Basic concepts in quantitative biology of metabolism

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KURZFASSUNG: **Grundbegriffe der quantitativen Biologie des Stoffwechsels.** In der quantitativen Erforschung des Stoffwechsels werden begriffliche Modelle zur Anordnung, Erklärung und Vorhersage der beobachteten Daten benötigt. Vier solcher Modelle werden besprochen, um an Hand dieser die Logik und Methodologie der quantitativen Forschung zu illustrieren. 1. Die Theorie der *offenen Systeme* und des *Fließgleichgewichts,* welche eine Erweiterung der konventionellen Kinetik und Thermodynamik erfordert. Sie behandelt die Aufrechterhaltung des Fließgleichgewichts (Umsatzgeschwindigkeiten der Komponenten auf verschiedenen Organisationsstufen) und die Prozesse, die zur Annäherung an diesen Zustand führen. 2. Das *Rückkopplungs-Modell,* das eine weite Anwendung bei biologischen Regulationen findet, aber für dynamische Wechselwirkungen zwischen vielen Prozessen weniger geeignet ist. 3. Das Prinzip der *Allometrie,* welches das einfachste quantitative Modell der Harmonisierung physiologischer Prozesse darstellt. Das sogenannte Oberflächengesetz ist ein sehr spezieller Fall des Allometrie-Prinzips. Im allgemeinen ist die Allometrie-Beziehung abhängig von der Natur der betrachteten physiologischen Systeme, von physiologischen Zuständen und experimentellen Bedingungen. 4. Das *Wachstums-Modell* nach v. BERTALANFFY und Mitarbeitern, das ein einfaches hypothetisch-deduktives System von Wachstums-Gleichungen darstellt. Sein Erklärungs- und Vorhersagewert, ebenso wie seine Grenzen werden im Hinblick auf allgemeine Probleme der quantitativen Biologie diskutiert. Besonderer Nachdruck wird auf die Existenz noch ungelöster und weitere Bearbeitung erfordernder Probleme gelegt.

INTRODUCTION

It is a great honor to me that you have invited me from Canada to be the introductory speaker in this Symposium. It does not make my task easier that I am well aware of the fact that I am going to address what probably is the most select and competent group of investigators engaged in problems of quantitative metabolism. Our program announces a large number of experimental papers which certainly will make important contributions to the topic. The task of the introductory speaker, it appears to me, is to outline the conceptual framework of the field – its leading ideas, theories or – as I would prefer to say – the *conceptual constructs* or *models* applied.

According to widespread opinion, there is a fundamental distinction between "observed facts" on the one hand – which are the unquestionable rock bottom of science and should be collected in the greatest possible number and printed in scientific journals – and "mere theory" on the other hand, which is the product of speculation and more or less suspect. I think the first point I should emphasize is that such antithesis does not exist. As a matter of fact, when you take supposedly simple data in our

field – say, determination of Q_{O_2}, basal metabolic rates or temperature coefficients – it would take hours to unravel the enormous amount of theoretical presuppositions which are necessary to form these concepts, to arrange suitable experimental designs, to create machines doing the job – and this all is implied in your supposedly raw data of observation. If you have obtained a series of such values, the most "empirical" thing you can do is to present them in a table of mean values and standard deviations. This presupposes the model of a binomial distribution – and with this, the whole theory of probability, a profound and to a large extent unsolved problem of mathematics, philosophy and even metaphysics. If you are lucky, your data can be plotted in a simple fashion, obtaining the graph of a straight line. But considering the unconceivable complexity of processes even in a simple cell, it is little short of a miracle that the simplest possible model – namely, a linear equation between two variables – actually applies in quite a number of cases.

Thus even supposedly unadulterated facts of observation already are interfused with all sorts of conceptual pictures, model concepts, theories or whatever expression you choose. The choice is not whether to remain in the field of data or to theorize; the choice is only between models that are more or less abstract, generalized, near or more remote from direct observation, more or less suitable to represent observed phenomena.

On the other hand, one should not take scientific models too seriously. KROEBER (1952), the great American anthropologist, once made a learned study of ladies' fashions. You know, sometimes skirts go down until impeding the lady in walking; again, up they go to the other possible extreme. Quantitative analysis revealed to KROEBER a secular trend as well as short-period fluctuations in the length of ladies' skirts. This is a perfectly good little law of nature; however, it has little to do with the ultimate reality of nature. I believe a certain amount of intellectual humility, lack of dogmatism, and good humor may go a long way to facilitate otherwise embittered debates about scientific theories and models.

It is in this vein that I am going to discuss four models which are rather fundamental in the field of quantitative metabolism and, no doubt, will reappear in special investigations about which we are going to hear. The models I chose are those of the organism as open system and steady state; of homeostasis; of allometry; and the so-called BERTALANFFY model of growth. This is not to say that these models are the most important ones in our field; but they are used rather widely and can illustrate the conceptual framework as well as others can do.

OPEN SYSTEMS AND STEADY STATES

Any modern investigation of metabolism and growth has to take into account that the living organism as well as its components are so-called open systems, that is, systems maintaining themselves in a continuous exchange of matter with environment (Fig. 1). The essential point is that open systems are beyond the limits of conventional physical chemistry in its two main branches, kinetics and thermodynamics. In other terms, conventional kinetics and thermodynamics are not applicable to many pro-

cesses in the living organism: For biophysics – the application of physics to the living organism – an *expansion* of theory is necessary.

The living cell and organism is not a static pattern or machine-like structure consisting of more or less permanent "building materials" in which "energy-yielding materials" from nutrition are broken down to provide the energy requirements for

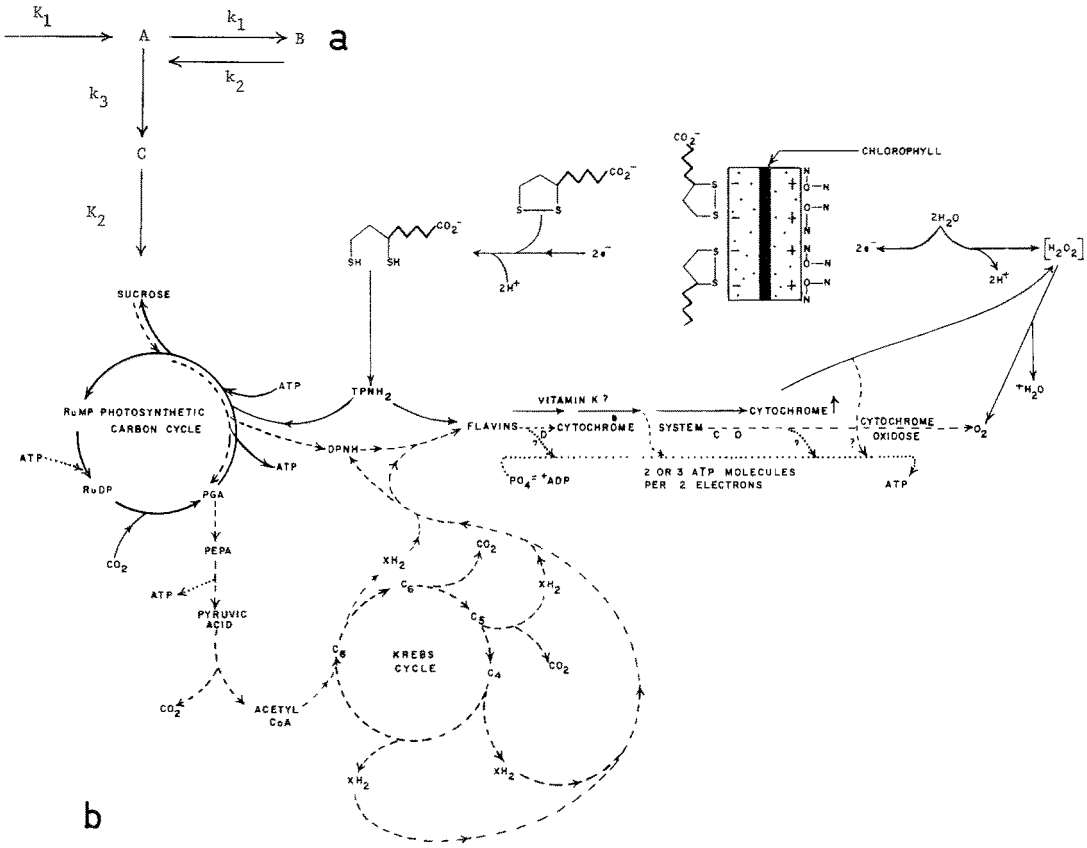

Fig. 1: *a* Model of a simple open system, showing maintenance of constant concentrations in the steady state, equifinality, adaptation and stimulus-response, etc. The model can be interpreted as a simplified schema for protein synthesis (*A*: amino acids, *B*: protein, *C*: deamination products; k_1: polymerization of amino acids into protein, k_2: depolymerization, k_3: deamination; $k_2 \ll k_1$, energy supply for protein synthesis not indicated). In somewhat modified form, the model is SPRINSON & RITTENBERG's (1949) for calculation of protein turnover from isotope experiments. (After VON BERTALANFFY 1953.) – *b* The open system of reaction cycles of photosynthesis in algae. (After BRADLEY & CALVIN 1957)

life processes. It is a continuous process in which both so-called building materials as well as energy-yielding substances (*Bau-* and *Betriebsstoffe* of classical physiology) are broken down and regenerated. But this continuous decay and synthesis is so regulated that the cell and organism are maintained approximately constant in a so-called steady state (*Fließgleichgewicht*, VON BERTALANFFY). This is the fundamental mystery

of living systems; all other characteristics such as metabolism, growth, development, self-regulation, reproduction, stimulus-response, autonomous activity, etc. are ultimately consequences of this basic fact. The organism's being an "open system" is now acknowledged as one of the most fundamental criteria of living systems, at least so far as German science is concerned (e. g. VON BERTALANFFY 1941, ZEIGER 1955, BUTENANDT 1955, 1959).

Before going further, I wish to apologize to the German colleagues for dwelling on matters which are familiar to them, and which I myself have often presented. As DOST (1962a) stated in a recent paper, "our sons already in their premedical examination take account of this matter", that is, of the theory of open systems in their kinetic and thermodynamic formulations. Remember – to quote but two examples – the presentation of the topic by BLASIUS (1962) in the new editions of our classic LANDOIS-ROSEMANN textbook, and NETTER in his monumental *Theoretical Biochemi-*

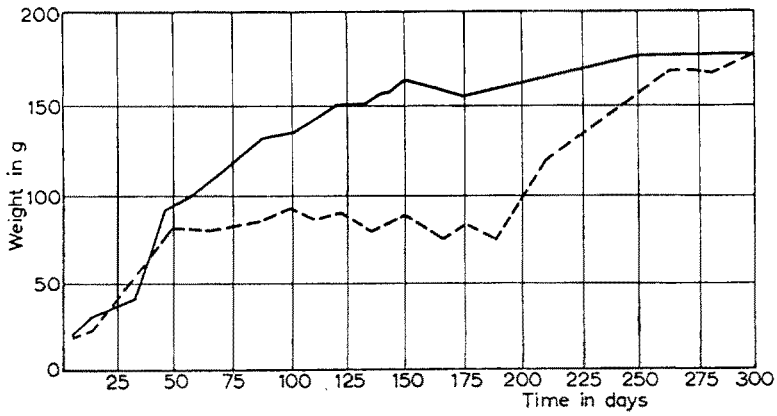

Fig. 2: Equifinality of growth. Heavy curve: normal growth of rats. Broken curve: at the 50th day, growth was stopped by vitamin deficiency. After re-establishment of normal regime, the animals reached the normal final weight. (After HÖBER from VON BERTALANFFY 1960)

stry (1959). I am sorry to say that the same does not apply to biophysics and physiology in the United States. I have looked in vain into leading American texts even to find the terms, "open system", "steady state" and "irreversible thermodynamics". That is to say, precisely that criterion which fundamentally distinguishes living systems from conventional inorganic ones, is generally ignored or bypassed.

