DEB theory restores coherence in Biology

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Abstract

We present the state of the art of the development of DEB theory, and the expected developments in the near future within the molecular, physiological and ecological domains. The degree of formalization in the set-up of the theory, with its roots in chemistry, physics, thermodynamics, evolution and the consistent application of Occam's razor, is discussed. We place the various contributions in the theme issue within this theoretical setting, and sketch the scope of actual and potential applications.

Keywords: DEB theory, biology, metabolism, ecology, evolution, energetics

I. REACHING OUT FOR GENERALITY

In Physics, there is a quest for a unified theory. Physical theories have a broad spectrum of application, a strong mathematical background and are subject to numerous empirical tests. In contrast, in Biology, mathematical theory has played a secondary role because Biology is frequently seen as a science of exceptions and particular cases, with little interest in abstraction and generalization. Exceptions are the research being done in the fields of Theoretical Biology and Mathematical Biology. However, Theoretical and Mathematical Biology have frequently been carried out without a concern for empirical testing. When this concern appears, models are of narrow application, reducing their theoretical breadth. The Dynamic Energy Budget (DEB) theory starts from the Dutch tradition of Theoretical and Mathematical Biology, but couples it with a fundamental concern in producing general theory that is subjected to careful empirical testing.

DEB theory aims to capture the quantitative aspects of metabolism at the individual level for organisms of all species. It builds on the premise that the mechanisms that are responsible for the organization of metabolism are not species specific [49, 52]. 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 [96]. Table I synthesizes the essential criteria for any general model for the metabolism of individuals. We explore the links between DEB theory and each of the proposed criteria in the following paragraphs.

DEB theory is explicitly based on the conservation of mass, isotopes, energy and time, including the inherent degradation of energy associated with all processes. So it complies to criteria 1 - table I.

The DEB theory is biologically implicit, so it applies to all species. Species-specific restrictions of DEB models are explained and predicted by the theory (criterion 5 - table I). For example, consider the most important difference between DEB models, the number of reserves (biomass components that fuel metabolism) and structures (biomass components that have maintenance needs) that are delineated. This depends on the degree of coupling of the various substrates an organism needs. Animals feed on other organisms, which couples uptake of the various substrates (proteins, carbohydrates, lipids, nutrients) tightly and explains why a single reserve and structure is appropriate for them. This does not hold for plants, for instance, where multiple reserves and structures (root, shoot) are required. This means that the applicability of a model can be judged a priori.

1 **Consistency with other scientific knowledge**: The models must be based on explicit assumptions that are consistent with thermodynamics, physics, (geo)chemistry and evolution.

2 **Consistency with empirical data**: The assumptions should be consistent with empirical patterns.

3 **Life-cycle approach**: The assumptions should cover the full life cycle of the individual, from initiation of development to death.

4 **Occam's razor**: The general model should be as simple as possible (and not more). The predictions should be testable in practice, which typically constrains its maximum complexity substantially (quantified in terms of number of variables and parameters).

5 **Taxon-specific adaptations**: Restrictions that make a model applicable to particular taxa only, should: (a) be consistent with an explicit evolutionary scenario; (b) be explicit to allow the prediction that the model will apply to those species.

TABLE I: Criteria for general explanatory models for the energetics of individuals

The structure of DEB theory is such that there is a smooth merging and splitting of reserves and structures, which is a key feature in response to evolutionary changes in acquisition strategies [50, 52, 53, 56, 60, 105]. It is possible to smoothly convert one DEB model into another, according to an evolutionary scenario which makes DEB species-specific models consistent with an evolutionary scenario (criterion 5 - table I). This includes organisms that evolved from the merging of ancestors such as the mitochondria and chloroplasts that once had an independent existence, and many of the symbioses (e.g. corals) that exist today.

In an attempt to be explicit on consistency with empirical observations (criterion 2 - table I), we organised generally observed patterns in empirical data on various aspects of energetics, life-stages and stoichiometry in Tables II and III, [96]. DEB theory has an explanation for each of them. Many empirical models, such as Droop's model for the nutrient limited growth of algae and Huggett and Widdas' model for foetal growth, are special cases of DEB theory (see Table IV). The large collection of empirical support for all these findings that accumulated in the literature and the bits of evidence that people working with DEB accumulated during the 30 years of DEB research makes DEB theory presently the best tested quantitative theory in biology[52].

