

Review

From empirical patterns to theory: a formal metabolic theory of life

Tânia Sousa^{1,*}, Tiago Domingos¹ and S. A. L. M. Kooijman²

¹*Environment and Energy Section, Instituto Superior Técnico, 1049-001 Lisboa, Portugal*

²*Department of Theoretical Biology, Vrije Universiteit, 1081 HV Amsterdam, The Netherlands*

The diversity of life on Earth raises the question of whether it is possible to have a single theoretical description of the quantitative aspects of the organization of metabolism for all organisms. However, similarities between organisms, such as von Bertalanffy's growth curve and Kleiber's law on metabolic rate, suggest that mechanisms that control the uptake and use of metabolites are common to all organisms. These and other widespread empirical patterns in biology should be the ultimate test for any metabolic theory that hopes for generality. The present study (i) collects empirical evidence on growth, stoichiometry, feeding, respiration and energy dissipation and exhibits it as stylized biological facts; (ii) formalizes assumptions and propositions in a metabolic theory that is fully consistent with the Dynamic Energy Budget theory; and (iii) proves that these assumptions and propositions are consistent with the stylized facts.

Keywords: Dynamic Energy Budget theory; metabolic theory; Kleiber's law; von Bertalanffy growth; stoichiometry; growth

1. INTRODUCTION

In the literature, two main approaches are followed to obtain insights into metabolic phenomena: (i) the study of the complex set of biochemical reactions occurring at different rates and (ii) the study of the organization of metabolism described by the mass and energy flows inside the organisms. We believe that the modelling of the biochemical networks of reactions that are taking place in the organism is useful but will not, by itself, lead to an understanding of life because the set of biochemical reactions occurring in the organism can be species specific and too complex, especially for multicellular organisms. Also, the standard modelling of biochemical networks neglects the spatial structure and the complex transport and allocation processes in the organism.

By contrast, this paper builds on the premise that the mechanisms that are responsible for the organization of metabolism are not species specific (Kooijman 2000). This hope for generality is supported by (i) the universality of physics and evolution and (ii) the existence of widespread biological empirical patterns among organisms.

The road map of this paper is as follows. In §2, the empirical patterns that characterize metabolism are discussed and presented as stylized facts. They are of the utmost importance because any biological non-species-specific metabolic theory should be compatible with these facts. We believe that such a theory has already been developed, the Dynamic Energy Budget (DEB) theory. This theory aims to capture the quantitative

aspects of the organization of metabolism at the organism level with implications for the sub- and supra-organismic levels (Kooijman 2000, 2001; Nisbet *et al.* 2000). In §3, the DEB theory is formalized for its standard model, which considers an isomorphic organism, with one reserve and one structure. This model is assumed to be appropriate for most heterotrophic unicellular organisms and animals. This theory is formalized such that (i) the assumptions are highlighted and separated from the propositions, (ii) the assumptions are supported by the stylized facts or the universal laws and (iii) the importance and validity of the propositions are discussed. Using the DEB theory, the difference between species can be reduced to differences in the set of parameter values. In §4, the DEB theory for the relationship between parameters among different species is formalized. Section 5 presents the links between empirical patterns, assumptions and propositions, and concludes.

2. EMPIRICAL PATTERNS

In this section, we summarize the stylized empirical patterns essential for a theoretical description of metabolic organization in biology (tables 1 and 2). They are related to (i) the metabolic processes common to all organisms, namely feeding, growth, reproduction, maturation and maintenance; (ii) the life stages, i.e. embryo, juvenile and adult; and (iii) the stoichiometry of organisms.

These patterns apply to most organisms in many (not all) circumstances. In particular, the behaviour of organisms deviates from the empirical patterns presented here. Some of these deviations are well understood and can be captured by the extensions of the present theory (Kooijman 2000).

* Author for correspondence (taniassousa@ist.utl.pt).

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Table 1. Stylized facts and empirical evidence on feeding, growth and respiration.

| | stylized facts | | empirical evidence |
|-------------|----------------|--|---|
| feeding | F1 | starving organisms may reproduce | animals (Kjesbu <i>et al.</i> 1991; Hirche & Kattner 1993; Kirk 1997) |
| | F2 | starving organisms may grow | animals (Stromgren & Cary 1984; Russell & Wootton 1992; Roberts <i>et al.</i> 2001; Dou <i>et al.</i> 2002; Gallardo <i>et al.</i> 2004; Zheng <i>et al.</i> 2005) |
| | F3 | starving organisms survive for some time | animals (Stockhoff 1991; Letcher <i>et al.</i> 1996) bacteria (Kunji <i>et al.</i> 1993) |
| growth | G1 | the growth of isomorphic organisms at abundant food is well described by the von Bertalanffy growth curve (Putter 1920; von Bertalanffy 1938) | animals (Frazer <i>et al.</i> 1990; Strum 1991; Chen <i>et al.</i> 1992; Schwartz & Hundertmark 1993; Ferreira & Russ 1994; Ross <i>et al.</i> 1995) |
| | G2 | many species do not stop growing after reproduction has started, i.e. they exhibit indeterminate growth (Kozłowski 1996; Heino & Kaitala 1999) | animals (Shine & Iverson 1995; Jorgensen & Fiksen 2006) |
| | G3 | holometabolic insects are an exception foetuses increase in weight proportional to cubed time (Huggett & Widdas 1951) | animals (Huggett & Widdas 1951; Zonneveld & Kooijman 1993) |
| | G4 | the logarithm of the von Bertalanffy growth rate of different species corrected for a common body temperature decreases almost linearly with the logarithm of the species maximum size | bacteria (Kooijman 2000, pp. 276–282) yeasts (Kooijman 2000, pp. 276–282) animals (Kooijman 2000, pp. 276–282) |
| | G5 | the logarithm of the von Bertalanffy growth rate for organisms of the same species at different food availabilities decreases linearly with ultimate length | animals (Galluci & Quinn 1979; Kooijman 2000, pp. 96) |
| | G6 | egg size covaries with the nutritional status of the mother | animals (Rossiter 1991 <i>a,b</i> ; Glazier 1992; Bertram & Strathmann 1998; Heath <i>et al.</i> 1999; McIntyre & Gooding 2000; Yoshinaga <i>et al.</i> 2001; Loman 2002; Nager <i>et al.</i> 2006) |
| respiration | R1 | freshly laid eggs do not use dioxygen in significant amounts | animals (Romijn & Lokhorst 1951; Pettit 1982; Bucher 1983; Whitehead 1987) |
| | R2 | the use of dioxygen increases with decreasing mass in embryos and increases with mass in juveniles and adults | animals (Romijn & Lokhorst 1951; Richman 1958; Pettit 1982; Bucher 1983; Whitehead 1987; Clarke & Johnston 1999; Savage <i>et al.</i> 2004) |
| | R3 | the use of dioxygen scales approximately with body weight raised to power 0.75 (Kleiber 1932) | animals (Richman 1958; Clarke & Johnston 1999; Savage <i>et al.</i> 2004) |
| | R4 | organisms show a transient increase in metabolic rate independent of their body mass after ingesting food—the heat increment of feeding | animals (Janes & Chappell 1995; Chappell <i>et al.</i> 1997; Hawkins <i>et al.</i> 1997; Rosen & Trites 1997; Nespolo <i>et al.</i> 2005) |

