THE SIGNIFICANCE OF OSCILLATIONS IN SCALING, AGEING, AND BIOLOGICAL TIME

KENNER T.

Institut für Physiologie der Karl-Franzens-Universität Graz, Austria

Received after revision October 2007

A b s t r a c t

The measurement of time is based on external and internal phenomena. These phenomena have something to do with periods, cycles, and oscillations. External phenomena are the daily periods of sunlight and darkness, the weekly periods, the four-week periods related to the appearance of the moon. Also the year-period and certain multiples of this period have to be added to this list – like the 11-year cycles of sunspots.

In biological systems such external cycles have been internalised by the development of biological clocks which synchronise the functions of the system.

In addition, biological systems have internal time-related functions which have interesting correlations to the size of the system. Here we will discuss the scaling functions particularly in mammals. One can say: the smaller an animal, the shorter are its internal time periods, including, e.g., heart period and lifetime. Therefore, ageing is a size-dependent process.

Several theories try to explain the process of ageing by genetic determinants, by genetic or metabolic defects, by immunological failure, or by other reasons. It is noteworthy that the duration of life is correlated to the size of the body of different animals. This fact indicates a close relation to metabolism. It can be assumed that under optimal conditions of life, defects in function or structure are repaired by special maintenance functions. During the process of ageing these functions lose effectivity.

It seems that the organism tries to achieve an optimisation of these maintenance functions. Optimisation is defined as a process by which the organism tries to minimise biological cost functionals.

Loss of optimality contributes to instability in the most sensitive periods of life: early development and old age. The concept of optimality and competence includes the need to stabilise vital functions by external aid. In addition to biological aspects of ageing, social and psychological factors have to be considered.

K e y w o r d s

Time and age, Ageing, Chronobiology, Stability, Optimality, Oscillations, Human value

INTRODUCTION

Franz Halberg, Germaine Cornélissen, Othild Schwartzkopff from Minnesota, USA, and Jarmila Siegelova, Bohumil Fiser, Jiri Dusek, and Pavel Homolka from Brno have in many studies contributed important results to the knowledge of the chronobiology of the cardiovascular system and during the last 15 years presented the latest results in yearly symposia in Brno. Therefore I am describing some notice about problems of time and time-related phenomena in physiology in this presentation.

TIME AND AGE

We all depend on the continuous flow of time. For all macroscopic physical phenomena in biological systems time can be considered as an independent variable. In other words: All our activities and actually everything on earth are functions of time. Ageing is a time-dependent process which starts at the moment of conception with the development of an individual. Ageing is a steadily proceeding function of time and ends with death, a catastrophic and irreversible event.

Although all of us experience ageing and time, nothing is known about what time really is. It may, thus, be permitted to cite the words of the Austrian poet Hugo von Hoffmansthal from the "Rosenkavalier" (*6*), (1911):

The ageing grand lady, the Marschallin, speaks to her young boyfriend:

"... Die Zeit, die ist ein sonderbar Ding. Wenn man so hinlebt, ist sie rein gar nichts. Aber dann auf einmal, da spürt man nichts als sie. Sie ist um uns herum, sie ist auch in uns drinnen. In den Gesichtern rieselt sie, im Spiegel da rieselt sie, in meinen Schläfen fließt sie. Und zwischen mir und dir da fließt sie wieder, lautlos, wie eine Sanduhr. ....Manchmal steh' ich auf mitten in der Nacht und laß die Uhren alle, alle stehn. Allein man muß sich auch vor ihr nicht fürchten. Auch sie ist ein Geschöpf des Vaters, der uns alle erschaffen hat. ...."

In this poetic description the fact is implicitly included that time can be seen as a physiological, biological and, especially, as a subjective event.

THE ARROW OF TIME

Thanks to the work of Maxwell, Boltzmann and Max Planck, we now know that the irreversible flow of time has something to do with entropy. And entropy is related to the time-dependent increasing probability of the condition of a closed system. The steady increase of entropy means loss of order, increase of confusion, decrease of information, and reduction of useful energy. An interpretation of the second law presented by Sir Arthur Eddington can be expressed as "entropy is the arrow of time".

The term Entropy was coined in 1868 by Richard Clausius (*16*), and can be described as "a measure of the amount of energy no longer capable of conversion into useful work". The so-called second law of thermodynamics can be summarised by the sentence: The entropy of a closed system can only increase with time.