The pragmatic application of Occam's razor (criterion 4 - table I) in the construction of DEB

theory privileged the smallest (possible) number of state-variables, the smallest (possible) number of parameters, constant functions instead of linear and linear functions instead of non-linear. For example, the variable stoichiometry of organisms, exposed to different food levels, is explained, in the DEB standard model, by describing biomass as two aggregated chemical compounds with constant chemical compositions and variable relative amounts.

Biomass is assumed to consist of one or more reserves and one or more structures. The dynamics of these metabolic pools is followed using five concepts of homeostasis, which are all meant for simplification and enhancing the testability of model predictions. The various forms of homeostasis are linked to the principle (criterion 1 - table I) that organisms have increased their control over metabolism during evolution allowing for some adaptation to environmental changes in short periods.

Strong homeostasis: metabolic pools do not change in composition and can be conceived as generalized compounds, i.e. mixtures of a large number of compounds of constant chemical composition and thermodynamic properties. The individual feeds on substrate (food, X) and produces products (faeces, water, carbon dioxide, ammonia, etc), biomass (reserve E and structure V) and gametes (reserve allocated to reproduction). The standard DEB model (but not DEB models in general) assumes a fixed chemical composition for food. All (generalised) compounds have constant thermodynamic properties, such as mass-energy couplers (chemical potentials) and mass-entropy couplers (specific entropies). Strong homeostasis imposes constant conversion coefficients on all aggregated chemical reactions occurring in the organism including assimilation, dissipation and growth, which comes with stoichiometric constraints. The combination of stoichiometric constraints and variations in the composition of biomass (reserve/structure ratio) leads to rather complex patterns at the various levels of organisation.

Weak homeostasis: the individual as a whole does not change in composition during growth in environments with constant food availability (possibly after an adaptation period). The composition (controled by the ratio of reserve to structure) varies with the level of food availability. This implies constraints on the dynamics of reserve relative to structure.

Structural homeostasis: the individual does not change shape during growth, which controls how surface area relates to volume as they change in time. This simplifies the control of

metabolism since some processes are proportional to surface area while others are proportional to volume. Transport processes, including food uptake, uptake and elimination of toxicants, osmosis and heat transfer, are proportional to surface area which is compatible with the description of these processes in non-equilibrium thermodynamics (criterion 1 - table I). In contrast, most maintenance costs are linked to (structural) mass (turnover), so to volume. The scaling of feeding relative to maintenance controls ultimate body size. Only the standard DEB model makes use of structural homeostasis, not the wider class of uni- and multi-variate DEB models.

Acquisition homeostasis: the individual eats what it needs (demand systems), rather than what is available (supply systems). Species can be ranked on the supply-demand spectrum; no species can follow the demand rules into the extreme (food must obviously be available at some minimum level). All demand systems are animals which have typically a higher behavioural flexibility and a lower metabolic flexibility. Demand systems evolved from supply systems and most are endothermic.

Thermal homeostasis: the individual (endotherms, mainly birds and mammals) heats the body to a constant temperature. This behaviour has an energetic cost, that might be significant under particular conditions, but it allows these species a higher independence over the environment since all metabolic rates depend on temperature.

The state variables of DEB theory are the structure(s), the reserve(s) and the level of maturity. The level of maturity controls life stage transitions that cover the full life cycle of the organism (criterion 3 - table I).

Consistency with the evolutionary principle (criterion 1 - table I) that organisms inherit parents' characteristics in a sloppy way allowing for some adaptation to environmental changes across generations makes the set of parameter values in DEB individual-specific. Selection leads to evolution characterized by a change in the species' parameters (mean) values. The differences between the mean parameters values of different species are an evolutionary amplification of the differences between the parameters values of individuals.

Parameters of the standard DEB model can be classified into two classes: size independent parameters which only depend on the very local physico-chemical sub-organismal (cell) conditions (but not on body size) and design parameters which depend on the maximum size of the individual. Size independent parameters are assumed to be constant across species because cells

are metabolically similar, regardless of the species or body size (see table III) which is consistent with Occam's razor (criterion 4 - table I) and evolution (criterion 1 - table I). The DEB body size scaling relationships predict how these parameter values change as a function of the maximum size of the species [52, 96].