Table 2. Stylized facts and empirical evidence on stoichiometry, energy dissipation and cells.

| | stylized facts | | empirical evidence |
|--------------------|----------------|---|---|
| stoichiometry | S1 | well-fed organisms have a different body chemical composition than poorly fed organisms | animals (Chen <i>et al.</i> 1981; Hirche & Kattner 1993; Du & Mai 2004; Molnar <i>et al.</i> 2006) yeasts (Hanegraaf <i>et al.</i> 2000) |
| | S2 | organisms growing with constant food density converge to a constant chemical composition | animals (Chilliard <i>et al.</i> 2005; Krol <i>et al.</i> 2005; Fink <i>et al.</i> 2006; Ingenbleek 2006; Steenbergen <i>et al.</i> 2006) |
| energy dissipation | I1 | dissipating heat is a weighted sum of three mass flows: carbon dioxide, dioxygen and nitrogenous waste—indirect calorimetry | animals (Seale <i>et al.</i> 1991) |
| cells | C1 | cells in a tissue are metabolically very similar independent of the size of the organisms (Morowitz 1968) | |

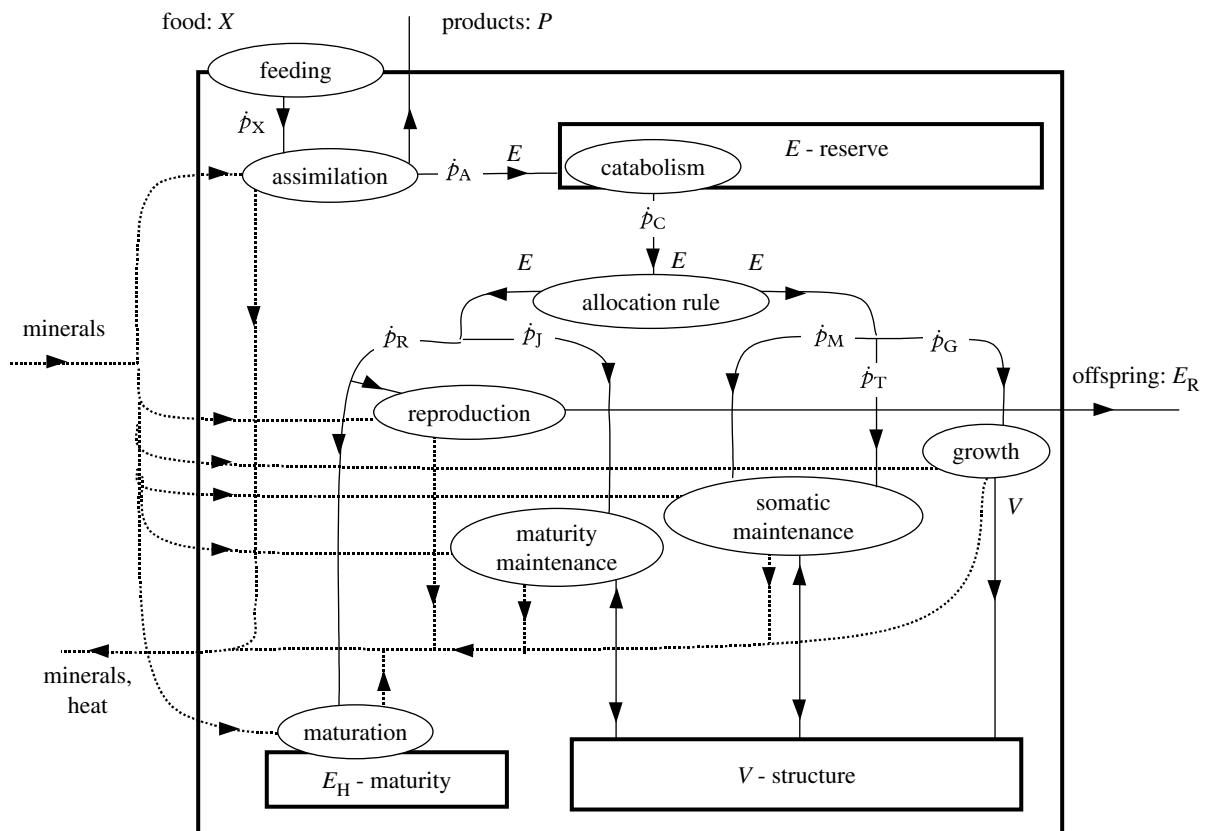


Figure 1. Metabolism in a DEB organism. Square, organism; ovals, processes; rectangles, state variables; arrows are flows of reserve (E), structure (V), minerals, food (X), products (P) or offspring (E_R).