Decrease of entropy needs external energy and permits an increase of internal organisation, which can be expressed as an increase of negentropy (*19*). Negentropy, therefore, describes a contribution to information and value (*2*). Life is only possible through continuous generation of negentropy.

Ageing can be observed in nonliving and in living systems. Of course, in nonliving systems, the term ageing in a certain sense is used as a metaphor. Living systems include cells, individuals, groups, and social systems. Life means that the increase of entropy is counteracted by systems which increase negentropy, like biological control systems, and by metabolism.

Ageing has something to do with increase of entropy and the loss of proper use of energy.

Power is the rate of use of energy, or work per unit time, and is equivalent to the term metabolic rate in a living system.

Efficiency relates performed work to used energy and thus describes the proper use of energy resources by a system. High efficiency means that in a system the energy provided by fuel or by some energy stores is used economically for purposeful work.

On the other hand, effectiveness is a purely outcome-related value. One can reach the same outcome with high or low efficiency (*3, 5*). It seems logical that under normal conditions high effectiveness should be related to high efficiency. It seems, however, that the process of ageing leads to a reduction of efficiency. As long as possible, however, the organism attempts to keep effectiveness as high as possible.

In living systems structure and function are supported by control mechanisms (*1, 9*) and maintenance mechanisms (*7*). The normal function of a control mechanism is stable. Stability means that the system permits to correct the effects of external or internal disturbances and thus to keep the controlled output corresponding to the reference input.

Any uncontrolled deviation of the output from the reference input indicates instability. Many phenomena during ageing can be explained as effects of instability. An example related to age-dependent changes in the arterial system is the continuous stiffening of the arterial wall, which leads to a consecutive increase of the pulse-wave velocity and also to the general trend towards an increase of the systolic blood pressure (*8, 21*).

Maintenance functions (*7*) are mechanisms which act to maintain the adult in a healthy state for a considerable proportion of the total lifetime. And, of course, each of these functions and mechanisms includes a whole set of control mechanisms:

Regeneration and healing
DNA proofreading and repair
Removal or repair of defective proteins
Removal of free radicals
Removal of toxic chemicals
Immune response
Control of internal milieu
Stress response (e.g. through heat-shock proteins)
Etc.

We can assume that all the control and maintenance functions in a normal healthy person have the capability of optimisation. This means that all the variables and parameters involved are adjusted in such a way as to increase the efficiency of the whole system or/and of subsystems.

STABILITY AND OPTIMALITY

In order to try to understand the role of optimality of control and maintenance mechanisms in ageing it is necessary to consider that ageing is characterised by multiple declines or failures of these mechanisms of functions. These multiple defects then may lead to overt instability.

The time periods after birth and before death represent two critical phases of life where failure and instability may easier be induced than during the main part of life. *Yates* (*22*) explains these phases of instability for a human being with respect to the level of "minimal stability for system autonomy". It may be mentioned that phases of low stability or of instability may also appear at times of major transformations such as puberty.

Medicine is still focussed very much to pathology or defects in order to provide quick interventions. Recently, however, the concept of optimality and the concept of competence have been combined with the idea of prevention, guidance, and aid.

The concept of optimality has been developed by *Heinz Prechtl* (*15*), see also *Perat* 1993) for the phase of low stability during early human development. Prechtl uses the term optimality in the sense of a score, i.e. a sum of 42 yes (1)- or no (0)-decisions corresponding to the presence or absence of normal or ideal conditions in the past or presence. Thus, the optimality score is a number which indicates the closeness of the biological status of the system to an ideal overall condition. The score has diagnostic significance: If the number of non-optimal conditions in the optimality list is high, this means that the system (i.e. the baby) is in danger because it exists below the limit of "minimal stability for system autonomy".

In the historical development of concepts for old age the earlier defect model has given way to a concept of competence (*11*). This means a preference of looking at the existence of optimal conditions. Competence is defined as the ability to act within the individual limits of undercharge and overcharge (*L. Rosenmayr* 1989, cited by *Olbrich* 1990). The list of optimality items has to be defined within the scope of the WHO definition of health: physical, psychological, and social factors.

The process of optimisation minimises a cost functional by adjusting system parameters to values within a range, which depends on momentary individual conditions. Typical examples for optimisation in the circulatory system are the minimisation of material, volume and energy consumption and, apparently, the continuous readjustment of the necessary parameters of the system during sleep.

Whereas the optimality concept is mainly related to the history of the system, optimisation adjusts the current or future conditions to the best possible compromise. This means that even under the condition of non-optimality the organism still attempts to optimise its functions. However, in general the existence of optimisation processes in biological systems is the prerequisite for the generation of normal conditions and for a high score of optimality.