Consideration of the living organism as an open system exchanging matter with environment, comprises two questions: first, their *statics,* that is, maintenance of the system in a time-independent state; secondly, their *dynamics,* that is, changes of the system in time. The problem can be considered from the viewpoints of kinetics and of thermodynamics.

Detailed discussion of the theory of open systems can be found in the literature (extensive bibliographies in VON BERTALANFFY 1953, 1960). So I shall restrict myself to saying that such systems have remarkable features of which I will mention only a few. One fundamental difference is that closed systems must eventually attain a

time-independent state of chemical and thermodynamic equilibrium; in contrast, open systems may attain, under certain conditions, a time-independent state which is called a steady state or in German, *Fließgleichgewicht,* using a term which I introduced some twenty years ago. In the steady state, the composition of the system remains constant in spite of continuous exchange of components. Steady states or "Fließgleichgewichte" are equifinal (Fig. 2); that is, the same time-independent state may be reached from different initial conditions and in different ways – much in contrast to conventional physical systems where the equilibrium state is determined by the initial conditions. Thus even the simplest open reaction systems show that characteristic which defines biological restitution, regeneration, etc. Furthermore, classical thermodynamics, by definition, is only concerned with closed systems, which do not exchange matter with environment. In order to deal with open systems, an expansion and generalization was necessary which is known as *irreversible thermodynamics.* One of its consequences is elucidation of an old vitalistic puzzle. According to the second principle of thermodynamics, the general direction of physical events is towards states of maximum entropy, probability and molecular disorder, levelling down existing differentiations. In contrast and "violent contradiction" to the second principle (ADAMS 1920), living organisms maintain themselves in a fantastically improbable state, preserve their order in spite of continuous irreversible processes and even proceed, in embryonic development and evolution, toward ever higher differentiations. This apparent riddle disappears by the consideration that the classic second principle by definition pertains only to closed systems. In open systems with intake of matter rich in high energy, maintenance of a high degree of order and even advancement toward higher order is thermodynamically permitted.

Living systems are maintained in a more or less rapid exchange, degeneration and regeneration, catabolism and anabolism of their components. The living organism is a

Table 1

Turnover rates of intermediates of cellular metabolism. (After HESS 1963)

structure	species	organ	turnover time in seconds
mitochondria	mouse	liver	1.3×10^{6}
hemoglobin	man	erythrocytes	1.5×10^{7}
aldolase	rabbit	muscle	1.7×10^{6}
pseudocholinesterase	man	serum	1.2×10^{6}
cholesterin	man	serum	9.5×10^{5}
fibrinogen	man	serum	4.8×10^{4}
glucose	rat	total organism	4.4×10^{3}
methionine	man	total organism	2.2×10^{3}
ATP glycolysis	man	erythrocytes	1.6×10^{3}
ATP glycolysis + respiration	man	thrombocytes	4.8×10^{2}
ATP glycolysis + respiration	mouse	ascites tumor	4.0×10^{1}
citrate cycle intermediates	rat	kidney	1 —10
glycolytic intermediates	mouse	ascites tumor	0.1— 8.5
$\text{flavoprotein}_{\text{red.}}/\text{flavoprotein}_{\text{ox.}}$	mouse	ascites tumor	4.6×10^{-2}
Fe^{2+}/Fe^{3+} – cytochrome a	grasshopper	wing muscle	10^{-2}
Fe^{2+}/Fe^{3+} – cytochrome a_3	mouse	ascites tumor	1.9×10^{-3}

hierarchical order of open systems. What imposes as an enduring structure at a certain level, in fact is maintained by continuous exchange of components of the next lower level. Thus, the multicellular organism maintains itself in and by the exchange of cells, the cell in the exchange of cell structures, these in the exchange of composing chemical compounds and so forth. As a general rule, turnover rates are the faster the smaller the components envisaged (Tables 1–3). This is a good illustration for the Heraclitean flow in and by which the living organism is maintained.

Table 2

Protein turnover determined by introduction of glycine labelled with ^{15}N.
(After SPRINSON & RITTENBERG 1949b)

		turnover rate (r)
RAT:		
	total protein	0.04
	proteins of liver, plasma and internal organs	0.12
	rest of body	0.033
MAN:		
	total protein	0.0087
	proteins of liver and serum	0.0693
	protein of musculature and other organs	0.0044

Table 3

Rate of mitosis in rat tissues. (After F. D. BERTALANFFY 1960)

	daily rate of mitosis (per cent)	renewal time (days)
Organs without mitosis		
nerve cells, neuroepithelium, neurilemma, retina, adrenal medulla	0	–
Organs with occasional mitosis but no cell renewal		
liver parenchyma, renal cortex and medulla, most glandular tissue, urethra, epididymis, vas deferens, muscle, vascular endothelium, cartilage, bone	less than 1	–
Organs with cell renewal		
upper digestive tract	7 –24	4.3–14.7
large intestine and anus	10 –23	4.3–10
stomach and pylorus	11 –54	1.9– 9.1
small intestine	64 –79	1.3– 1.6
trachea and bronchus	2 – 4	26.7–47.6
ureter and bladder	1.6– 3	33 –62.5
epidermis	3 – 5	19.1–34.5
sebaceous glands	13	8
cornea	14	6.9
lymph node	14	6.9
pulmonary alveolar cells	15	6.4
seminiferous epithelium	–	16

So much about the statics of open systems. If we take a look at changes of open systems in time, we also find remarkable characteristics. Such changes may occur because the living system initially is in an unstable state and tends toward a steady state; such are, roughly speaking, the phenomena of growth and development. Or else, the steady state may be disturbed by a change in external conditions, a so-called stimulus; and this – again roughly speaking – comprises adaptation and stimulus-response. Here too characteristic differences to closed systems obtain. Closed systems generally tend toward equilibrium states in an asymptotic approach. In contrast, in open systems, phenomena of false start and overshoot may occur (Fig. 3). In other terms: If we find

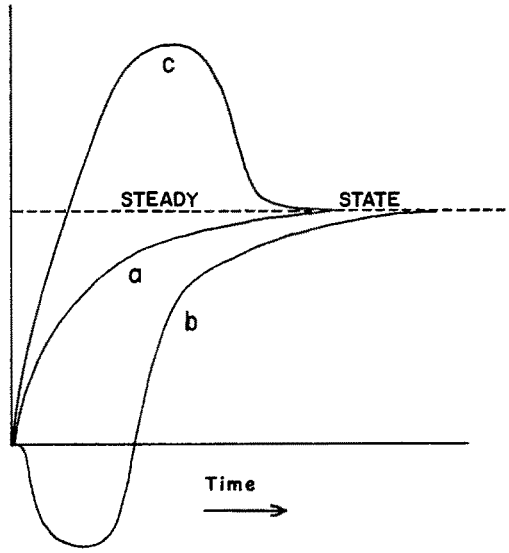

Fig. 3: Asymptotic approach to steady state (*a*), false start (*b*), and overshoot (*c*), in open systems. Schematic

overshoot or false start – as is the case in many physiological phenomena – we may trust this is a process in an open system with certain predictable mathematical characteristics.

It would by far exceed my time to discuss in detail experimental applications of the theory of open systems. Some examples must suffice to illustrate the broad range of application.

Models of open systems in order to analyze characteristic phenomena and to permit numerical calculation were developed as hydrodynamic analogs by BURTON (1939), GARAVAGLIA et al. (1958) and RESCIGNO (1960); more recently as electronic analogs by ZERBST (1963a, b). The relations of the second principle to organismic "anamorphosis" (increase in structure and organization) were discussed by HAASE (1951, 1957, 1959), JUNG (1956) and MORCHIO (1959). Calculation of turnover rates from isotope determinations are based upon open-system models (SPRINSON & RITTENBERG 1949, REINER 1953). So are, in a different way, calculations of cell turnover from

colchicine experiments (survey: F. D. BERTALANFFY & LAU 1962). This also permits calculation of energy requirements for protein synthesis (SCHULZ 1950) and for the maintenance of the organism in a steady state (SCHULZ 1950, VON BERTALANFFY 1953). Applications to cell metabolism and steady states in cells are found in LETTRÉ (1951), NETTER (1953, 1959), HESS (1963), HESS & CHANCE (1959); the latter especially studying the system of respiratory enzymes. Similar considerations were applied and, naturally, similar conclusions obtained in investigation of the network of reactions in photosynthesis (BRADLEY & CALVIN 1956). The levels of concentrations of natural and alien components in the blood were investigated by DOST (1953, 1958, 1958/1959, 1962a, b) by application of open systems models. In the field of radiation biology, similar considerations apply to elimination of radon from the blood in radium-poisoned subjects (MARTIN 1957a, b). The hit theory of radiation effects, if the system is metabolizing, was studied by HUG & WOLF (1955). Pharmacodynamic actions also are processes in open systems (WERNER 1947, DRUCKREY & KUPFMÜLLER 1949). Thus a steadily increasing field of biochemical and physiological phenomena is subordinated to the new concepts.

This enumeration which is by no means complete, will show that the theory of the organism as an open system is a vividly developing field as it should be, considering the basic nature of biological "Fließgleichgewicht". The above examples are given because, after the basic investigations by SCHÖNHEIMER (1947) and his group into the "Dynamic State of Body Constituents" by way of isotope tracers, the field is strangely neglected in American biology which, under the influence of cybernetic concepts, rather has returned to the machine concept of the cell and organism; thereby neglecting the important principles offered by the theory of open systems. I would like especially to mention that the field offers many problems for further research which partly are of a fundamental nature.

One such question is that we do not have at present a thermodynamic characteristic which would characterize the steady state in open systems in a similar way as maximum entropy characterizes equilibrium in closed systems. For a time it was thought that minimum entropy production would provide such characteristic – a statement known as "PRIGOGINE's theorem". Since this is still taken for granted by some biologists (e. g. STOWARD 1962) it should be emphasized that PRIGOGINE's theorem – as was well known to its author – only applies under very restrictive conditions and, in particular, does not apply to steady states of chemical reaction systems (DENBIGH 1952, VON BERTALANFFY 1953, 1960, FOSTER et al. 1957).

Another unsolved problem of very fundamental nature originates in a basic paradox of thermodynamics. EDDINGTON has called entropy "the arrow of time". As a matter of fact, it is the irreversibility of physical events – expressed by the entropy function – which gives time its direction. Without entropy, that is, in a universe of completely reversible processes, there would be no difference between past and future. Paradoxically, however, the entropy functions do not contain time explicitly – and this is true both of the classical entropy function for closed systems by CLAUSIUS and the generalized function for open systems and irreversible thermodynamics by PRIGOGINE. Here is an obvious gap in physical theory – it should be possible to follow entropy changes in their development in time. The only attempt I know of in this

important matter is a further generalization of irreversible thermodynamics undertaken by REIK (1953).