The theory that describes the metabolism of organisms should also be compatible with physics and evolution. The physical principles considered here are: (P1) mass and energy are conserved quantities; (P2) any energy conversion process leads to dissipation; (P3) mass and energy flows depend only on intensive properties; and (P4) mass and energy transport are proportional to surface areas because they occur across surfaces.

The evolutionary principles taken into account are: (P5) organisms have increased their control over their metabolism during evolution allowing for some adaptation to environmental changes in short periods and (P6) organisms inherit parents' characteristics in a sloppy way allowing for some adaptation to environmental changes across generations.

3. THEORY ON METABOLIC ORGANIZATION

The standard DEB model considers an isomorphic organism, i.e. an organism whose surface area is proportional to volume raised to the power $2/3$, with one reserve and one structure. Figure 1 shows the standard DEB model, and tables 3–5 summarize the notation.

Assumption 3.1 (state variables). *The state of the organism is completely described by the volume of the structure V , the amount of energy in the reserve E and the amount of energy invested into maturation E_H . The structure and the reserve are generalized compounds, i.e. mixtures of a large number of compounds that compose the biomass of the organism.*

Empirical evidence on the variable chemical composition of the organisms (S1) justifies the need for at least two aggregate chemical compounds, i.e. structure V and reserve E to describe the organism.

Empirical evidence on the different life stages that an organism goes through during its life cycle justifies the need for an additional variable, the level of maturity. Although maturity represents neither mass nor energy, it is quantified as the cumulative energy investment into maturation because an organism has to spend energy to increase its complexity (P2).

Assumption 3.2 (life-history events). *Life-stage events are linked with maturity, i.e. they occur when E_H exceeds certain thresholds. Feeding begins when $E_H = E_H^b$ and allocation to reproduction coupled to the ceasing of maturation begins when $E_H = E_H^p$. The dynamics of E_H is given by*

$$\frac{dE_H}{dt} = \dot{p}_R, \quad E_H < E_H^p, \quad (3.1)$$

where \dot{p}_R is the power allocated to maturation if $E_H < E_H^p$ and the power allocated to reproduction if $E_H = E_H^p$.

Other life-history events, such as cell division, metamorphosis or other stage transitions (e.g. to the pupal stage), also occur at threshold values for E_H .

The rationale for this assumption is the following: an organism that develops and produces offspring increases its complexity (or maturity) from the embryo to the adult stage. It is reasonable to assume that the amount of energy invested to achieve the degrees of maturity that organisms need to start feeding or allocating to reproduction are intraspecies constants,

Table 3. List of symbols of variables. (Dimensions: —, no dimension; L , length; T , time; #, moles or C-moles; \mathcal{E} , energy. Symbols with [] are per unit structural volume and dots above are per unit time.)

| | dimensions | interpretation |
|-----------------------|---------------------|----------------------------------|
| <i>state variable</i> | | |
| V | L^3 | structural volume |
| E | \mathcal{E} | energy in reserve |
| E_H | \mathcal{E} | energy allocated to maturation |
| <i>variable</i> | | |
| t | T | time |
| $[E]$ | $\mathcal{E}L^{-3}$ | reserve density |
| e | — | scaled reserve density |
| X | # L^{-3} | substrate density |
| L | L | volumetric length |
| f | — | scaled functional response |
| \dot{p}_X | $\mathcal{E}T^{-1}$ | feeding power |
| \dot{p}_A | $\mathcal{E}T^{-1}$ | assimilation power |
| \dot{p}_C | $\mathcal{E}T^{-1}$ | catabolic power |
| \dot{p}_M | $\mathcal{E}T^{-1}$ | volume-related maintenance power |
| \dot{p}_J | $\mathcal{E}T^{-1}$ | maturity maintenance power |
| \dot{p}_G | $\mathcal{E}T^{-1}$ | growth power |
| \dot{p}_R | $\mathcal{E}T^{-1}$ | reproduction power |
| \dot{r} | T^{-1} | specific growth rate |

Table 4. List of symbols of parameters. (Dimensions: —, no dimension; L , length; M , mass; T , time; \mathcal{E} , energy. Symbols with { } are per unit surface area, [] are per unit structural volume and dots above are per unit time. Chemical compounds and process specifiers appear as subscripts to other variables.)

| parameter | dimensions | interpretation |
|--------------------|---------------------------|--|
| { \dot{p}_{Am} } | $\mathcal{E}L^{-2}T^{-1}$ | surface-specific assimilation power |
| $[E_m]$ | $\mathcal{E}L^{-3}$ | maximum reserve density |
| $[\dot{p}_M]$ | $\mathcal{E}L^{-3}T^{-1}$ | volume-specific maintenance power |
| $[\dot{p}_M]^*$ | $\mathcal{E}L^{-3}T^{-1}$ | specific maintenance power |
| { \dot{p}_T } | $\mathcal{E}L^{-2}T^{-1}$ | surface-specific maintenance power |
| $[E_G]$ | $\mathcal{E}L^{-3}$ | volume-specific growth costs |
| \dot{v} | LT^{-1} | energy conductance |
| κ | — | fraction of catabolic power spent on maintenance plus growth |
| κ_R | — | fraction of reproduction power fixed in eggs |
| g | — | investment ratio |
| \dot{k}_M | T^{-1} | maintenance rate coefficient |
| \dot{k}_J | T^{-1} | maturity rate coefficient |
| L_m | L | maximum length |
| L_h | L | heating length |
| E_H^b | \mathcal{E} | threshold of energy investment at birth |
| E_H^p | \mathcal{E} | threshold of energy investment at puberty |
| E_0 | \mathcal{E} | energy cost of one egg |
| μ_E | $\mathcal{E}M^{-1}$ | chemical potential |

because the levels of maturity at the onset of these behaviours are the same among the organisms of the same species.