The first focus of DEB theory is the individual level, but it has many implications for the sub- and supra-organismic levels [49, 52, 58, 75]. There is a direct coupling of sub-organismal processes to the individual level. For instance, hormonal regulation might stimulate growth and reproduction in particular situations, but it will not occur if substrate is not available. This testifies that our understanding of regulation processes must come from a multi-level analysis. There is also a direct coupling of the individual to the supra-individual level. For instance, the processes of food selection, feeding and product formation at the individual level directly link to interaction between individuals and species, in terms of competition, predation and syntrophy. These are key processes at the population level.

II. METABOLIC ORGANIZATION IN THE STANDARD DEB MODEL

We here present the DEB standard model that will be used as a departure point for the papers published in this volume. This model considers an isomorphic individual (structural homeostasis), which might be a flea or a whale that feeds on a single type of food (substrate). Other substrates (such as dioxygen) are assumed to be non-limiting. The standard model is assumed to be appropriate for most animals. Univariate DEB models allow for variations in shape during development, as an extension of the standard model. Multivariate DEB models account for several food types, several reserves (to allow for more metabolic flexibility, e.g., bacteria and phototrophs such as microalgae) and several structures (such as roots and shoots of plants, or body parts (organs)), see [52]. Figure 1 summarizes the standard DEB model while Tables VI, VII and V summarize the notation.

Table VI lists the state variables of the standard DEB model; we here use time (T), length (L), mass (M) and energy (E) to present the standard DEB model. Mass can be quantified in gram (which allows for changes in chemical composition) or C-moles (which does not allow for changes in composition); we here use the latter quantification. Strong homeostasis allows for simple relationships between quantification in volume, mass and energy because specific densities, molecular weights and chemical potentials, are constant for all compounds. The length-description

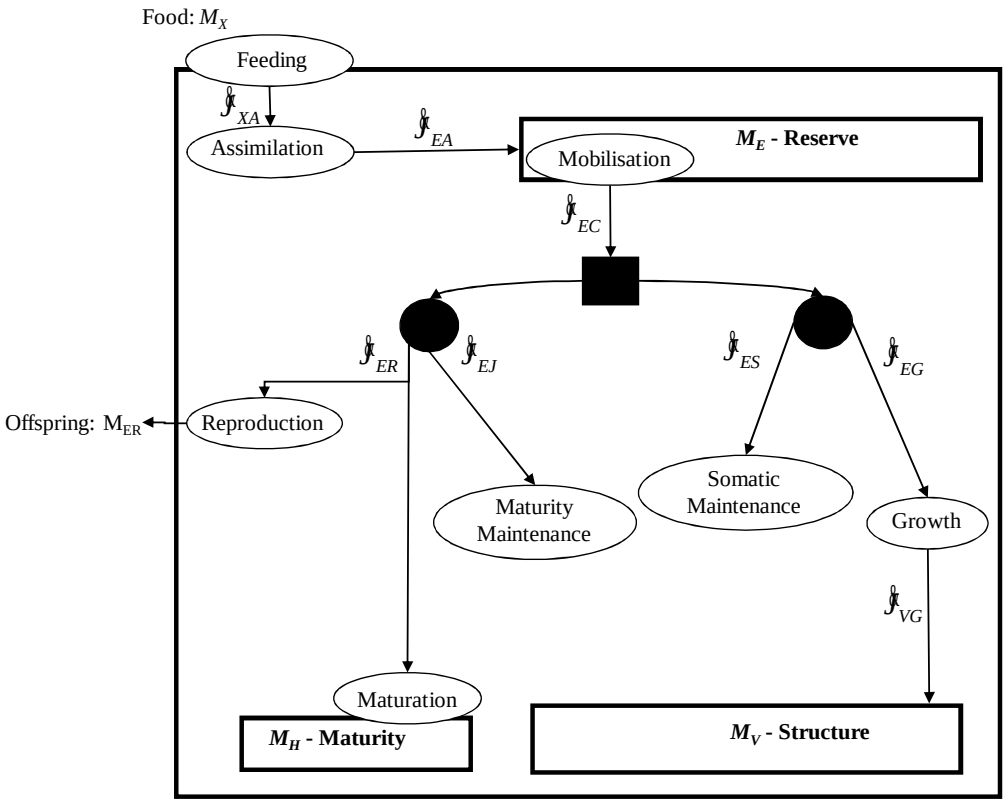

FIG. 1: Metabolism in a DEB individual. Circles are processes and rectangles are state variables. Arrows are flows of food $\dot{J}_{XA}$, reserve $\dot{J}_{EA}$, $\dot{J}_{EC}$, $\dot{J}_{EM}$, $\dot{J}_{ET}$, $\dot{J}_{EG}$, $\dot{J}_{ER}$, $\dot{J}_{EJ}$ or structure $\dot{J}_{VG}$. The full square is a fixed allocation rule (the κ rule) and the full circles are priority allocation rules.

