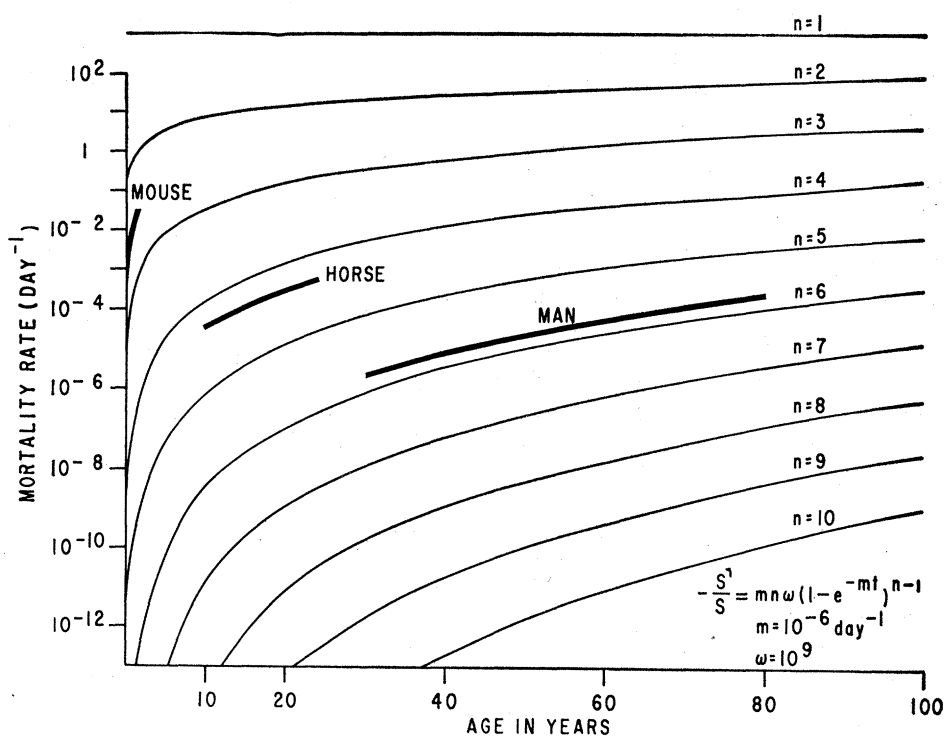


Fig. 1. Age-specific mortality rates of mouse, horse, and man plotted together with the family of curves generated by varying the redundancy in Eq. 2.

m will be the probability of an error occurring in any one matrix element in the course of one day. This will depend upon temperature and chemical factors, since in reality m is a mean of many chemical reaction rate constants, but it should be fairly constant with time and fairly uniform among various mammalian species. Information held in the DNA of germinal cells is very stable, the probability of mutation of one locus being about 10^{-5} per mouse generation or per year. Failla (11) esti-

mated that the mutation rate of somatic cells is greater than that of germinal cells by a factor of 12. Judging from turnover rates, information held in RNA and proteins is also less stable. An error rate of between 10^{-3} and 10^{-4} per year or 10^{-6} per day is a reasonable approximation, although here again tenfold variations in m will not greatly alter the shapes of the $-S'/S$ curves.

When $mt < 10^{-1}$, the product of the last two terms in Eq. 1 becomes nearly unity and varies only slightly over a

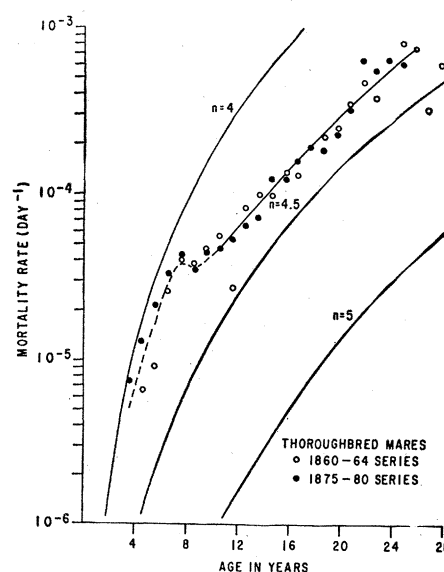
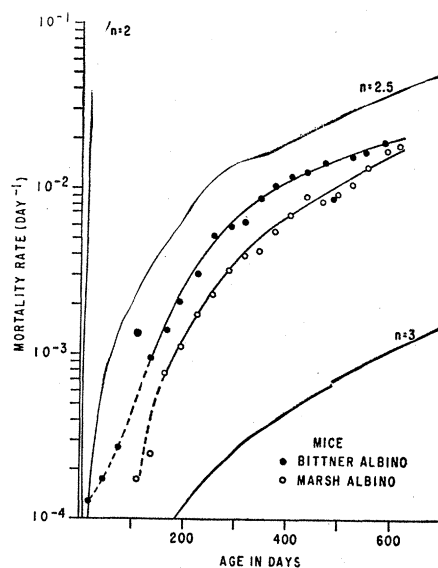


Fig. 2 (left) and Fig. 3 (right). Detail of Fig. 1, showing, respectively, mouse data of Murray and Hoffman (12) and mortality rates of English thoroughbred horses given by Comfort (13).

period of 100 years. Equation 1 can then be simplified to

$$-\frac{S'}{S} \approx \omega mn (1 - e^{-m})^{n-1} \quad (2)$$

Solving Eq. 2 for the case of no redundancy, $n = 1$, the mortality rate of essential messages, or individuals, does not vary with time, and the system is extremely unstable, nearly all essential messages being lost in the course of 1 day. Introducing redundancy into the system by increasing n , a family of curves with positive slopes is generated as in Fig. 1.