When $E_H^p > E_H^b$ the multicellular organisms have three life stages: they start as an embryo or foetus that does not feed; become juveniles when feeding starts; and reproduce as adults. The life history of organisms that reproduce by fission is well described by a single life stage, the juvenile.

Assumption 3.3 (strong homeostasis). *The structure V and the reserve E do not change in chemical composition and thermodynamic properties. The organism feeds on a resource X and produces products P , also of fixed chemical compositions and constant thermodynamic properties.*

The rationale for strong homeostasis is (P5). A stable internal chemical composition means that organisms have a higher control over their own metabolism (P5) because the rate of chemical reactions depends on the chemical composition of the surrounding environment.

Assumption 3.4 (metabolic processes). *Metabolism can be characterized by the following processes:*

- (i) *feeding, i.e. the uptake of food by the organism, where \dot{p}_X is the energy of the food flow;*
- (ii) *assimilation, i.e. the set of reactions that transform food into reserve, where \dot{p}_A is the reserve energy flow; and*

Table 5. List of symbols of compounds and processes.

| | interpretation |
|---------------------------|-------------------------------|
| <i>compound specifier</i> | |
| X | substrate (food) |
| E | reserve |
| V | structure |
| P | products |
| M_i | mineral compound i |
| <i>process specifier</i> | |
| A | assimilation |
| C | catabolism |
| M | maintenance (volume related) |
| T | maintenance (surface related) |
| G | growth |
| R | reproduction or maturation |

- (iii) *catabolism*, i.e. the mobilization of the reserve to fuel the organism's activities, where \dot{p}_C is the energy of the mobilized flow. Thus, reserve dynamics is

$$\frac{dE}{dt} = \dot{p}_A - \dot{p}_C. \quad (3.2)$$

The mobilized reserve is allocated to

- (iv) *growth*, i.e. the increase of structure

$$\frac{dV}{dt} = \frac{\dot{p}_G}{[E_G]}, \quad (3.3)$$

where \dot{p}_G is the reserve energy flow allocated to growth and $[E_G]$ is the specific cost of growth;

- (v) *somatic maintenance*, i.e. the energy necessary to fuel the set of processes that keep the organism alive, where \dot{p}_M is the reserve energy flow;
- (vi) *maturity maintenance*, i.e. the use of reserve to maintain the complexity of the structure, where \dot{p}_J is the reserve energy flow; and
- (vii) *maturation*, i.e. the use of reserve to increase the complexity of the structure called maturity, where \dot{p}_R is the reserve energy flow; or
- (viii) *reproduction*, i.e. the use of the reserve of the mother to create reserve for the offspring, where \dot{p}_R is the reserve energy flow allocated to this process and $(1 - \kappa_R)\dot{p}_R$ is the fraction dissipated. Thus,

$$\dot{p}_C = \dot{p}_M + \dot{p}_G + \dot{p}_J + \dot{p}_R. \quad (3.4)$$

The fraction of catabolic power allocated to somatic maintenance and growth is a general function $0 \leq \kappa(V, E) \leq 1$, i.e.

$$\dot{p}_M + \dot{p}_G = \kappa \dot{p}_C. \quad (3.5)$$

The remaining fraction is allocated to maturity maintenance, maturation or reproduction

$$\dot{p}_J + \dot{p}_R = (1 - \kappa)\dot{p}_C. \quad (3.6)$$

The processes of somatic maintenance, maturity maintenance, maturation and dissipation in reproduction consist in an aggregate chemical reaction that transforms reserve plus minerals into minerals. For this reason, the sum of these powers is identified as the dissipation power

$$\dot{p}_D = \dot{p}_M + \dot{p}_J + (1 - \kappa_R)\dot{p}_R, \quad (3.7)$$

where $\kappa_R = 0$ for the embryo and juvenile stages.

All metabolic processes depend only on V , E and DEB parameters with the exception of feeding and assimilation that also depend on X .

Empirical evidence (R4) shows that there are processes associated with food processing only, which suggests that food goes through a set of chemical reactions that transform it into reserves, assimilation. Organisms have to spend energy on growth, maintenance and reproduction (P2). The fact that organisms are capable of spending energy on these metabolic processes in the absence of food (F1, F2, F3) shows that the energy mobilized is obtained from the reserve and not directly from food. The energy mobilized for maturation is also obtained from the reserve because eggs do not take up food from the environment but they must allocate energy to maturation (assumption 3.2). Maturity maintenance includes maintaining regulating mechanisms and defence systems. The need to allocate energy to maturity maintenance is intimately related with the second law of thermodynamics (P2) because the level of maturity, i.e. the complexity of the organism, would decrease in the absence of energy spent in its maintenance. Also, the existence of an overhead cost of the reproduction process $(1 - \kappa_R)\dot{p}_R$ is consistent with the dissipation principle (P2).

This assumption on metabolic organization considers that there is a flow of energy \dot{p}_R , which is first allocated to maturation and then to reproduction because reproduction starts only when the maturation level reaches E_H^p (assumption 3.2).

Assumption 3.5 (reserve and structure: maintenance needs). Reserve has no maintenance needs while structure has (positive) maintenance needs.

Structure maintenance costs are

$$\dot{p}_M = [\dot{p}_M]^* V, \quad (3.8)$$

where specific maintenance costs $[\dot{p}_M]^*$ are a general function of volume

$$[\dot{p}_M]^* = \left([\dot{p}_M] + \frac{\{\dot{p}_T\}}{L} \right), \quad (3.9)$$

where $L \equiv V^{1/3}$ is the volumetric length and $[\dot{p}_M]$ and $\{\dot{p}_T\}$ are the constant volume and the surface-specific maintenance costs, respectively.

The rationale for this assumption is that the organism does not invest in the reserve compounds because they are used for metabolism, i.e. they have a limited lifetime, while the structure compounds are much more permanent implying maintenance costs.