A third problem which will have to be solved is the relation between irreversible thermodynamics and information theory. Order is the basic principle of organization and therefore the most fundamental problem of biology. In a way, order can be measured by negative entropy in the conventional BOLTZMANN sense. This has for example been shown by SCHULZ (1951) for the non-random arrangement of amino acids in a protein chain: their organization in contrast to hazard arrangement can be measured by "Kettenentropie" or chain entropy. However, there is a quite different measure of order, namely, in terms of yes-or-no decisions or so-called bits within the framework of information theory. It turns out that information is of the dimension of negative entropy, thus showing a formal correspondence between the two different theoretical systems of thermodynamics and of information theory. It would seem that elaboration of a dictionary, as it were, for translating from the language of thermodynamics into that of information theory and vice versa would be the next step. Obviously, generalized irreversible thermodynamics will have to be used for this purpose; for it is only in open systems that maintenance and elaboration of order does not run contrary to basic physical principles. It may be guessed that such developments will become important for fundamental biological problems. Protein synthesis has to be considered in terms of energy required for arranging building blocks in a certain order. On the other hand, chromosomes and nucleic acids are considered as bearers of genetic information, and the DNA code for protein synthesis is at present in the process of being broken. Some synthesis of energetic and informational viewpoints will become a desideratum.

The problems mentioned, of course, transcend conventional physiology of metabolism. I have briefly listed them to show that the theory of open systems opens up new vistas in physics proper. That is to say, inclusion of phenomena in the living world is apt to lead to novel developments in the physical sciences – a consequence which is of high importance from the viewpoints both of science and philosophy. Let us get back now to physiology of metabolism and the theoretical models here applied.

FEEDBACK AND HOMEOSTASIS

Instead of the theory of open systems, another model construct is more familiar to the American school. It is the concept of feedback regulation, which is basic in cybernetics and was biologically formulated in CANNON's concept of homeostasis (e. g. WIENER 1948, WAGNER 1954, MITTELSTAEDT 1954, 1956, KMENT 1957). We can give it here only a brief consideration.

As is generally known, the basic model is a circular process where part of the output is monitored back, as information on the preliminary outcome of the response, into the input (Fig. 4a), thus making the system self-regulating; be it in the sense of maintenance of certain variables or of steering toward a desired goal. The first is the case, for example, in a simple thermostat and in the maintenance of constant temperature and many other parameters in the living organism; the second, in self-steering missiles

and proprioceptive control of voluntary movements. More elaborate feedback arrangements in technology and physiology (e. g. Fig. 4b) are variations or aggregates of the basic scheme.

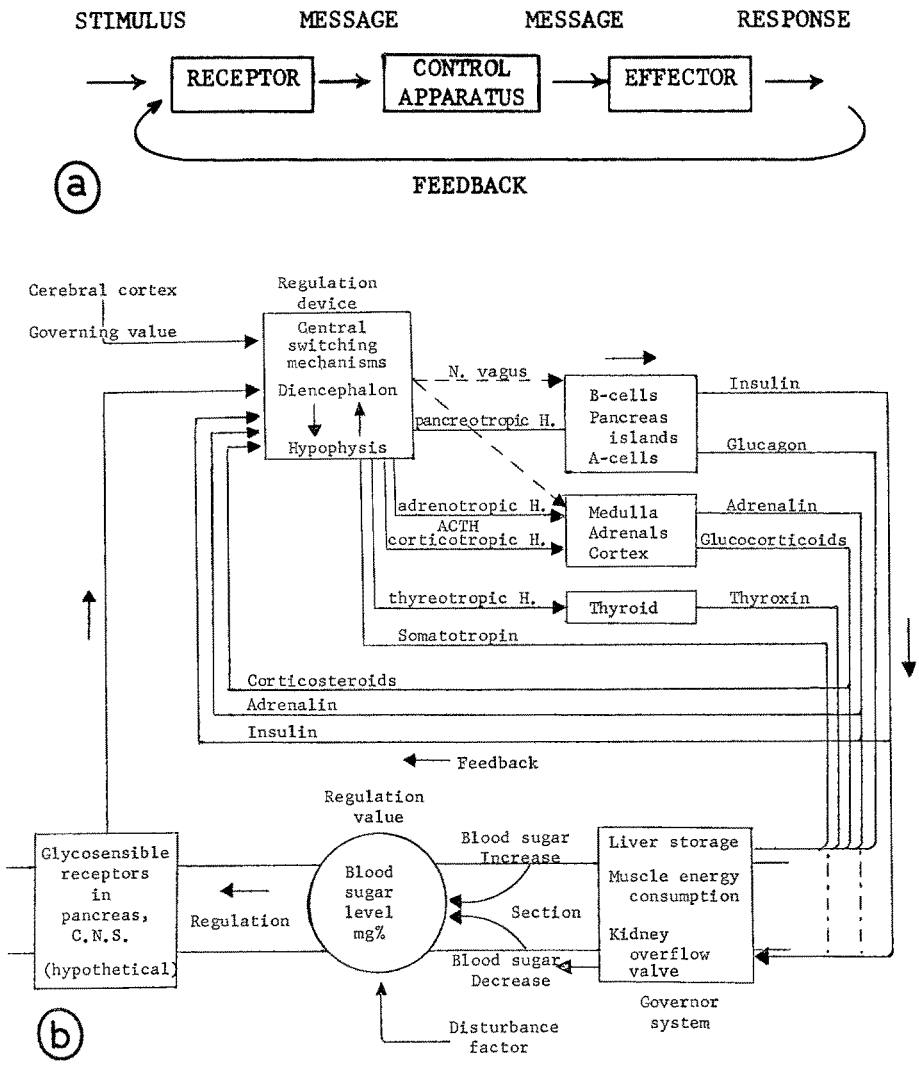

Fig. 4: *a* Simple feedback scheme. *b* Homeostatic regulation of the blood sugar level. (After MITTELSTAEDT 1954)

Phenomena of regulation following the feedback scheme are of widest distribution in all fields of physiology. Furthermore, the concept appeals to a time when control engineering and automation are flourishing, computers, servomechanisms, etc., are in the center of interest, and the model of the "organism as servomechanism" appeals to the "Zeitgeist" of a mechanized society. Thus the feedback concept sometime has

assumed monopoly supressing other, equally necessary and fruitful viewpoints: The feedback model is equated with "systems theory" in general (GRODIN 1963, JONES & GRAY 1963, CASEY 1962), or "biophysics" is nearly identified with "computer design and information theory" (ELSASSER 1958, p. 9). It is therefore important to emphasize that feedback systems and "homeostatic" control are an important but special class of self-regulating systems and phenomena of adaptation (cf. VON BERTALANFFY 1951, 1962). The following appear to be the essential criteria of feedback control systems:

1. Regulation is based upon pre-established arrangements ("structures" in a broad sense). This is well expressed by the German term "Regelmechanismen" which makes it clear that the systems envisaged are of the nature of "mechanisms" – in contrast to regulations of a "dynamic" nature resulting from free interplay of forces and mutual interaction between components and tending toward equilibrium or steady states.

2. Causal trains within the feedback system are linear and unidirectional. The basic feedback scheme (Fig. 4a) is still the classical stimulus-response (S-R) scheme, only the feedback loop being added so that causality becomes circular.

3. Typical feedback or homeostatic phenomena are "open" with respect to incoming information, but "closed" with respect to matter and energy. The concepts of information theory – particularly in the equivalence of information and negative entropy – therefore correspond to "closed" thermodynamics (thermostatics) rather than irreversible thermodynamics of open systems. However, the latter is presupposed if the system (like the living organism) is to be "self-organizing" (FOERSTER & ZOPF 1962), i. e. is to go toward higher differentiation. As was mentioned above, no synthesis is reached as yet. The cybernetic scheme permits, by way of block diagrams, clarification of many important phenomena of self-regulation in physiology and lends itself to information-theoretical analysis. The open-system scheme permits kinetic and thermodynamic analysis.

Comparison of flow diagrams of feedback (Fig. 4) and open systems (Fig. 1) intuitively shows the difference. Thus dynamics in open systems and feedback mechanisms are two different model concepts, each in its right in its proper sphere. The open-system model is basically non-mechanistic, and transcends not only conventional thermodynamics, but also one-way causality as is basic in conventional physical theory (cf. VON BERTALANFFY 1962). The cybernetic approach retains the Cartesian machine model of the organism, unidirectional causality and closed systems; its novelty lies in the introduction of concepts transcending conventional physics, especially those of information theory. Ultimately, the pair is a modern expression of the ancient antithesis of "process" and "structure"; it will eventually have to be resolved dialectically in some new synthesis.

Physiologically speaking, the feedback model accounts for what may be called "secondary regulations" in metabolism and other fields, i. e. regulations by way of pre-established mechanisms and fixed pathways, as in neurohormonal control. Its mechanistic character makes it particularly applicable in the physiology of organs and organ systems. On the other hand, dynamic interplay of reactions in open systems applies to "primary regulations" such as in cell metabolism (cf. HESS & CHANCE 1959) where the more general and primitive open-system regulation obtains.

ALLOMETRY AND THE SURFACE RULE

Let us now proceed to the third model which is the so-called principle of allometry. As is well known, many phenomena of metabolism, and of biochemistry, morphogenesis, evolution, etc., follow a simple equation:

$$y = bx^{\alpha}, \tag{1}$$

that is, if a variable y is plotted logarithmically against another variable x, a straight line results. There are so many cases where this equation applies that examples are unnecessary; certainly our symposium will present a number of applications. Let us therefore rather look at fundamentals. The so-called allometric equation is, in fact, the simplest possible law of relative growth, the term taken in the broadest sense; that is, increase of one variable, y, with respect to another variable x. We see this immediately by writing the equation in a somewhat different form:

$$\frac{dy}{dt} \cdot \frac{1}{y} : \frac{dx}{dt} \cdot \frac{1}{x} = \text{Rel. Gr. Rate } (y, x) = \alpha. \tag{2}$$

As can easily be seen, the allometric equation is a solution of this function which states that the ratio of the relative increase of variable y to that of x is constant. We arrive at the allometric relation in a simple way by considering that any relative growth – only presupposed it is continuous – can generally be expressed by:

$$\text{R. G. R } (y, x) = F, \tag{3}$$

where F is some undefined function of the variables concerned. The simplest hypothesis is that F be a constant, α, and this is the principle of allometry.

However, it is well-known that historically the principle of allometry came into physiology in a way very different from the derivation given. It appeared in a much more special form when SARRUS and RAMEAU found around 1840 that metabolic rate in animals of different body weight does not increase in proportion to weight, but rather in proportion to surface. This is the origin of the famous surface law of metabolism or law of RUBNER, and it is worthwhile to take a look at RUBNER's original data of about 1880 (Table 4). In dogs of varying weight, metabolic rate decreases if calculated per unit of weight; it remains approximately constant per unit surface, with a daily rate of about 1000 kcal per square meter. As is well known, the so-called

Table 4

Metabolism in dogs. (After RUBNER around 1880)

weight in kg	cal. production per kg	cal. production per sq. m body surface
3.1	85.8	1909
6.5	61.2	1073
11.0	57.3	1191
17.7	45.3	1047
19.2	44.6	1141
23.7	40.2	1082
30.4	34.8	984

surface law has caused an enormous debate and literature. In fact, RUBNER's law is a very special case of the allometric function, y representing basal metabolic rate, x body weight, and the exponent α amounting to 2/3.