allows us to deal with shape of the structure. The basic variable is volumetric structural length L, i.e. the cubic root of structural volume. We need surface areas L^2 for food uptake and volumes $V = L^3$ for maintenance; we treat the volume-specific structural mass $[M_V] \equiv M_V/V$ as a constant (strong homeostasis). The mass-description allow us to deal with mass conservation, the energy-description with energy conservation and the entropy description (not presented in table VI) with irreversibilities [97]. Entropy balances can only be made when energy balances are known, which in their turn can only be made when mass balances are known.

The total biomass of the individual (in C-moles) has contributions from reserve, structure and the reproduction buffer: $M_E + M_V + M_{ER}$. Maturity has no mass or energy, it is information that reflects the level of metabolic learning; stage transitions (from embryo to juvenile to adult) occur when maturity exceeds threshold values. We quantify maturity as cumulated mass of reserve

invested in maturity, but this invested mass dissipates into the environment as products (carbon dioxide, water, ammonia, heat).

None of the state variables can be measured directly, only indirectly (a problem known as hidden variables). This complicates the practical testability, and necessitates the development of auxiliary theory apart from core theory (that deals with mechanisms) to link measurements to model predictions [59]. The solution of the problem of hidden variables is that a set of measured variables is linked to a set of hidden variables. This involves the estimation of a set of parameters from several data sets simultaneously, simulating the development of appropriate statistical theory for such more advanced applications. The software package DEBtool (http://www.bio.vu.nl/thb/deb/deblab) is developed specifically for this purpose. The auxiliary theory exploits the strong homeostasis assumption that is also used by the core theory, together with the rule that a well-chosen physical length measure L_f (e.g. the head-body length excluding a tail) is proportional to the volumetric structural length L, i.e. the cubic root for structural volume: $L = \delta_{\mathcal{M}} L_f$, where $\delta_{\mathcal{M}}$ is the constant shape coefficient, see [59].

Fig. 1 presents an overview of the various processes that are delineated by the standard DEB model. In our description of the various processes below, we assume that temperature is constant. In the standard DEB model all rates depend on temperature in the same way to avoid that conversion efficiencies (from food to reserve, structure, offspring, products) become temperature dependent; multiple-reserve systems are more flexible in this respect.

Reserve dynamics drives metabolism

The core of DEB theory is that metabolism is fuelled by the mobilisation of reserve $\dot{J}_{EC}$ during all life stages (embryo, juvenile and adult); reserve being replenished by assimilation $\dot{J}_{EA}$ after the maturity threshold for birth has been passed,

$$\frac{dM_E}{dt} = \dot{J}_{EA} - \dot{J}_{EC}, \tag{1}$$

with $\dot{J}_{EA} = 0$ for embryos (they do not feed), i.e., maturity $M_H < M_H^b$. This not only explains why embryos can grow (i.e. increase structure) without feeding, but also why starving individuals can for some time survive and pay maintenance costs without dying [96].

The flux of mobilised reserve equals the sum of all metabolic activities, excluding feeding (and

assimilation)

$$\dot{J}_{EC} = \dot{J}_{ES} + \dot{J}_{EG} + \dot{J}_{EJ} + \dot{J}_{ER} \tag{2}$$

i.e. somatic (S) and maturity maintenance (J), maturation (or reproduction, R) and growth (G).

In combination with the constraint that mobilisation only depends on the amounts of reserve and structure, weak homeostasis implies that the mobilisation rate is (see [96])

$$\dot{J}_{EC} = M_E \left(\frac{\dot{v}}{L} - \dot{r} \right) \tag{3}$$

where specific growth rate $\dot{r} = \frac{1}{V}\frac{dV}{dt}$ and structural length L can vary (see Eq. 10), but energy conductance $\dot{v}$ is constant. The residence time of 'molecules' in the reserve is $t_E = M_E/\dot{J}_{EC}$, so the energy conductance for a fully-grown individual ($\dot{r} = 0$ at $L = L_\infty$) equals $\dot{v} = L_\infty/t_E$. This relationship provides a simple interpretation of energy conductance as a parameter. The independence of the reserve dynamics of food availability provides the individual with some protection against environmental fluctuations and some control over its own metabolism; $\dot{J}_{EA}$ typically varies wildly, but $\dot{J}_{EC}$ always varies slowly.