Structure-specific maintenance needs, $[\dot{p}_M]$ and $\{\dot{p}_T\}$, are considered to be constant because the chemical composition and thermodynamic properties of the structure are constant (assumption 3.3). Surface-related maintenance costs are associated with heating (endotherms) and osmosis (fresh water organisms).

Assumption 3.6 (maturity: maintenance needs). Maturity maintenance costs \dot{p}_J are proportional to the cumulative amount of energy invested into maturation

$$\dot{p}_J = \dot{k}_J E_H, \quad (3.10)$$

where $E_H \leq E_H^P$ and k_j is a positive maturity rate coefficient.

In an adult, the maturity maintenance costs are constant because maturity does not increase after the onset of reproduction, while in a juvenile they increase with the level of maturity.

Proposition 3.7 (maturation and reproductive power). The amount of energy allocated to maturation in a juvenile is

$$\dot{p}_R = (1 - \kappa)\dot{p}_C - k_j E_H, \quad (3.11)$$

and to reproduction in an adult is

$$\dot{p}_R = (1 - \kappa)\dot{p}_C - k_j E_H^P. \quad (3.12)$$

All proofs are in the electronic supplementary material, appendix I.

The flow of energy a juvenile allocates to maturation is invested by an adult in reproduction. Thus, an organism kept at a low food density such that the accumulated amount of energy invested into maturation never reaches the threshold E_H^P will never reproduce.

The amount of energy invested continuously into reproduction is accumulated in a buffer and then it is converted into eggs providing the initial endowment of the reserve to the embryo. This conversion is species specific and typically linked to the seasons in species with a relatively large body size.

Proposition 3.8 (embryo). Embryos start their development with a negligible amount of structure and a significant amount of reserve.

Proposition 3.9 (yield coefficients). The stoichiometries of assimilation, growth and dissipation are, respectively,

$$X \rightarrow y_{PX}^A P + y_{EX}^A E + y_{M_1X}^A M_1 + \dots + y_{M_zX}^A M_z, \quad (3.13)$$

$$E \rightarrow y_{VE}^G V + y_{M_1E}^G M_1 + \dots + y_{M_zE}^G M_z, \quad (3.14)$$

$$E \rightarrow y_{M_1E}^D M_1 + \dots + y_{M_zE}^D M_z, \quad (3.15)$$

where M_1 to M_z are the mineral compounds and y^A, y^G and y^D are the yield coefficients in the assimilation, growth and dissipation processes, respectively, e.g. y_{EX}^A is the number of C-moles of the reserve produced per each C-mole of food processed in the assimilation process.

Yield coefficients of the assimilation (resp. growth, dissipation) process are constant if the number of chemical elements that participate is more than or equal to $z + 2$ (resp. $z + 1, z$). If the yield coefficient y_{*1*2} is constant, then the yield coefficient η_{*1*2} between mass flow $*1$ and energy flow $*2$ is also constant.

This proposition means that if the number of chemical elements that participate in the chemical reactions occurring in the organism is higher than the number of mineral compounds, then the yield coefficients are constant.

Proposition 3.10 (organism stoichiometry). The stoichiometry of the aggregate chemical transformation that describes the functioning of the organism has 3 d.f. More specifically, any flow produced or consumed in the organism is a weighted average of any three other flows.

The method of indirect calorimetry (II) is a particular case of proposition 3.10, i.e. the flow of heat is a weighted average of carbon dioxide, dioxygen and nitrogenous waste.

Assumption 3.11 (dependence on the environment: feeding). Ingestion at abundant food is proportional to surface area $\dot{J}_{Xm} = \{J_{Xm}\}V^{2/3}$, where $\{J_{Xm}\}$ is the maximum surface-specific feeding rate. Thus,

$$\dot{p}_X = \{J_{Xm}\}V^{2/3}f(X)\mu_X = \dot{J}_X\mu_X, \quad (3.16)$$

where the non-dimensional functional response

$$f(X) = \frac{\dot{J}_X}{\dot{J}_{Xm}} \quad (3.17)$$

is an increasing function of food with $0 \leq f(X) \leq 1$; \dot{J}_X is the rate of ingestion at food density X ; and μ_X is the chemical potential of food, which converts the mass flow \dot{J}_X to the energy flow \dot{p}_X .

Feeding is proportional to surface area within the same species because acquisition processes and digestion and other food processing activities depend on mass transport processes that occur through surfaces (P4).

Proposition 3.12 (dependence on the environment: assimilation). The assimilation power is proportional to surface area,

$$\dot{p}_A = \{\dot{p}_{Am}\}V^{2/3}f(X), \quad (3.18)$$

where $\{\dot{p}_{Am}\} \equiv \dot{J}_{Xm}/\eta_{XA}$ is the maximum surface-specific assimilation rate.

Proposition 3.13 (partitionability of reserve dynamics). The organism's reserve E is partitioned in the organism among the categories of chemical compounds, $E_i \equiv \lambda_i E$ with $0 \leq \lambda_i \leq 1$, with constant energy fractions λ_i such that

$$\frac{d}{dt}E = \sum_i \frac{d}{dt}E_i. \quad (3.19)$$

The specific somatic maintenance costs and the specific cost of growth paid by each category E_i are proportional to its amount, i.e. $[\dot{p}_{M_i}]^* = \lambda_i[\dot{p}_M]^*$ and $[E_{G_i}] = \lambda_i[E_G]$. Also, the catabolic power mobilized from each category E_i is proportional to its amount, i.e. $\dot{p}_{C_i} = \lambda_i\dot{p}_C$, while the fraction of \dot{p}_{C_i} allocated to growth and maintenance is the same for all the categories, i.e. $\kappa_i = \kappa$.