I believe that the general derivation just mentioned puts the surface law into correct perspective. Endless discussions of some 80 years are overcome when we consider it a special case of allometry, and take the allometric equation for what it really is: a highly simplified, approximate formula which applies to an astonishingly broad range of phenomena, but is neither a dogma nor an explanation for everything. Then we shall expect all sorts of allometric relationships of metabolic measures and body size – with a certain preponderance of surface or 2/3-power functions, considering the fact that many metabolic processes are controlled by surfaces. This is precisely what we find (Table 5). In other words, 2/3 is not a magic number; nor is there anything sacred about the 3/4 power which more recently (BRODY 1945, KLEIBER 1961) has been

Table 5

Equations relating quantitative properties with body weights among mammals. (After ADOLPH 1949; modified)

	regression α =		*regression* α =
intake of water (ml/hr)	.88	myoglobin wt (g)	1.31
urine output (ml/hr)	.82	cytochrome wt (g)	.62
urea clearance (ml/hr)	.72	nephra number	.62
inulin clearance (ml/hr)	.77		
creatinine clearance (ml/hr)	.69	diameter renal corp. (cm)	.08
diodrast clearance (ml/hr)	.89	kidneys wt (g)	.85
hippurate clearance (ml/hr)	.80	brain wt (g)	.70
O_2 consum. basal (ml STP/hr)	.734	heart wt (g)	.98
heartbeat duration (hr)	.27	lungs wt (g)	.99
breath duration (hr)	.28	liver wt (g)	.87
ventilation rate (ml/hr)	.74	thyroids wt (g)	.80
		adrenals wt (g)	.92
tidal volume (ml)	1.01	pituitary wt (g)	.76
gut beat duration (hr)	.31	stom. + intes. wt (g)	.94
N total output (g/hr)	.735	blood wt (g)	.99
N endogenous output (g/hr)	.72		
creatinine N output (g/hr)	.90	*Surface law:* α = .66 relative to absolute weight ($y = bw^{\alpha}$); — .33 relative to unit weight $\left(\frac{y}{w} = bw^{\alpha}\right)$	
sulphur output (g/hr)	.74		
O_2 consum. liver slices (ml STP/hr)	.77		
hemoglobin wt (g)	.99		

preferred to the classical surface law. Even the expression: "Gesetz der fortschreitenden Stoffwechselreduktion" (LEHMANN 1956) – law of progressive reduction of metabolic rate – is not in place because there are metabolic processes which do not regress with increasing size.

From this follows furthermore that the dependence of metabolic rates on body size is not invariable as was presupposed by the surface law. It rather can vary, and indeed does vary, especially as a function of (1) the organism or tissue in question; (2) physiological conditions; (3) experimental factors.

As to the variation of metabolic rate depending on the *organism* or *tissue* con-

cerned, I shall later on give examples with respect to total metabolism. Differences in size dependance of Q_{O_2} in various tissues are shown in Figure 5. A similar example is presented in Table 6 with respect to comparison of intra- and interspecific allometries. Variations of size-dependance of metabolic rate with *physiological conditions* are demonstrated by data obtained in our laboratory in an important aspect which has been little investigated. The size-dependence of metabolism as expressed in the allo-

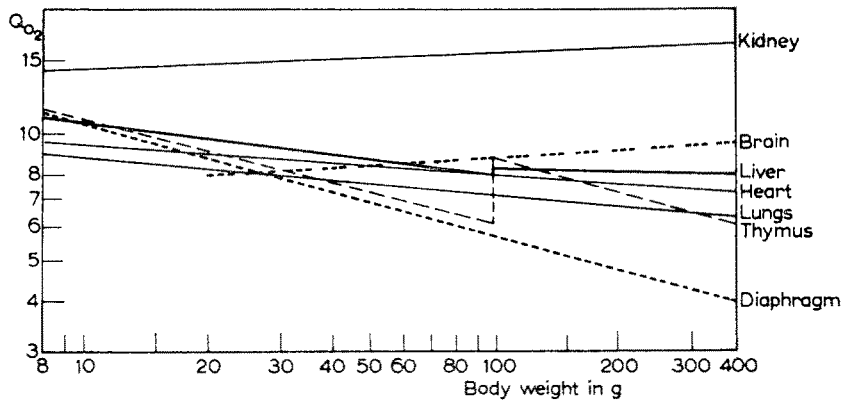

Fig. 5: Q_{O_2} (μl O_2/mg dry wt./hr.) of several rat tissues. Only regression lines are shown in this and following figures; for complete data see originals. (After VON BERTALANFFY & PIROZYNSKI 1953)

Table 6

Intraspecific and interspecific allometry (constants α) in organs of mammals. (After VON BERTALANFFY & PIROZYNSKI 1952)

	rat		cat	dog	monkey	cattle	horse	adult mammals inter-specific
	B. & P.	BRODY	various authors					
brain	0.20	0.17		0.25	0.62	0.30	0.24	0.66 0.69 0.58 0.54
heart	0.82	0.80	♂ 0.92 ♀ 0.82	1.00 0.86 0.93	0.69	0.93		0.83 0.82 0.85 0.84 0.98
lungs	0.73	0.75		0.82	0.92		0.58	0.98 0.99
liver	1. Cycle: 1.26 2. Cycle: 0.67	1. Cycle: 1.14 2. Cycle 0.68		0.71		0.70	0.61	0.87 0.88 0.92
kidneys	0.80	0.82	♂ 0.65 ♀ 0.61	0.70			0.66	0.85 0.87 0.76

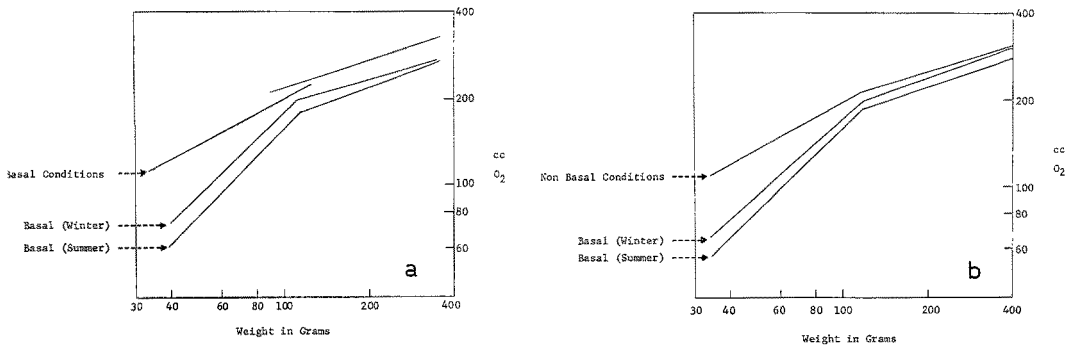

Fig. 6: Size dependence of metabolic rates in rat under basal and non-basal conditions. Animals fasted for 18 hrs. prior to experiment (small animals less); determinations at 29° to 30° C; conditions of muscular rest. A break in the regression lines is assumed at a body weight of 110 gm., corresponding with many physiological changes (cf. Fig. 11). "Basal Summer" determinations were made with a climatization period of 15–18 hours at thermoneutrality preceding experiment; "Basal Winter" without climatization; "Non basal conditions" with 10 hours fasting, followed by a meal 45–60 minutes prior to experiment. *a* ♂, *b* ♀. (Unpublished data by RACINE & VON BERTALANFFY)

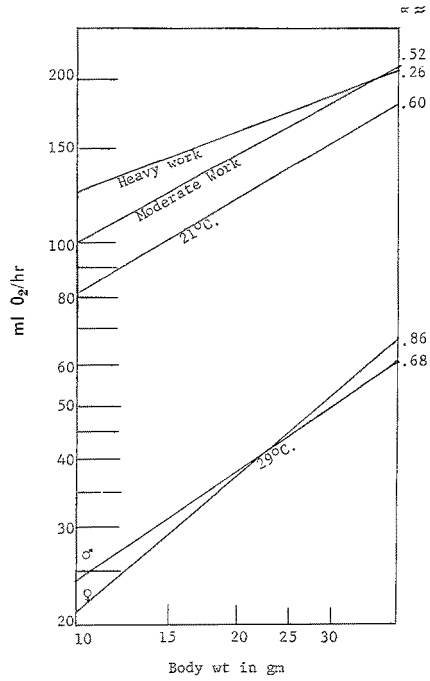

Fig. 7: Size dependence of metabolic rates in mice. Determinations at 29° and 21° C: previous fasting and climatization. In the experiments with muscular activity, the scattering of values is considerable owing to the difficulty to keeping the performed work constant. Therefore the qualitative statement that the slope of the regression lines decreases, is well established but no particular significance should be attached to the numerical values of α. (Unpublished data by RACINE & VON BERTALANFFY)

metry exponent α varies, depending on whether basal metabolic rate (B.M.R.), resting metabolism, or metabolism in muscular activity is measured. Figure 6 shows such variation in rats, comparing basal and non-basal metabolic rates. Figure 7 gives a more extensive comparison in mice, including different degrees of muscular activity. These

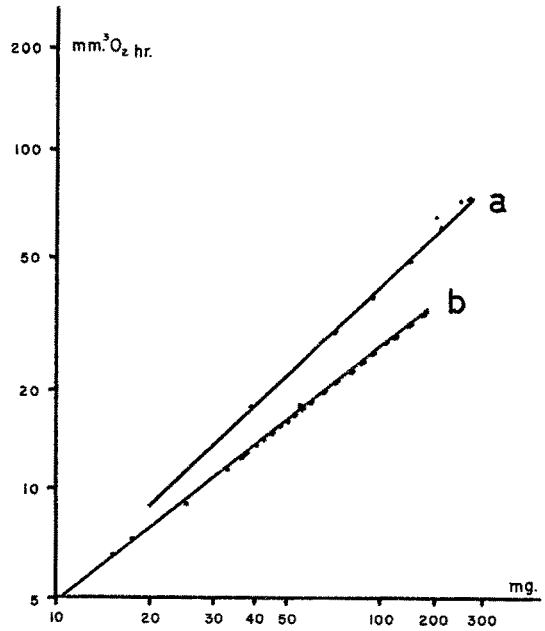

Fig. 8: O_2 consumption of larvae of *Tenebrio molitor* (20° C). *a* larvae fed, *b* starved for two days. In *b* MÜLLER's and TEISSIER's values combined. (After VON BERTALANFFY & MÜLLER 1941)

data confirm LOCKER's statement (1961a) that with increasing intensity of metabolic rate, α tends to decrease. Variations in the slope of the regression lines are also found in invertebrates when metabolic rates of fasting and non-fasting animals are compared (Fig. 8). Variations of α with *experimental conditions* deserve much more attention than usually given. Often the attitude is taken as if Q_{O_2} were a constant characteristic of the tissue under consideration. This is by no means the case. Variations appear, for example, with different bases of reference such as fresh weight, dry weight, N-content, etc. (LOCKER 1961b). The simplest demonstration is change of the medium. Not only – as every experimenter knows – does the absolute magnitude of Q_{O_2} vary greatly depending, for example, on whether saline or medium with metabolites is used; the same is true of size dependence or the parameter α (Fig. 9). LOCKER's rule, as mentioned previously, again is verified; its confirmations by the experiments summarized in Figures 6, 7 and 9 are particularly impressive because they were obtained independent of and prior to statement of the rule. The variation of Q_{O_2} in different media indicates that different partial processes in respiration are measured.