In general, the optimal condition means that efficiency as well as effectiveness has high or maximal values. During the process of ageing efficiency may decrease. Therefore it may be necessary to make a compromise: keep the effectiveness at a high level at the cost of decreasing efficiency. In other words: the limitation of effectiveness leads to a shift of the optimal condition towards lower values of efficiency.

OPTIMALITY AND OSCILLATIONS

There are many arguments suggesting that biological functions are optimised (*10, 14*). It is extremely difficult to prove such assumptions in specific examples. It can be shown that mathematical algorithms to optimise certain functions yield results which agree well with experimental observation. One example, which was studied by *Pfeiffer and Kenner* (1978), is the characteristic triangular contour of the time-course of the left-ventricular ejection.

It is a matter of fact that most biological functions oscillate. Typical examples are the heart beat, the respiration, the blood pressure. Besides the interesting fact that several of these oscillations tend to synchronise – which again suggests some kind of optimisation – the question is not definitely answered whether these oscillations have specific functions in the control of biological systems. *Monos and Szücs* (1995) and other authors suggested that oscillations are necessary to guide a control system according to an optimising search strategy to find the best possible value or path of a variable. These authors presented the blood pressure control system as an example.

If the presence of optimal control strategies in each animal is assumed, then it seems plausible that these strategies have been developed in animals of different size, like mouse or elephant – as we actually observe. As a consequence we find general rules of biological similarity.

BIOLOGICAL SIMILARITY

Biological similarity may be interpreted as the apparent fact that evolutionary selection retains the result of optimisation. E.g.: the assumption of optimisation in the relation between the function of the heart and the properties of the arterial system permits to predict the typical relation between body weight and heart rate.

There are still many other viewpoints concerning the phenomenon of time and time-dependent processes. For example, we may consider the many periodic events which can be found in physiological functions. We are continuously involved in daily, monthly and longer periods of biological functions. One particular phenomenon has to be mentioned in greater detail: Time periods and intervals, including the maximal lifetime, are in mammals closely related to body mass and metabolism.

Allometric functions relating ageing, intervals, and energy of mammals to the body mass M (kg) according to *Schmidt-Nielsen* (*18*) are:

Pulse Interval (min) = $(1/241)\, M^{0.25}$

Lifetime (y) = $11.8\, M^{0.2}$

Metabolic Rate = $70\, M^{0.75}$

Specific Metabolic Rate (Metabolic rate per unit body mass) = $70\, M^{-0.25}$

As far as the exact values of the exponents of allometric functions are concerned there is a discrepancy between diverse statistical estimates and also between statistical estimates and theoretical assumptions. Recently, an interesting discussion was stimulated by the attempt to answer the question why the metabolic rate grows with the exponent 3/4 and not with the exponent 2/3. The latter would be expected by the assumption that the loss of metabolic heat is proportional to the surface of the body. *West at al*. (*20*) had suggested that the fractal structure of the vascular distribution plays a major role. Using such an assumption these authors tried to prove the exponent 3/4. In contrast, *Dodds et al*. (*4*) reanalysed statistical data sets from the literature and came to the conclusion "that present theories for exponent 3/4 require assumptions that render them unconvincing for rejecting the hypothesis for exponent 2/3".

Nevertheless, the main conclusions agree between both assumptions. The so-called specific metabolic rate is the larger, the smaller is the mass of the animal. The specific metabolic rate of a 30g mouse is tenfold higher as compared to a 300kg cow.

The lifetime – and also intervals of rhythmic biological functions like heart beat or ventilation – are the shorter, the smaller is the mass of the animal.

It can easily be calculated from the so-called allometric equations as shown above that a mouse in its lifetime has as many heartbeats as a cow in a tenfold longer lifetime.

THE HUMAN VALUE

In human life not only the metabolic efficiency counts, but also psychological aspects and human values. *Robert Rushmer* (*17*) discussed the economic values. The two periods in which a human being, from the viewpoint of economy, is "a drain on family or society" correspond – according to *Yates* (*22*) – to periods of threatening instability. The highest mortality rate can be observed during the first year of life. The second unstable period is the time of old age, and is again "a drain on family or society". To become old – due to the help of modern medicine – is becoming a more and more increasingly difficult problem.