Therefore, the relationship between the overall metabolic power and the metabolic power mobilized from each category is as follows:

$$\dot{p}_{C_i}(\lambda_i E, V, \lambda_i[\dot{p}_M]^*, \lambda_i[E_G], \kappa) = \lambda_i\dot{p}_C(E, V, [\dot{p}_M]^*, [E_G], \kappa). \quad (3.20)$$

The sum of the dynamics of the partitioned reserves is identical to that of the lumped reserve (equation (3.19)). Thus, the reserve can be described with only one state variable (assumption 3.1).

Proposition 3.14 (the kappa rule I). The κ function, i.e. the fraction of the catabolic power allocated to maintenance and growth, is independent of E , i.e.

$$\kappa(\lambda E, V) = \kappa(E, V). \quad (3.21)$$

Assumption 3.15 (the kappa rule). The κ function is independent of V .¹

Note that assumption 3.15 together with proposition 3.14 imposes that κ is constant. This means that reproduction does not compete with growth, which is in agreement with the fact that many organisms do not stop growing after reproduction has started (G2), e.g. daphnia grows a lot during reproduction. The fact that the simplifying assumption that kappa is a constant can match this pattern as well as the pattern that reproduction occurs after growth (as in most mammals and birds) is a good support for this assumption because simple direct competition between growth and reproduction (a variable κ) cannot explain the daphnia case.

Proposition 3.16 (allocation priorities). *Maintenance has priority over growth and maturity maintenance has priority over maturation or reproduction.*

Assumption 3.17 (weak homeostasis). *For adults and juveniles at any constant food level, $X = X^* > 0$, there is a reserve density, $[E]^*(X^*) \equiv E/V$, which remains constant along the growth process.*

The weak homeostasis assumption says that growing biomass converges to a constant chemical composition as long as the food density remains constant. This is supported by the empirical evidence (S2).

Proposition 3.18 (catabolic power). *The specific catabolic power, $[\dot{p}_C] \equiv \dot{p}_C/V$, is given by*

$$[\dot{p}_C] = [E](\dot{v}V^{-1/3} - \dot{r}), \quad (3.22)$$

where \dot{v} is the energy conductance and $\dot{r} \equiv (1/V)(dV/dt)$.

The mobilization of reserves given by equation (3.22) is independent of the environment (food). This is essential because (i) the mobilization of reserves occurs inside the organism at a molecular level, and at that level no information concerning the external environment is available (P3) and (ii) it provides the organism an increased protection against environmental fluctuations and an increased control over its own metabolism (P5). Also, the mobilization of reserves should be uncoupled from the metabolic functions of feeding and assimilation. If the metabolic functions were dependent on each other, then it would be much more difficult to change a particular node at random in the metabolic network (P6) while avoiding complex consequences for the whole organism. The result would be that evolutionary progress would stop, while the environment would continue to change.

The specific catabolic flux $[\dot{p}_C]$ is constant for a fully grown organism at constant food level ($dV/dt=0$ and $[E] = [E]^*$) implying a higher degree of control over its metabolism (P5).

Parameter \dot{v} is an energy conductance because it is the proportionality constant between the flux of reserves per unit structural volume of a fully grown organism and the reserve density gradient

$$[\dot{p}_C] = \dot{v} \frac{[E]}{V^{1/3}}. \quad (3.23)$$

Proposition 3.19 (maximum reserve density). *Organisms of the same species have a maximum reserve*

density

$$[E_m] = \frac{\{\dot{p}_{Am}\}}{\dot{v}} < \infty. \quad (3.24)$$

Organisms achieve maximum reserve density $[E]^ \equiv [E_m]$ at abundant food, i.e. $\lim_{X \rightarrow \infty}$.*

Proposition 3.20 (maximum size). *Organisms of the same species have a maximum (structural) length:*

$$L_m \equiv V_m^{1/3} = \frac{\kappa \{\dot{p}_{Am}\}}{[\dot{p}_M]}. \quad (3.25)$$

Organisms grow to L_m when specific surface maintenance costs are null, i.e. $\{\dot{p}_T\} = 0$.

Somatic maintenance competes directly with and has priority over growth (see proposition 3.16) implying that somatic maintenance increases proportionally to size (see assumption 3.6), which imposes a maximum size on the organism. In the literature, the existence of a maximum size (including reserve and structure) is generally accepted (G4, G5) implying that the structure also has a maximum size V_m , and that the maximum amount of energy in the reserve E_m is limited. Therefore, the maximum reserve density $[E_m] \equiv E_m/V_m$ is also limited.

Proposition 3.21 (reserve density at weak homeostasis). *The reserve density under weak homeostasis is given by*

$$[E^*] = f(X)[E_m]. \quad (3.26)$$

The reserve density that growing organisms achieve for any constant food level (assumption 3.15) is proportional to the scaled functional response, i.e. the higher the constant food level the higher the reserve density at equilibrium.

Assumption 3.22 (embryo reserve density). *The initial amount of reserve is such that the embryo reserve density at birth equals that of the mother at egg formation.*

This assumption is supported by the empirical evidence (G6). The reasoning is the following: if the egg is big, then it has a higher amount of reserve. This will fuel a higher catabolic flux (equation (3.22)) implying that the maturity level E_H^0 is reached sooner when the amount of reserve is higher.

Proposition 3.23 (Dynamic Energy Budget). *The DEB of an organism and the change in structural length are*

$$\frac{de}{dt} = \dot{v}L^{-1}(f(X) - e), \quad (3.27)$$

$$\frac{dL}{dt} = \frac{\dot{v}}{3} \frac{e - L_h/L_m - L/L_m}{g + e}, \quad (3.28)$$

where $e \equiv [E]/[E_m]$ is the scaled reserve density and $L \equiv V^{1/3}$ is the volumetric length.

$$g \equiv \frac{[E_G]}{\kappa[E_m]} \quad (3.29)$$

is the investment ratio, i.e. the ratio of the costs of growth to the maximum amount of energy allocated to growth and maintenance and $L_h \equiv \{\dot{p}_T\}/[\dot{p}_M]$ is the heating length.