With the combination of Eq. 1 and 3 and the definition of surface specific maximum assimilation rate $\dot{J}_{EA} = \{\dot{J}_{EA}\}V^{2/3}$, the dynamics of the reserve density $m_E = M_E/M_V$ amounts to:

$$\frac{dm_E}{dt} = \frac{1}{M_V}\frac{dM_E}{dt} - \dot{r}m_E = \frac{\dot{v}}{L}\left(\frac{\{\dot{J}_{EA}\}}{\dot{v}[M_V]} - m_E \right). \tag{4}$$

which is independent of the specific growth rate $\dot{r}$. If assimilation is at the maximum $\{\dot{J}_{EA}\} = \{\dot{J}_{EAm}\}$ then the reserve density m_E goes to a maximum value. This

$$m_{Em} = \frac{\{\dot{J}_{EAm}\}}{\dot{v}[M_V]} \tag{5}$$

is independent of the organism body size; only the embryo can exceed this maximum, because it obtained its reserve from the mother.

It turns out to be convenient to introduce the scaled reserve density $e = m_E/m_{Em}$; this dimensionless quantity varies between 0 and 1.

Feeding and assimilation

Embryos do not feed; only juveniles and adults. Feeding only depends on substrate (food) density and amount of structure, not partaking in the other metabolic interactions. The heat increment

of feeding suggests that there are processes associated with food processing only, i.e., that food goes through a set of chemical reactions that transform it into reserves [96]. This is the assimilation process that is characterized by a yield coefficient y_{EX} of reserve on food that is assumed to be constant (for a given type of food) due to the strong homeostasis assumption.

Food uptake $\dot{J}_{XA}$ at food density X is linked to assimilation $\dot{J}_{EA}$ as

$$\dot{J}_{XA} = \frac{\dot{J}_{EA}}{y_{EX}} = f(X)\frac{\dot{J}_{EAm}}{y_{EX}} \quad \text{with } \dot{J}_{EAm} = \{\dot{J}_{EAm}\}V^{2/3} \tag{6}$$

where the scaled functional response $f(X) = \frac{X}{X+K}$ is a monotonous increasing function of food density X with $0 \leq f(X) \leq 1$, with half saturation constant $K = \{\dot{J}_{XAm}\}/\{\dot{F}_m\}$, where $\{\dot{F}_m\}$ is the maximum specific searching rate. The scaled functional response f results from the idea that the individual behaves as a Synthesising Unit (SU) [47] with two sequential behavioural modes: searching and handling (including digestion and other metabolic work). Many extensions of this idea have been proposed. The original formulation of the behaviour SUs is stochastic but the standard DEB model only uses the mean feeding rate.

The maximum surface-specific assimilation rate $\{\dot{J}_{EAm}\}$ is assumed to be constant, which is explained by the fact that digestion and other food processing activities depend on mass transport processes that occur through surfaces.

At constant food density, the reserve density evolves to $m_E^* = f\frac{\{\dot{J}_{EAm}\}}{[M_V]\dot{v}} \equiv f m_{Em}$ (see Eq. 5), which is independent of size and proportional to the scaled functional response. The scaled reserve density $e = m_E/m_{Em}$ equals the scaled functional response f in equilibrium.

Allocation

DEB's κ-rule for the allocation of mobilised reserve states that there is a constant fraction κ, with $0 \leq \kappa \leq 1$, of mobilised reserve that is allocated to the soma (somatic maintenance and growth), i.e.,

$$\dot{J}_{ES} + \dot{J}_{EG} = \kappa \dot{J}_{EC} \quad \text{and} \quad \dot{J}_{EJ} + \dot{J}_{ER} = (1-\kappa)\dot{J}_{EC}. \tag{7}$$

Somatic maintenance has priority over growth (i.e. increase in structure) and maturity maintenance has priority over maturation or reproduction. The ultimate size an individual can reach directly results from the competition between somatic maintenance and growth. Reproduction and growth do not compete directly with each other, which explains why they can occur simultaneously, as listed in the stylised empirical facts in Table II.