According to this model, with proper constants Eq. 2 should determine the shape and slope of the mortality rate curve of a population of animals of a given species. Moreover, since various mammalian species all have about the same levels of organization, and since they all utilize similar chemical processes and similar information coding systems, m and ω should be about the same for different species. This leaves only differences in redundancy to account for the variations in slopes of mortality rate curves. It might be expected, then, that the mortality rate curves of various mammalian species should be members of the family of curves generated by varying n in Eq. 2. This appears to be very nearly the case with the three species shown in Fig. 1, and in more detail in Figs. 2, 3, and 4. The empirical curves fit those of Eq. 2 generally better, in fact, than they do the Gompertz function, which is linear in these coordinates. The value of n for each species is only approximate be-

cause of the roughness of the model and the lack of detailed knowledge of m and ω , but it should still be of the right order of magnitude, since it can be seen that tenfold variations in m or ω result in variations of only about ± 1 in n . Conversely, it is interesting to see what small variations in redundancy could account for the very great differences in rates of aging of various species.

HORTON A. JOHNSON*

Department of Pathology,
University of Utah College of
Medicine, Salt Lake City

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- * Present address: Medical Department, Brookhaven National Laboratory, Upton, N.Y.
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Nuclear Bodies: Their Prevalence, Location, and Ultrastructure in the Calf

Abstract. Nuclear bodies, averaging 0.8 to 1.2 μ in diameter, were observed in various parenchymatous and interstitial cells of the calf. They were most prevalent and complex in structure in the parenchymatous cells of the adrenal cortex, and consisted of a fibrillar outer portion and a central or core area of varying size that was composed of electron-opaque particulate matter. These bodies, as far as the authors are aware, are of unknown significance.

Collaborative clinical and morphological investigations were undertaken in our laboratories in an attempt to correlate the structure of the adrenal cortex with function in the ox, particularly with reference to salt and water balance.

During electron-microscopic studies of the adrenal cortex of clinically normal Holstein calves of both sexes, our attention was drawn to the presence of nuclear bodies apparently similar in kind to those described in brief by Brody in human epidermis (1), and by Latta and Maunsbach (2), and also Farquhar and Palade (3) in renal glomerular mesangial cells of the rat. Somewhat similar bodies were described by Lafontaine in interphase nuclei of meristematic cells of *Allium cepa* (4). In our laboratory, the nuclear bodies were first observed in adrenal zona glomerulosa cells of the calf, and subsequently in parenchymatous and most interstitial cells of all portions of the adrenal gland, kidney, pituitary gland, nasal olfactory epithelium, and in agranulocytes from the effluent of the thoracic duct. They appeared not to be present, or at least not identifiable, in nuclei of the various

cells of the pineal gland and smooth muscle cells of blood vessels. Their numbers and location seemed to be correlated, especially in the adrenal cortex, with the prevalence and disposition of nucleoli.

From studies of individual sections of the various tissues, and also of serial sections (up to twelve in a sequence) of zona fasciculata cells, two to five nuclear bodies were found to be typically present per nucleus. In approxi-

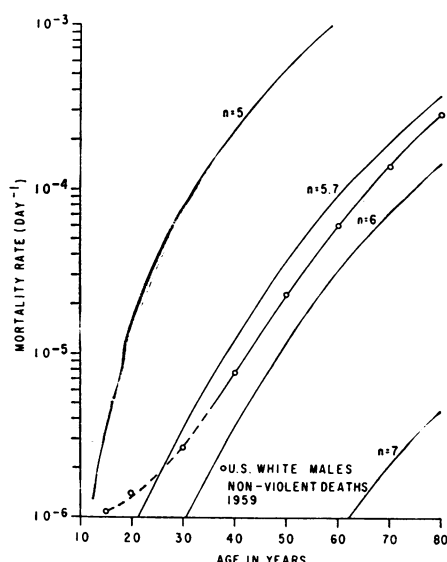


Fig. 4. Detail of Fig. 1, showing non-violent mortality rates of U.S. white males (14).

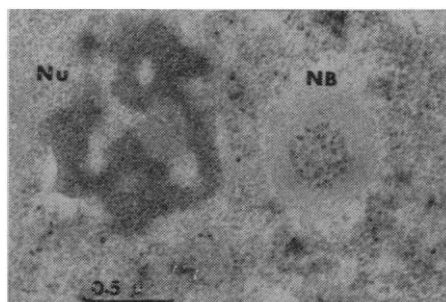


Fig. 1. Portion of the nucleus of a parenchymatous cell from the adrenal zona fasciculata of a calf, showing a nuclear body (NB) adjacent to the nucleolus (Nu). Only a portion of the nucleolus is shown. The section is embedded in Maraglas and stained with uranyl acetate-lead monoxide.