If an organism has no surface maintenance costs, i.e. $\dot{p}_T = 0$ and $L_h = 0$, then its ultimate length is $L_\infty = fL_m$ (see equation (3.28)). For endotherms, the surface maintenance costs are associated mainly with heating, where L_h is the reduction in length due to the energy allocated to these costs. In this case, the ultimate length is (see equation (3.28))

$$L_\infty = (fL_m - L_h). \quad (3.30)$$

Proposition 3.24 (von Bertalanffy law). *The growth curve of an isomorphic juvenile or adult individual at constant food availability X^* or at abundant food ($f \approx 1$) is*

$$\frac{dL}{dt} = \dot{r}_B(L_\infty - L). \quad (3.31)$$

The von Bertalanffy growth rate \dot{r}_B is given by

$$\begin{aligned} \dot{r}_B &= \frac{\dot{v}}{3L_m} \frac{1}{g+f} = \frac{\dot{k}_M g}{3(g+f)} \\ &= \left(\frac{3}{\dot{k}_M} + \frac{3L_h}{\dot{v}} + \frac{3L_\infty}{\dot{v}} \right)^{-1}, \end{aligned} \quad (3.32)$$

where $\dot{k}_M \equiv [\dot{p}_M]/[E_G]$ is the maintenance rate coefficient, i.e. the ratio between the costs of maintenance and growth of structure.

von Bertalanffy's law (equation (3.31)) is one of the most universal biological patterns (G1). Also, organisms of the same species at different food availabilities exhibit von Bertalanffy growth rates that are inversely proportional to ultimate length in accordance with the behaviour predicted by equation (3.32) (G5).

This proposition provides a strong support for assumption 3.15 because (i) the growth rate \dot{r}_B is constant only if g is constant and (ii) g is constant if κ is independent of V (equation (3.29)).

Proposition 3.25 (foetal development). *If the reserves of the mother, continuously supplied to the embryo via the placenta, are considered very large, i.e. $e = \infty$, then foetal growth is given by*

$$\frac{dL}{dt} = \frac{\dot{v}}{3}. \quad (3.33)$$

According to equation (3.33), the structural volume of the foetus is proportional to cubed time

$$V(t) = \left(\frac{\dot{v}t}{3} \right)^3. \quad (3.34)$$

Equation (3.34) is validated by the empirical data that suggest that foetal weight is proportional to cubed time (G3) because the structural volume of the foetus is proportional to weight when the reserve density is constant (see electronic supplementary material, appendix II).

Proposition 3.26 (intraspecific Kleiber's law). *The metabolic rate measured by the dioxygen consumption \dot{J}_{O_2} of fasting animals is proportional to w^α with $\alpha \in [0.66, 1]$. If animals have the same reserve density e , then the proportionality constant is the same.*

Empirical evidence on Kleiber's law is amply available in the literature (R3).

4. THEORY ON PARAMETER VALUES

In the DEB theory, the set of parameter values is individual specific. Individuals differ in parameter values and selection leads to evolution characterized by a change in the (mean) value of these parameters (P6). The differences between species are just an evolutionary amplification of the differences between individuals, i.e. they are reduced to differences in the mean value of DEB parameters. In this section, the theory for the covariation of (mean) parameter values among the species is presented.

Assumption 4.1 (constant primary parameters). *Constant parameters are identical to related species and independent of the ultimate size of the organism. These parameters include $[E_G]$, $[\dot{p}_M]$, $\{\dot{p}_T\}$, \dot{k}_J , κ , κ_R and \dot{v} .*

Constant parameters characterize molecular-based processes and do not vary between related species because cells are very similar, independent of the size of the organism (C1). Cells of about equal size have similar growth, maintenance and maturation costs, i.e. $[E_G]$, $[\dot{p}_M]$, $\{\dot{p}_T\}$, \dot{k}_J and κ_R are equal for related species. The partitioning of energy mobilized from the reserves is done at the level of the somatic and reproductive cells, and therefore κ is also a molecular-based process. Kooijman & Troost (2007) presented a possible molecular mechanism that makes clear that \dot{v} is a molecular-based parameter. A simpler but less precise argument to justify this is the following. Two fully grown organisms with the same V and the same $[E]$, which belong to different but related species with different maximum lengths, have similar metabolic needs. Therefore, they must have a similar rate of mobilization of reserves, i.e. the same \dot{v} (see equation (3.22)).

Assumption 4.2 (design primary parameters). *Design parameters depend on the maximum length of the species, L_m . These parameters include E_H^b and E_H^p , which are proportional to L_m^3 .*

Cells of about equal size have similar specific maturation thresholds, i.e. $[E_b^H] \equiv E_b^H/L_m^3$ and $[E_p^H] \equiv E_p^H/L_m^3$. Thus, life-stage parameters E_H^b and E_H^p are proportional to L_m^3 .

Proposition 4.3 (maximum surface-specific assimilation rate). *The maximum surface-specific assimilation rate $\{\dot{p}_{Am}\}$ is proportional to L_m .*

Proposition 4.4 (compound parameters). *Parameters that are functions of primary parameters depend on L_m in predictable ways. Examples are:*

- L_h is independent of L_m , $[E_m]$ is proportional to L_m and g is proportional to $1/L_m$.
- **von Bertalanffy law.** *The growth rate for species A at abundant food is*

$$\log \dot{r}_B^A = \log \frac{\dot{v}}{3} - \log(gL_m + L_m^A), \quad (4.1)$$

where all parameters with the exception of L_m^A are for a reference species.

- **Kleiber's law.** *The metabolic rate measured by the dioxygen consumption \dot{J}_{O_2} of fasting fully grown adult animals that belong to the species with different maximum body sizes is proportional to w^α with $\alpha \in [0.5, 1]$.*

The interspecies comparison of von Bertalanffy growth rate corrected for a common body temperature is supported by empirical data (G4) (for a comparison between empirical data and DEB model predictions see (Kooijman 2000, fig. 8.3).