This is the reason why I doubt that total metabolism or B.M.R. can be obtained by so-called summated tissue respiration (MARTIN & FUHRMANN 1955). Which Q_{O_2} of

the individual tissues should be summated? The Q_{O_2} as obtained, say, in RINGER solution or that obtained with metabolites which may be twice as high? How do the different α's of the various tissues add up to the 2/3 or 3/4 observed in B.M.R. of the entire animal? Similarly, LOCKER (1962) has shown that also the component processes of Q_{O_2}, such as carbohydrate and fat respiration, may have different regressions.

Before leaving this topic, I would like to make another remark on principle. We have to agree that the allometric equation is, at best, a simplified approximation.

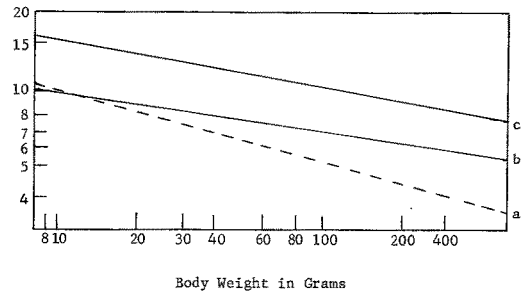

Fig. 9: Size dependence of Q_{O_2} of diaphragm in different media. *a* KREBS-RINGER phosphate solution; *b* KREBS medium II, type A, with glucose; *c* Same medium, with glucose and metabolites. (After VON BERTALANFFY & ESTWICK 1953)

Nevertheless, it is more than a convenient way of plotting data. Notwithstanding its simplified character and mathematical shortcomings, the principle of allometry is an expression of the interdependence, organization and harmonization of physiological processes. Only because processes are harmonized, the organism remains alive and in a steady state. The fact that many processes follow simple allometry, indicates that this is a general rule of the harmonization of processes (ADOLPH 1949): "Since so many properties have been found to be adequately interrelated by equations of one form, it seems very unlikely that other properties would be related according to a radically different type of equation. For if they were, they would be imcompatible with the properties reviewed."

Furthermore, although we encounter a wide range of values of allometry constants, these certainly are not accidental. At least to a wide extent, they depend on biotechnical principles. It is a truism in engineering that any machine requires changes in proportion to remain functional if it is built in different size, for example, if a small-scale model is increased to the desired working size. To an extent, it can be understood why certain types of allometry, such as dependence on surface, body mass, etc., obtain in particular cases. The studies by GÜNTHER & GUERRA (1955) and GUERRA & GÜNTHER (1957) on biological similarity, the relations of birds' wings (MEUNIER 1951), pulse rate (VON BERTALANFFY 1960) and brain weight (VON BERTALANFFY & PIROZYNSKI 1952) to body size are examples of functional analysis of allometry which, I believe, will become an important field for further research.

THEORY OF ANIMAL GROWTH

The last model I wish to discuss is the model of growth honorifically called the BERTALANFFY equations (VON BERTALANFFY 1957, 1960); basic ideas go back to the great German physiologist PÜTTER (1920). Here, too, I am not primarily concerned with details or even the merits and shortcomings of the model; I rather wish to use it to make clear some principles in quantitative metabolism research.

We all know, firstly, that the process of growth is of utmost complexity; and secondly, that there is a large number of formulas on the market which claim satisfactorily to represent observed growth data and curves. The general procedure was that some more or less complex and more or less plausible equation was proposed. Then the investigator sat down to calculate a number of growth curves with that formula, and was satisfied if a sufficient approximation of empirical data was obtained.

Here is a first illusion we have to destroy. It is a mathematical rule of thumb that almost every curve can be approximated if three or more free parameters are permitted – that is, if an equation contains three or more so-called constants that cannot be verified otherwise. This is true quite irrespective of the particular form of the equation chosen; the simplest equation to be applied is a power series ($y = a_0 + a_1x + a_2x^2 + \ldots$) developed to, say, the cubic term. Such calculation is a mere mathematical exercise. Closer approximation can always be obtained by permitting further terms.

The consequence is that curve-fitting may be an indoor sport, and may be useful for purposes of interpolation and extrapolation. However, approximation of empirical data is not a verification of particular mathematical expressions used. We can speak of verification and of equations representing a theory only if (1) the parameters occuring can be confirmed by independent experiment; and if (2) predicitions of yet unobserved facts can be derived from the theory. It is in this sense that I am going to discuss the so-called BERTALANFFY growth equations because, to the best of my knowledge, they are the only ones in the field which try to meet the specifications just mentioned.

The argument is very simple. If an organism is an open system, its increase or growth rate (G. R.) may, quite generally, be expressed by a balance equation of the form:

$$\frac{dw}{dt} = \text{G. R.} = \text{Synth.} - \text{Deg.} + \ldots, \tag{4}$$

that is, growth in weight is represented by the difference between processes of synthesis and degeneration of its building materials, plus any number of indeterminate factors that may influence the process. Without loss of generality, we may further assume that the terms are some undefined functions of the variables concerned:

$$\text{G. R.} = f_1(w, t) - f_2(w, t) + \ldots \tag{5}$$

Now we see immediately that time t should not enter into the equation. For at least some growth processes are equifinal, that is, the same final values can be reached at different times (Fig. 2). Even without strict mathematical proof, we see intuitively that this would not be possible if growth rate directly depends on time; for if this

were the case, different growth rates could not occur at given times as is sometimes the case.

Consequently, the terms envisaged will be functions of body mass present:

$$\text{G. R.} = f_1(w) - f_2(w), \tag{6}$$

if we tentatively limit the consideration to the simplest open-system scheme. The simplest assumption we can make is that the terms are power functions of body mass. And indeed, we know empirically that quite generally the size dependence of physiological processes can well be approximated by allometric expressions. Then we have:

$$\frac{dw}{dt} = \eta w^n - \varkappa w^m, \tag{7}$$

where η and $\varkappa$ are constants of anabolism and catabolism, respectively, corresponding to the general structure of allometric equations.

Mathematical considerations show furthermore that smaller deviations of the exponent m from unity do not much influence the shape of the curves obtained. Thus, for further simplification let us put $m = 1$. This makes things much easier mathematically, and appears to be justified physiologically, since physiological experience – limited it is true – seems to show that catabolism of building materials, especially proteins, is roughly proportional to body mass present.

Now let us make a big leap. Synthesis of building materials needs energy which, in aerobic animals, is provided by processes of cell respiration and ultimately the ATP

Table 7

Metabolic types and growth types. w, l: Weight, length at time t; w_0, l_0: initial weight, length; w^*, l^*: final weight, length; η, $\varkappa$: constants of anabolism and catabolism. (After VON BERTALANFFY 1942)

Metabolic type	*Growth type*	*Growth equations*	*Examples*
I. Respiration *surface-proportional*	(a) Linear growth curve: attaining *without inflexion* a steady state. (b) Weight growth curve: *sigmoid*, attaining, with inflexion at *c.* 1/3 of final weight, a steady state	$dw/dt = \eta w^{2/3} - \varkappa w$ a) $l = l^* - (l^* - l_0)e^{-\varkappa t/3}$ b) $w = [\sqrt[3]{w^*} - (\sqrt[3]{w^*} - \sqrt[3]{w_0})e^{-\varkappa t/3}]^3$	Lamellibranchs, fish, mammals
II. Respiration *weight-proportional*	Linear and weight growth curves *exponential*, no steady state attained, but growth intercepted by metamorphosis or seasonal cycles	$dw/dt = \eta w - \varkappa w = cw$ a) $l = l_0 e^{ct/3}$ b) $w = w_0 e^{ct}$	Insect larvae, Orthoptera, Helicidae
III. Respiration *intermediate between surface- and weight-proportionality*	(a) Linear growth curve: attaining *with inflexion* a steady state. (b) Weight growth curve: *sigmoid*, similar to I (b)	$dw/dt = \eta w^n - \varkappa w$; $2/3 < n < 1$ $dl/dt = \frac{\eta'}{3} l^{3n-2} - \frac{\varkappa}{3} l$	Planorbidae

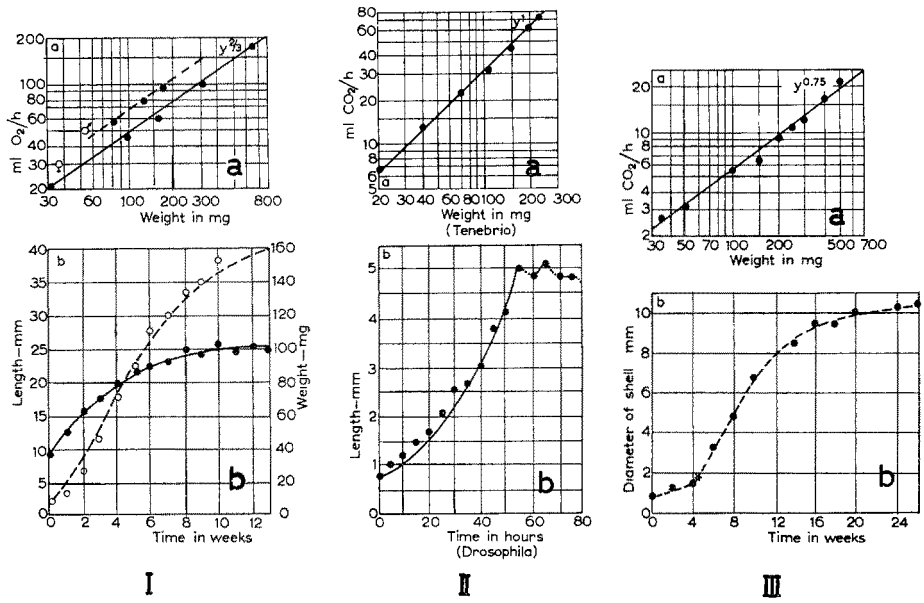

Fig. 10: Metabolic and growth types. Type I: *Lebistes reticulatus;* type II: insect larvae; type III: *Planorbis sp. a* dependence of metabolic rate on body size; *b* growth curves. (After VON BERTALANFFY 1942)