In order to illustrate the problem of decreasing power and efficiency and the steady increase of entropy – in the sense of disorder and disarrangement – in old age, I shortly comment on a concept by *Moreno* (cited by *Petzold and Bubolz (13)*). He symbolises the connectivity of a person by circles. The person has to be seen as the centre; the circles represent the distances of social contact. With increasing age the contacts either get lost by death of friends and relatives or by difficulties to walk or even by loss of interest.

With increasing age the general efficiency of the body in the sense of metabolic and physical as well as psychological and motivational efficiency decreases. Therefore, with increasing age it becomes less important if a certain action is performed with high or low efficiency. The main goal is primarily the outcome. The term effectiveness (in contrast to efficiency) describes any measures that improve the outcome by – let us say – external or internal aid or help and relates achievement to desire. In other words, the ageing person needs the support of the family and the society.

Olbrich (*11*) uses the term competence of age, which corresponds to the behavioural effectiveness in the area of age-specific demands. Instead of focussing particularly on defects of age it seems to be important to optimise age-specific functions. In order to increase effectiveness there are the following possibilities: (*1*) Give external aid or measures of help. There is a tremendous lack of the most simple daily needs for old people, e.g. in the kitchen, in the bathroom, or the ever increasing difficulty to find a grocer's store close enough to the living quarter. (*2*) Adjust the demands to the capabilities. This second internal aid is a question of personality and also of caretaking. This concept, extended to the final stages of life, has led to the idea of Hospiz movement.

In contrast to earlier aspects of old age, which were concentrating on negative aspects like defect or disuse, the model of competence actually follows the concept of optimality as a guide to increase effectiveness by adjusting properly scaled help.

Furthermore, it must be concluded that not only physical and metabolic and economic needs of human life have to be provided, but also social, psychological and religious support has to be given according to the requirements of the individual.

Acknowledgement

Supported by the Austrian Research Fund (FWF): SFB "Optimierung und Kontrolle", by MSM0021622402.

REFERENCES

1. *Attinger EO.* Global systems dynamics. Karger (1970).
2. *Brillouin L.* Scientific uncertainty and information. New York: Academic Press, 1964.
3. *Dezsy J, Schwanzer H.* Einführung in das Krankenanstaltenmanagement. Springer, 1993.
4. *Dodds PS, Rothman DH, Weitz JS*. Re-examination of the 3/4-law of metabolism. J Theor Biol 2001; 209: 9–27.
5. *Ellencweig AY*. Analysing health systems. Oxford University Press, 1992.
6. *Hofmannsthal H, Strauss R*. Der Rosenkavalier. Fürstner: 1911.
7. *Holliday R*. The ancient origins and causes of ageing. NIPS 1992; 7: 8–40.
8. *Kenner T.* Physical and mathematical modeling in cardiovascular systems. In: Hwang NHC, et al. (eds). Quantitative Cardiovascular Studies. Baltimore: University Park Press, 1979.
9. *Milsum JH*. Biological control systems analysis. McGraw-Hill, 1966.
10. *Monos E, Szücs B*. Optimization of hemodynamic energy expenditure in the arterial system. Obesity Research 1995; 3: 811S – 818S.
11. *Olbrich E.* Seelische Entwicklung im Alter. Arzt und Christ 1990; 36: 20–28.
12. *Perat MV.* The optimality concept and its clinical value. Early Hum Dev 1993; 34: 133–141.
13. *Petzold H, Bubolz E.* Psychotherapie mit alten Menschen. Jungfermann-Verlag: 1979.
14. *Pfeiffer KP, Kenner T*. Minimization of the external work of the left ventricle and optimization of flow and pressure pulses. In: Bauer RD, Busse R (eds) 1978: pp. 215–223.
15. *Prechtl HFR*. The optimality concept. Early Hum Dev 1980; 4: 201–205.
16. *Rifkin J.* Entropy. Viking Press: 1980.
17. *Rushmer RF.* Humanizing health care. MIT Press: 1975.
18. *Schmidt-Nielsen K.* Scaling. Cambridge: Cambridge University Press, 1984.
19. *Talbot SA, Gessner* U. Systems physiology. New York: Wiley, 1973.
20. *West GB, Brown JH, Enquist BJ.* A general model for the origin of allometric scaling laws in biology. Science 1997; 27: 122–126.
21. *Wetterer E, Kenner T.* Die Dynamik des Arterienpulses. Springer, 1968.
22. *Yates FE.* Self-organizing systems. In: Boyd CAR, Noble D, eds. The logic of life. Oxford: Oxford Univ Press, 1993.