Dodds *et al.*'s (2001) re-analyses of datasets supported the fact that the power in Kleiber's law is in the interval [0.5,1] instead of having a unique value of 3/4. These authors tested whether the power is 3/4 or 2/3 finding little evidence for rejecting the power 2/3. Also, Vidal & Whitley (1982) found powers of 0.72 and 0.85 for crustaceans and Phillipson (1981) found values of 0.66 for unicellular organisms and 0.88 for ectotherms.

5. CONCLUSIONS

The DEB theory considers that biomass is partitioned into structure and reserve, which is supported by the empirical evidence that organisms can have a variable stoichiometry (S1). The reserve does not require maintenance because it is continuously used and replenished, while the structure requires maintenance because it is continuously degraded and reconstructed. This is supported by the fact that freshly laid eggs (composed only of reserve) do not use dioxygen in significant amounts and that the use of dioxygen increases with decreasing mass in the embryo as the reserves are transformed into structure and with increasing structure in the juvenile and adult (R1, R2).

Feeding is considered to be proportional to surface area within a species because transport occurs across surfaces (P4). In the organism, (i) food is transformed into the reserve and (ii) the reserve is mobilized to fuel growth, maturation, maintenance and reproduction. This internal organization is suggested by the empirical evidence on the heat increment of feeding (R4) and by the fact that starving organisms survive, grow and reproduce (F1–F3). Additionally, to the processes of growth, maturation, maintenance and reproduction, organisms also allocate energy to maturity maintenance, which is imposed by the need to spend energy to keep the organism far away from equilibrium (P2). The assumption on metabolic organization considers that the flow of energy allocated to reproduction, in an adult, was allocated to maturation in a juvenile instead of being allocated to growth because many organisms do not stop growing after reproduction has started (G2).

The amount of energy invested into maturation is the third state variable. It controls life-history events such as the initiation of feeding and reproduction coupled to the ceasing of maturation.

Metabolic organization is further restricted by the κ rule and the weak homeostasis assumption. The κ rule imposes that (i) the allocations of energy to reproduction and growth do not compete with each other, which is suggested by the laws of mass and energy transfer (P3) and (ii) the energy allocation to growth competes with the energy allocation to somatic maintenance imposing a maximum size within a species (G4, G5). The weak homeostasis assumption imposes that organisms tend to a constant chemical composition in an environment with constant food availability; this is supported by the empirical evidence on a constant

stoichiometry under certain conditions (S2) and motivated by evolutionary theory (P5).

The propositions obtained explain the following empirical findings: (i) the method of indirect calorimetry (I1), (ii) von Bertalanffy growth curves (G1), (iii) the variation of von Bertalanffy growth rates within (G5) and across species (G4), (iv) Kleiber's law on metabolic rate (R3) and (v) the pattern of foetal growth (G3).

In physics, it is easy to enforce simplicity in experiments bringing observations closer to theory. In biology, this is more difficult because simple organisms are still very complex and need to live in environments that are not homogeneous. Therefore, organisms deviate from the DEB theory more substantially than the real objects do from physics. In the context of DEB theory, deviations are treated as case-specific modifications that provide important insights into the evolutionary adaptations and the physical–chemical details of that particular species. The DEB theory strategy to deal with exceptions is the following. First, the DEB theory on metabolic organization is used to develop a quantitative expectation for the eco-physiological behaviour of a generalized species. Then, the parameters are estimated for a specific case and their values are compared with the expectations based on the DEB theory on parameter values. Differences highlight the evolutionary adaptations of this particular species. Deviations between the behaviour of this species and the DEB behaviour that is predicted using the estimated parameters are due to physical–chemical details that turn out to be important in this particular case. Although these details are ignored in the DEB theory because they do not always apply, it is still useful to detect the deviations and to provide guidance as to what physical–chemical details were missing in that particular case.

In this paper, we have focused on the standard DEB model for isomorphs with one reserve and one structure. They are ideal to explain the concepts and demonstrate the importance of surface area–volume interactions, which is an important organizing principle, in combination with mass and energy conservation. However, from an evolutionary perspective, they represent an advanced state that evolved from the systems with more reserves and, therefore, less homeostatic control. The evolution of metabolism as a dynamic system is discussed by Kooijman & Troost (2007). Extensions to the standard DEB model, which were not discussed in this paper, include (i) shape corrections for the surface area of the organisms that do not behave as isomorphs but deviate from this in predictable ways Kooijman (2000, pp. 26–29); (ii) the dependence of physiological rates on body temperature (Kooijman 2000); (iii) the inclusion of more reserves (for organisms feeding on simple substrates) and more structures (plants; Kooijman 2000, pp. 168); (iv) an ageing model that explains the phenomenological Weibull (Kooijman 2000, pp. 141) and Gompertz laws (Leeuwen *et al.* 2002); (v) shrinking whenever the catabolic power mobilized from the reserves is not enough to pay maintenance (Tolla *et al.* 2007); and (vi) implications for cellular levels (Kooijman & Segel 2005), trophic chains and population dynamics (Muller *et al.* 2001; Kuijper *et al.* 2003, 2004a,b; Kooi *et al.*

2004) and ecosystem dynamics (Kooijman & Nisbet 2000; Kooijman *et al.* 2002; Omta *et al.* 2006).

The DEB theory and discussions of the underlying concepts have already been presented in the literature (Nisbet *et al.* 2000; Kooijman 2001; van der Meer 2006*a,b*). However, in this paper, we prove that (i) the DEB theory is fully supported by empirical biological patterns and the universal laws of physics and evolution and (ii) it is a theory on metabolic organization that is as formal as physics. Also, we (i) propose a set of stylized empirical patterns that are the ultimate test for any metabolic theory and (ii) use these facts to establish a set of assumptions and obtain the propositions. The validity of each assumption and the empirical fact considered can be independently discussed, leading to a wider consensus in the metabolic field.

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ENDNOTE

¹Deviations from this assumption are necessary in special cases like prolonged starvation.

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