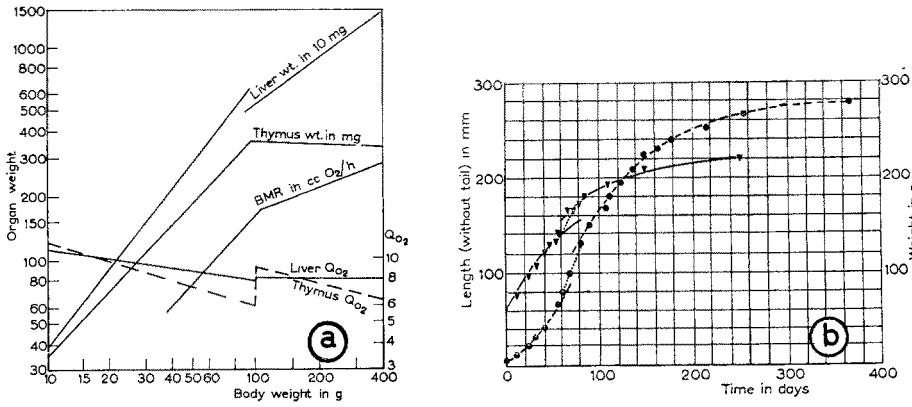

Fig. 11: Calculation of growth of the white rat. Many physiological processes in the rat show discontinuities at about 100 gm. body weight, i. e. in the prepubertal stage (*a*). Such "cycle" also appears in metabolism (Fig. 6), metabolic rates in animals under 100 gm. increasing more, and in animals above this size much less than would correspond to the surface rule. However, if regression is calculated over the whole weight range, a value near 2/3 results as gross average. Hence, in the calculation of the growth curve (*a*) two "cycles" separated at $\approx$ 100 gm. should appear, and (*b*) in first approximation, rat growth should be calculable with the equations of "Type I", i. e. $\alpha \approx 2/3$. Calculation of growth data made previous to the physiological determinations (*b*) verifies both expectations. The catabolic constant ($\varkappa$) results, for the second (postpubertal) cycle, as $\varkappa_{calc.} \approx 0.045$/day, in close correspondence with protein turnover determined by isotope tracers ($r = 0.04$/day). (After VON BERTALANFFY 1960)

Table 8

Growth of *Acipenser stellatus*. (After VON BERTALANFFY 1951)

time in years	length in cm *observed*	length in cm *calculated*	k
1	21.1	21.1	
2	32.0	34.3	0.062
3	42.3	41.5	0.062
4	51.4	50.8	0.061
5	60.1	59.5	0.061
6	68.0	67.8	0.061
7	75.3	75.5	0.060
8	82.3	82.8	0.060
9	89.0	89.7	0.059
10	95.3	96.2	0.059
11	101.6	102.3	0.059
12	107.6	108.0	0.060
13	112.7	113.4	0.059
14	117.7	118.5	0.059
15	122.2	122.5	0.058
16	126.5	127.9	0.059
17	130.9	132.2	0.059
18	135.3	136.2	0.059
19	140.2	140.0	0.060
20	145.0	143.5	0.061
21	148.6	146.9	0.061
22	152.0	150.0	0.061

Growth equation: $l = 201.1 - (201.1 - 21.1)^{-0.06\,t}$. Owing to the regularity of growth curves, the BERTALANFFY equations are most suitable for calculation of growth in fish. In this example, the growth constant k ($= \varkappa/3$) was calculated in a way similar to calculation of reaction constants in chemical reactions. Variations of this parameter are minimal, so showing the adequacy of the equation.

system. Let us assume there are correlations between energy metabolism of an animal and its anabolic processes. This is plausible insofar as energy metabolism must, in one way or the other, provide the energies that are required for synthesis of body components. We therefore insert for size dependence of anabolism that of metabolic rates ($n = \alpha$) and arrive at the simple equation:

$$\frac{dw}{dt} = \eta w^{\alpha} - \varkappa w. \tag{8}$$

Empirically, we find that resting metabolism of many animals is surface-dependent, that is, that they follow RUBNER's rule. In this case, we set $\alpha = 2/3$. There are other animals where it is directly dependent on body mass, and then $\alpha = 1$. Finally, cases are found where metabolic rate is in between surface and mass proportionality, that is $2/3 < \alpha < 1$. Let us tentatively refer to these differences in size-dependence of metabolic rate as "metabolic types".

Now if we insert the different values for α into our basic equation, we easily see that they yield very different curves of growth. Let us refer to them as "growth types". These are summarized in Table 7; corresponding graphs, showing the differences in metabolic behavior and concomitant differences of growth curves, are presented in

Figure 10. Detailed discussions of the theory have been given elsewhere. It has been shown that the above derivations apply in many cases; no less than fourteen different arguments in verification of the theory can be presented (Table 8, Figs. 11, 12). We shall limit the present discussion to a few remarks on principle.

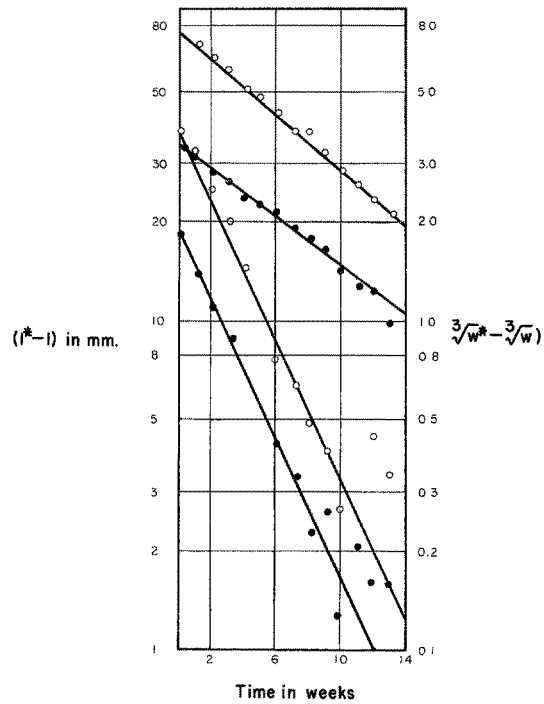

Fig. 12: Growth of *Lebistes reticulatus*. Upper lines: ♀, lower lines: ♂. ○ weight, ● length. In the Guppy, growth in females and males shows considerable difference, the females reaching a multiple of body weight of the males. Data are logarithmically plotted according to the integral of Equation 8; the close fit shows that the growth curves are correctly reproduced. The growth equations so obtained give a ratio of 1:1.5 for the anabolic constants η in females and males. According to theory, metabolic rates in females and males should stand in the same ratio, 1:1.5 as is actually found (Fig. 10, I). (After VON BERTALANFFY 1938, 1960)

All parameters of the growth equations are verifiable experimentally. α, the size dependence of metabolic rate, determines the shape of the growth curve. This correlation has been confirmed in a wide range of cases, as seen in Table 7. $\varkappa$, constant of catabolism, can in first approximation be identified with turnover of total protein *(r)* as determined by isotope tracers and other techniques. For example, from the growth curves catabolic rates of 0.045/day for the rat, and 1.165 g protein/kg body wt./day for man were calculated (VON BERTALANFFY 1938). Determinations of protein catabolism then available did not agree with these predictions: protein loss determined by minimum N-excretion was 0.00282/day for the rat after TERROINE, and some 0.4–0.6 g protein/kg body wt./day for man, according to the conceptions then prevailing in physiology (VON BERTALANFFY 1942, p. 180 f., 186–188). It was therefore

a striking confirmation of the theory when later on determinations using the isotope method (SPRINSON & RITTENBERG 1949, Table 2) yielded turnover rates of total protein (r) of 0.04/day for the rat, and of 1.3 g protein/kg body wt./day for man in an amazing agreement between predicted and experimental values. It may be noted in passing that an estimate of the turnover time of the human organism similar to that found in isotope experiments ($r \approx 0.009$, $t \approx 110$ days) can be obtained in different ways, e. g. also from calorie loss in starvation ($t \approx 100$ days: DOST 1962a). η, constant of anabolism, is dimensionally complex. It can, however, be checked by comparison of growth curves of related organisms: according to theory, the ratio of metabolic rates should correspond to the ratio of η's of the animals concerned. This also has been confirmed (Fig. 12).

The theory, therefore, fulfills the first postulate indicated above, i. e. verification of calculated parameters in independent experiments. As has been shown elsewhere, it also fulfills the second postulate: Predictions from the theory were made which came as "surprises", that is, were unknown at the time, but later on confirmed.

Discussion of some typical objections is in place because it may contribute to better understanding of mathematical models in general.

1. The main reproach against models and laws for physiological phenomena is that of "oversimplification". In a process such as animal growth there is, at the level of cells, a microcosm of innumerable processes of chemical and physical nature: all the reactions in intermediary metabolism as well as factors like cell permeability, diffusion, active transport and innumerable others. On the level of organs, each tissue behaves differently with respect to cell renewal and growth; beside multiplication of cells, formation of intercellular substances is included. The organism as a whole changes in composition, with alterations of the content in protein, deposition of fat or simple intake of water; the specific weight of organs changes, not to speak of morphogenesis and differentiation which presently elude mathematical formulation. Isn't any simple model and formula a sort of rape of nature, pressing reality into a Procrustean bed and recklessly cutting off what doesn't fit into the mould? The answer is that science in general consists to a large extent of oversimplifications in the models it uses. These are an aspect of the idealization taking place in every law and model of science. Already GALILEO's student, TORRICELLI, bluntly stated that if balls of stone, of metal, etc., don't follow the law, it's just too bad for them. BOHR's model of the atom was one of the most arbitrary simplifications ever conceived – but nevertheless became a cornerstone of modern physics. Oversimplifications progressively corrected in subsequent development are the most potent or indeed the only means toward conceptual mastery of nature. In our particular case it is not quite correct to speak of oversimplification. What is involved are rather *balance equations* over many complex and partly unknown processes. The legitimacy of such balance expressions is established by routine practice. For example, if we speak of B.M.R. – and are, in fact, able to establish quantitative relationships such as the "surface law" – it is balances we express which nevertheless are important both theoretically and practically (e. g. diagnostic use of B.M.R.). The regularities so observed cannot be refuted by "general considerations" of oversimplification, but only empirically and by offering better explanations. It would be easy to make the growth model seemingly more realistic and to

improve fitting of data, by introducing a few more parameters. However, the gain is spurious as long as these parameters cannot be checked experimentally; and for the reasons mentioned, a closer fit of data tells nothing about the merits of a particular formula if the number of "free constants" is increased.

2. Another question is the choice of parameters. It has been noted above that metabolic rate under basal and non-basal conditions changes not only in magnitude but also with respect to allometry expressing its relation to body size. What is the justification of taking "resting metabolism" as standard and to range various species into "metabolic" and "growth types" accordingly? The answer is that among available measures of metabolism – none of them ideal – resting metabolism appears to approach best those natural conditions which prevail during growth. The B.M.R. standard (i. e. thermoneutrality of environment, fasting and muscular rest) makes the values so determined a laboratory artifact because at least the first condition is unnatural; although it is most useful because B.M.R. values show the least dispersion. In cold-blooded animals, B.M.R. cannot be used as standard because there is no condition of thermoneutrality, and the fasting condition often cannot be exactly established. Activity metabolism, on the other hand, changes with the amount of muscular action (Fig. 7); and the growing animal is not under conditions of hard muscular work all the time. Hence resting metabolic rate is comparatively the best approximation to the natural state; and choice of this parameter leads to a useful theory.

3. The most important criticism becomes apparent from the above discussion. It was said that there appear to be so-called metabolic types and growth types and correlations between both. However, earlier it has been emphasized that the parameters implied, especially the relation of metabolic rate to body size expressed in the exponent α, can be altered and shifted with experimental conditions (Figs. 6–8). Similarly, also growth curves are not fixed. Experiments on the rat have shown that the shape of the growth curve, including location and existence of a point of inflexion, can be changed by different nutrition (L. ZUCKER et al. 1941a, b, 1942, T. F. ZUCKER et al. 1941, DUNN et al. 1947, MAYER 1948). None of the characteristics is rigid – and, incidentally, within my own biological concepts, I would be the last to presuppose rigidity in the dynamic order of physiological processes. According to my whole biological outlook, I am rather committed to the ancient Heraclitean concept that what is permanent, is only the law and order of change.

However, the apparent contradiction can well be resolved when we remain faithful to the spirit of the theory. What is really invariable is the organization of processes expressed by certain relationships. This is what the theory states and experiments show, namely, that there are *functional relationships* between certain metabolic and growth parameters. This does not imply that the parameters themselves are unchangeable – and the experiment shows that they are not. Hence, without loss of generality, we may understand "metabolic" and "growth types" as *ideal cases* observable under certain conditions, rather than as rigid species characteristics. "Metabolic" and "growth types" appear in the respective groups of animals if certain standard conditions are met. However, it is clearly incorrect that "the reduction of metabolic rates is a fundamental magnitude, not changing in different external conditions" (LEHMANN 1956). Under natural or experimental conditions, the relationships c a n be

shifted, and then a corresponding alteration of growth curves should take place. There are indications that this is actually the case; it is a clear-cut problem for further investigation.

A case to the point are seasonal changes. BERG (1959, 1961), while in general confirming previous data, found that the size-metabolism relation varies seasonally in snails: "Thus the relation, oxygen consumption to body size, is not a fixed, unchangeable

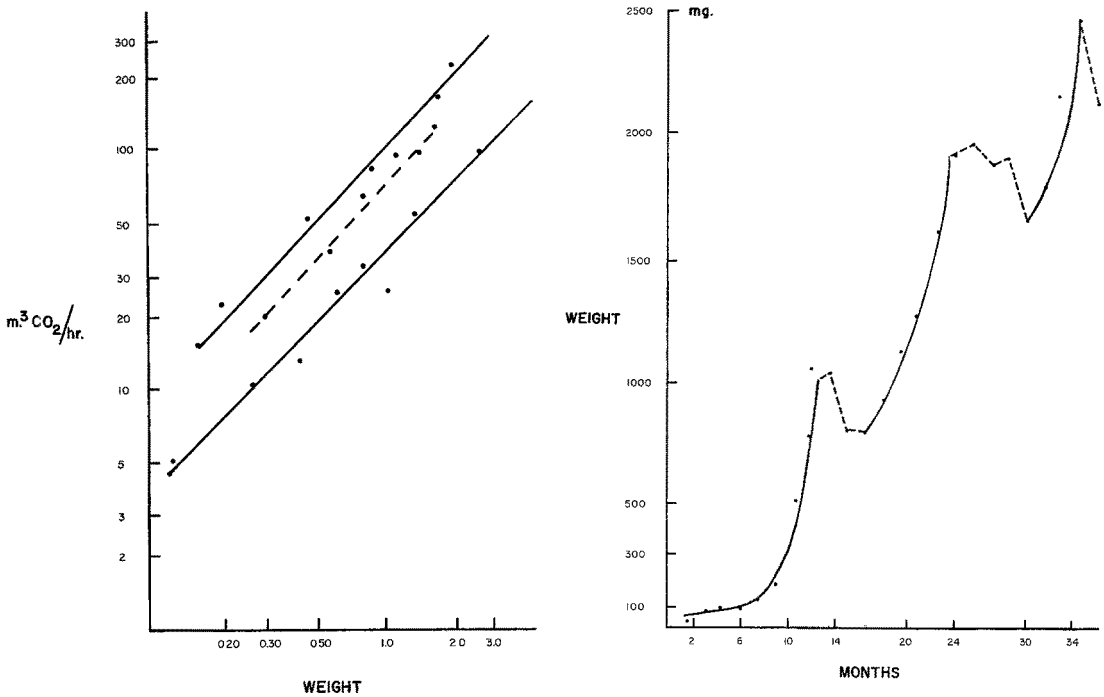

Fig. 13: Metabolism and growth in land snails. *a* Seasonal variations in metabolic rates. The regression lines show, from bottom to top, resting metabolism of *Cepaea vindobonensis* inactive shortly after hibernation at 20° C, same at 28° C, and in activity period at 20° C. (Weight in gm.). Other conditions being equal, resting metabolism is considerably higher in the active compared to the inactive season. *b* Growth in a related species *(Eulota fruticum)*. The growth curve is exponential (Type II with $\alpha \approx 1$), but shows seasonal fluctuations. (After VON BERTALANFFY & MÜLLER 1941)

quantity characteristic of all species as supposed by BERTALANFFY ... If (BERTALANFFY's theory) were true, then the observed seasonal variation in metabolic type would imply a seasonal variation in the type of growth rate."

As a matter of fact, precisely this has been found in our laboratory long ago (VON BERTALANFFY & MÜLLER 1943). Seasonal variations of metabolic rate in snails have been described (Fig. 13a). But correspondingly, also the growth curve (exponential in this case because these snails belong to "Type II"), shows breaks and cycles (Fig. 13b). Therefore this certainly is a problem deserving more detailed investigation; however, the data available are a hint toward confirmation rather than refutation of the theory.

I would have been much surprised, indeed, suspicious if this first crude model would have provided a conclusive theory. Such things just do not happen, as is witnessed by many examples from history of science. MENDEL's laws were the beginnings of genetics but – with linkage, crossing-over, position effect and what not – it is only a minute part of genetic experience that is described by the classical laws. GALILEO's law is the beginning of physics, but only highly idealized cases – such als bodies falling in vacuo – actually follow the simple law. It is a long way from BOHR's simple model of the hydrogen atom to present atomic physics, and so on. It would be fantastically improbable if this were different with a proposed model of growth. The most we can say about it is that it is backed by a considerable amount of experimental evidence, has proved to have explanatory and predictive capacities, and offers clear-cut problems for further research.

It is obvious that the theory has been developed for a limited number of cases only, owing to the limited number of good data and the time-consuming nature both of observation and calculation of growth. HEMMINGSEN (1960) has made this clear: "With n varying as much as the examples show, within any group with allegedly (or at least first allegedly) uniform growth type, it seems impossible to accept BERTALANFFY's generalizations unless a statistically significant correlation between n and growth type can be demonstrated on a much larger number of examples than the few ones which BERTALANFFY has repeatedly published." I entirely agree with this criticism; many more data would be desirable, although one should not cavalierly bypass those offered in confirmation of the theory, even if they are some 20 years old. I would amend HEMMINGSEN's criticism by suggesting re-examination on a broader basis. This should include at least the following items: analysis of a large number of growth data, now made possible by electronic computers; concurrent determination of size-dependence of resting metabolism (constant a) in these cases; determinations of protein catabolism (constant $\varkappa$); determination, in related species, of the ratios between allometry exponents of metabolic rates and the theoretically identical ratios of the anabolic constants (η). These are all interesting and somewhat neglected research problems; and if the model does no more than bring them to the fore, it has proved its usefulness.

Such investigation may bring additional confirmation of the model; it may lead to its modification and elaboration by taking into account additional factors; or it may lead to abandoning the model altogether and replacing it by a better one. If the latter should happen, I would in no way be disappointed. This is exactly what models are for – to serve as working hypotheses for further research.

What I have tried to show in the models discussed are general ways of analysis of quantitative data. I wanted to make clear both the usefulness and the limitations of such models. Any model should be investigated according to its merit with a view at the explanations and predictions it is able to provide. General criticism does not help, and the decision whether or not a model is suitable, exclusively rests with facts of observation and experiment. On the other hand, no model should be taken as conclusive; at best it is an approximation to be progressively worked out and corrected. In close interaction between experiment and conceptualization, but not in confinement to experimentation or construction of purely speculative models, lies the further development of a field like quantitative biology of metabolism.

SUMMARY

1. The theories of open systems, feedback, allometry and growth according to BERTALANFFY are reviewed with respect to their experimental applications.
2. The models of both open system and feedback apply to a wide range of phenomena in physiology, and represent essential expansions of physical theory. The two conceptions should be clearly distinguished; the feedback model (homeostasis) should not be considered a cover-all for physiological regulation in general or identified with "systems theory".
3. The allometric equation represents the simplest possible relation between body size and metabolic processes. It is of a wide applicability and expresses the harmonization of processes in living systems. However, there is no "surface-" or "$^3/_4$-power law" or "law of progressive reduction of metabolic rates". The allometric relationship greatly varies in physiological phenomena.
4. Variations of the relation between body size and metabolic rate may occur (a) in different tissues or in different species; (b) due to changes of physiological conditions; (c) due to different experimental designs. Among the conditions altering this relation are such factors as physiological activities, sex, season, previous acclimation, etc.
5. The size-dependence of total metabolism in mammals is different under basal conditions, in a non-thermoneutral environment, and under conditions of muscular activity. The variations follow LOCKER's rule, i. e., with an absolute increase of metabolic rate (expressed by the constant b of the allometric equation), regression with respect to body size (expressed by the slope of the allometric line, α) tends to decrease.
6. The growth equations after BERTALANFFY represent a highly simplified model which, however, covers many phenomena and regularities found in the physiology of metabolism and growth. The parameters occurring in these equations have been verified by physiological experiments in many cases.
7. In view of the changes of the size-metabolism relation mentioned under (5), BERTALANFFY's so-called "metabolic" and "growth types" should be considered as ideal cases realizable under certain standard conditions, rather than as invariable characteristics of the species or group of species concerned.
8. Seasonal variations of metabolic rates and growth rates seem to show correspondence.
9. Urgent problems for further research with respect to each of the basic models are outlined.

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Discussion following the paper by VON BERTALANFFY

HEUSNER: Die Gleichung

$$v_{O_2} \cdot p^{-1} = a\, P^{b-1}$$

(v_{O_2} = Organsauerstoffverbrauch, p = Organgewicht, a = Konstante, P = Körpergewicht, b = interspezifischer Gewichtsexponent [$\sim 0{,}7$])

kann nicht die Beziehung zwischen Gewebsatmung eines bestimmten Organs zu dem Körpergewicht darstellen. Folgende Beziehungen müssen in Betracht gezogen werden:

(1) $V_{O_2} = a\, P^b$ (V_{O_2} = Ganztier-Sauerstoffverbrauch, c = Konstante,

(2) $p = c\, P^\gamma$ γ = Allometrische Konstante, k = Konstante, ω = Exponent des Ganztier-Sauerstoffverbrauchs)

(3) $v_{O_2} = k\, V_{O_2}{}^\omega$

Löst man die Gleichung (1) mit Hilfe der Gleichungen (2) und (3) auf, so ergibt sich folgende Beziehung zwischen dem Sauerstoffverbrauch pro Gewichtseinheit eines Organs und dem Körpergewicht:

(4) $$v_{O_2} = a^\omega \cdot k \cdot P^{b\omega}$$

(5) $$v_{O_2} \cdot p^{-1} = a^\omega \cdot k \cdot c^{-1} \cdot P^{b\omega-\gamma}$$

Wenn $\alpha = a^\omega \cdot k \cdot c^{-1}$ und $\beta = b\omega - \gamma$ gesetzt wird, so nimmt die Gleichung (5) folgende Form an:

(6) $$v_{O_2} \cdot p^{-1} = \alpha \cdot P^\beta$$

Es ergibt sich, daß $\beta = b - 1$ nur unter ganz bestimmten Bedingungen, nämlich wenn $\omega = 1$ und $\gamma = 1$ ist, zustande kommen kann. Die Beziehung ist an Hand von experimentellen Daten der Literatur (KLEIBER 1941, KREBS 1950) bestätigt worden. Diese theoretische Betrachtung zeigt, daß der Gewichtsexponent β der Gewebsatmung sich mit der Art des Gewebes verändert und daß die experimentell beobachtete Abweichung des Wertes β, von dem angenommenen Wert $b - 1$, auf die Veränderung des Verhältnisses zwischen Organgewicht und Körpergewicht zurückzuführen ist. Die Gewebsatmung kann also nur in Ausnahmefällen ($\omega = 1$; $\gamma = 1$) der Oberflächenregel folgen.

LOCKER (zu HEUSNER): Was Sie hier darstellen, bedeutet, daß neben der Allometriebeziehung des Gewebs- bzw. Organstoffwechsels noch die Gewichtsallometrie des Organs selbst gegenüber der Körpergröße berücksichtigt werden muß. Ich formuliere unter Vermeidung jeglicher Annahmen über eine etwaige vorgegebene Oberflächenabhängigkeit (etwa im Sinne der BRODY-KLEIBER-Exponenten) etwas einfacher, indem ich die Organgewichts-Allometrie

(1) $O = b_1 W^{a_1}$ O = Organgewicht (Feuchtgewicht), W = Körpergewicht

neben der Umrechnung der Gewebsatmung von Trockengewichts- auf Feuchtgewichtsbasis (mit den Konstanten b_2 und α_2) mit der gewichtsspezifischen Stoffwechselallometrie

(2) $\frac{M}{W} = b_3 W^{a_3-1}$ $\frac{M}{W}$ = O_2-Verbrauch/mg Trockengewicht

verbinde. Statt $a_3 - 1$ setze ich α_3 und erhalte:

(3) $M_{(O,\,T/W)} = b_1 b_2 b_3 W^{a_1+\alpha_2+\alpha_3}$ $M_{(O,\,T/W)}$ = Stoffwechsel eines Organs nach Umrechnung auf Feuchtgewichtsbasis

Werden $b_1 b_2 b_3 = b$ und $a_1 + \alpha_2 + \alpha_3 = a$ (die korrigierte Allometriekonstante) gesetzt, dann komme ich zu Ihrer Formel (6), nämlich

(4) $$M_{(O.\,T/W)} = b W^a$$

Hier wäre wohl zunächst auch der Vorschlag angebracht, daß man sich bei der mathematischen Darstellung des Problems der Stoffwechselreduktion, also der Abhängigkeit des Stoffwechsels

von der Körpergröße, über die Symbole einigen sollte. Auch möchte ich (im Hinblick auf die eben gegebene Darstellung von Herrn VON BERTALANFFY) den Vorschlag machen, daß man vielleicht mit griechischen Buchstaben – also vor allem mit α – nur einen gewichtsspezifischen Stoffwechsel beschreibt. In einer in Veröffentlichung befindlichen Untersuchung (1964; *Zool. Anz. Suppl.* **27**) über die Stoffwechselallometrie der wichtigsten Organe (Muskel, Haut, Leber, Gehirn, Niere, Milz, Herz, Darm, Lunge, Ovar, Fettkörper) und des Gesamtstoffwechsels weiblicher Wasserfrösche (Winter- und Sommerfrösche) bei 12,5°–32,5° C (Gewichtsbereich 1–90 g), über die ich auch in meinem Vortrag noch berichten werde, fand ich, daß unter dem Einfluß der Parameter Saison, Temperatur (und Dinitrokresol in vitro) sowohl die Konstante b („Intensitätskonstante" in der Terminologie von KAYSER) als auch die Konstante a verschiedene, zum Teil systematische Änderungen erfuhren. Eine Abweichung vom Oberflächengesetz scheint demnach nicht nur durch verschiedene Allometriebeziehungen der Organgewichte, sondern auch durch den Stoffwechsel selbst herbeigeführt zu werden. Meine Untersuchung diente vor allem der Frage, ob eine „summierte Gewebsatmung", die bisher bei verschiedenen Tieren nur bei einem einzigen Gewicht bestimmt worden war, über dem gesamten Gewichtsbereich mit dem Gesamtstoffwechsel verglichen werden kann. Hier gilt folgende Ungleichung:

$$W_i^a + W_{ii}^a + W_{iii}^a + \ldots = (W_i + W_{ii} + W_{iii} + \ldots)^a \tag{5}$$

W_i^a, W_{ii}^a . . .: Gewichtsbeziehung verschiedener individueller Organe

wobei a = 1 und b = 1. Ungleichung (5) zeigt, daß die Stoffwechselallometrie der einzelnen Organe nicht gleich der des Gesamtstoffwechsels sein kann. Beim Sommerfrosch von 22,5° C konnte tatsächlich über dem gesamten Gewichtsbereich eine (statistisch ununterscheidbare) Übereinstimmung von „summierter Gewebsatmung" und Gesamtstoffwechsel beobachtet werden.

HEUSNER (zu LOCKER): Ich habe die Symbole von BRODY übernommen. Sie stimmen auch mit den in der Statistik üblichen Symbolen überein, nämlich: $a + bx + cx^2 + dx^3 \ldots$ wobei a eine Konstante und b einen Koeffizienten ($\log V_{O_2} = \log a + b \log P$) darstellen. Die griechischen Buchstaben beziehen sich auf die Gewebsatmung. Nach den Experimenten der Autoren FIELD, MARTIN, HUSTON und FUHRMAN an Mäusen, Ratten (150, 263 bzw. 300 g) und Hunden, darf man heute mit großer Wahrscheinlichkeit annehmen, daß die Gewebsatmung in vitro der Gewebsatmung in vivo entspricht (Grundumsatz). Warum sollte dies nicht allgemein der Fall und vom Körpergewicht unabhängig sein? Meine theoretische Formulierung stimmt gut mit den experimentellen Befunden von KLEIBER (1941) und KREBS (1950) überein. Das bedeutet aber nicht, daß diese Beziehung die einzig mögliche ist. Sie bietet jedoch den Vorteil, daß der Gewichtsexponent der Gewebsatmung aus anderen Daten als denen der Gewebsatmung errechnet werden kann. Sie erlaubt auch, in einer ersten Annäherung von den ja so zahlreichen Faktoren, welche den Sauerstoffverbrauch eines Tieres beeinflussen, abzusehen. Praktisch wirkt sich der Einfluß anderer Faktoren um so stärker auf die Beziehung zwischen Sauerstoffverbrauch und Körpergewicht aus, je kleiner die Gewichtsamplitude ist. Man kann also nur einen sicheren und allgemeingültigen Schluß aus Daten mit großer Gewichtsamplitude ziehen. Schließlich kommt es uns doch darauf an, „Invariante" des Energiewechsels von genereller Gültigkeit herauszuarbeiten. Meiner Ansicht nach stellt der Gewichtsexponent b eine solche „Invariante" dar.

KRÜGER (zu VON BERTALANFFY): Eine Frage: Stehen die Parameter Ihrer Wachstumsformel in irgendeiner mathematisch ableitbaren Beziehung zu den Parametern der allometrischen Wachstumsfunktion? Die Wachstumsfunktion einer anderen Größe als der Länge können Sie nur auf dem Umweg über die allometrische Funktion berechnen. Daher besteht meines Erachtens keine Möglichkeit, die Parameter der allometrischen Gleichung aus Ihrer Wachstumsfunktion abzuleiten.

VON BERTALANFFY: I would like to take the questions raised in the order in which they appeared. First, the relation of tissue respiration to metabolism of the total animal (HEUSNER, LOCKER). That there is no simple relation between the allometries of the first and the latter is a consequence of a well-known, mathematical short-coming of the allometric equation:

$b_1 \times a_1 + b_2 \times a_2 + b_3 \times a_3 \neq bx^a$, that is, the sum of exponential terms is not a simple exponential term (cf. VON BERTALANFFY, 1960, *l.* c., p. 226 f.). This leads to "summated tissue respiration". As LOCKER has correctly remarked, the studies in which summated tissue respiration was found to equate B.M.R. refer to adult organisms (rat: FIELD, BELDING & MARTIN 1939; mouse, dog: MARTIN & FUHRMAN 1955). He has now investigated this aspect over the total range of weights (or course of growth). We have discussed this question in some detail, using estimates for the mature and young rat (VON BERTALANFFY & PIROZYNSKI 1953, p. 254). It appeared that if summated tissue respiration approached B.M.R. in the adult rat, this was not the case in the small rat of a body weight of, say, 10 g. The questions posed by KRÜGER refer to the relations of growth-in-time and relative growth. In the system of equations used by us, growth-in-time of a magnitude other than weight is calculated via the allometric function. This is a consequence of the theoretical model which underlies them, and simplifications used for mathematical convenience. The equation for linear growth is obtained via weight growth, using the relation $w = const. \times l^3$. There is nothing sacred about this relation, and an exponent $\neq 3$ ("unproportional growth") could be introduced. However, this would make the mathematics rather messy and would hardly repay the effort, for it is empirically found that the weight exponent is not far from 3, even if – as, for example, in the female Guppy – changes in form are considerable. A consequence of the fact that weight is not exactly $= const. \times l^3$ is that the growth parameters $\varkappa$ and η come out somewhat different, depending on whether they are calculated from observed l or $w^{1/3}$. However, the difference remains within the limits of experimental error (Fig. 12). A similar result was obtained in calculations of growth in the rat (VON BERTALANFFY 1938, p. 205). I would like to mention that the whole system of growth equations can be derived deductively from only two hypothetical assumptions, namely, that (a) growth-promoting and growth-inhibiting factors can be summated in two over-all terms and that (b) their rate depends on body mass in the simplest possible way, namely, as a power function. From this, the whole family of growth equations and the empirically observed differences of growth curves follow by mathematical considerations (VON BERTALANFFY 1960, pp. 200–204). Growth-in-time of organs can be derived from growth of the total organism by insertion of the respective allometric equations. In this way, rather interesting and empirically verifiable relations between both are obtained which explain the variety of curves found in the growth of organs. In conclusion: The model is based on considerations of growth of body mass ("weight"), and other growth curves are derived via allometries empirically observed or justified. However, in this way, the model comprises all these relationships as derivative cases, many interesting and hitherto unaccounted features being derivable, explainable and predictable.

LOCKER: In this connection I would like to refer to a recent paper by D. E. WOHLSCHLAG (*Ecol.* **43**, 589, 1962), who was working with the antarctic fish *Trematomus bernacchii*, which lives at temperatures near 0^0 C. In this fish, females grow faster than males, although they have a lower rate of metabolism. WOHLSCHLAG was able to explain this interesting result by applying the BERTALANFFY-equations in the modification that BEVERTON and HOLT have given. This fact speaks again in favour of the usefulness of the growth equations of BERTALANFFY.