Static and dynamic generalisations of the κ-rule allow for the accurate description of the growth of body parts (including tumours), and the relationship with energetics. In particular fields, such as in fisheries research, it is standard to let growth directly compete with reproduction dynamically. This can be done by allowing κ to be a function of structure. The partitionability requirement for reserve dynamics (which is implied by weak homeostasis) allows this dependence [48, 96]. However, the dependence of κ on structure makes κ a design parameter implying that the maximum surface area specific assimilation rate can no longer be proportional to maximum length [96]. The consequence is that scaling relationships such as the interspecific Kleiber's Law would be lost as implied properties of the model. Moreover, if κ would depend on size, the von Bertalanffy growth curve no longer applies at constant food density. This empirical evidence together with the fact that the inverse von Bertalanffy growth rate increases linearly in the ultimate length (see Table II) is strong support of the assumption that κ is generally constant.

Somatic and maturity maintenance

The need to allocate energy to maintenance is intimately related with the second law of thermodynamics because the level of maturity, i.e., complexity of the organism, would decrease in the absence of energy spent on its maintenance.

Somatic maintenance is the use of reserve to fuel the set of processes that keep the organism alive, where $\dot{J}_{EM}$ and $\dot{J}_{ET}$ are the reserve flows allocated to volume, e.g., protein turnover, and to surface maintenance costs, e.g., heating in endotherms:

$$\dot{J}_{ES} = \dot{J}_{EM} + \dot{J}_{ET} = [\dot{J}_{EM}]L^3 + \{\dot{J}_{ET}\}L^2 \tag{8}$$

The volume-specific somatic maintenance costs $[\dot{J}_{EM}]$ are assumed to be constant; the turnover of structure comprises a big proportion of these costs, but they also include activity, for instance. The surface-specific somatic maintenance costs $\{\dot{J}_{ET}\}$ are only positive for particular taxa (endotherms and osmotic work for freshwater species). It is convenient to introduce the heating length $L_T = \{\dot{J}_{ET}\}/[\dot{J}_{EM}]$. This turns out to be the reduction in ultimate length due to surface-linked somatic maintenance.

Ultimate length L_∞ (when $\dot{r} = 0$) follows from the balance between assimilation and maintenance and does not depend on growth. Growth ceases if $\kappa \dot{J}_{EC} = \dot{J}_{ES}$ (cf Eq. 7). Using Eq. 3 and 5, the result is $L_\infty = fL_m - L_T$ with maximum length $L_m = \kappa\{\dot{J}_{EAm}\}/[\dot{J}_{EM}]$.

Reserve is assumed to require no maintenance, as empirically supported by the fact that freshly produced eggs almost exclusively consist of reserve and hardly respire (see [96] for a detailed explanation). Reserves do not need turnover; they have a limited residence time due to assimilation and mobilisation. In fully grown individuals the residence time amounts to $t_E = L_\infty/\dot{v}$, but it is shorter in smaller individuals. This explains why babies need to feed more frequently than adults.

Maturity maintenance is the use of reserve to maintain the complexity of the structure where $\dot{J}_{EJ}$ is the reserve flow allocated to this process and $\dot{k}_J$ is the maturity maintenance rate coefficient:

$$\dot{J}_{EJ} = \dot{k}_J M_H. \tag{9}$$

The $\dot{J}_{EJ}$ is constant in adults since for them maturity is constant, $M_H = M_H^p$.

Growth

Growth is the increase of structure; the specific growth rate $\dot{r}$ follows from the reserve dynamics (Eq. 3), the κ-rule (Eq. 7) and the somatic maintenance costs (Eq. 8). The result is

$$\frac{dM_V}{dt} = \dot{J}_{VG} = \dot{J}_{EG}\, y_{VE} = \dot{r} M_V \quad \text{with} \quad \dot{r} = \dot{v}\frac{e/L - (1 + L_T/L)/L_m}{e + g} \tag{10}$$

where $\dot{J}_{EG}$ is the mobilised reserve allocated to growth and y_{VE} is the yield of structure on reserve. Maximum length L_m, heating length L_T, investment ratio g are all given in Table VII. Now the specific growth rate $\dot{r}$ is specified, the mobilisation rate $\dot{J}_{EC}$ in Eq. 3 is specified as well, so is the residence time t_E of 'molecules' in the reserve during ontogeny.

For any constant food level the scaled reserve density e settles at the level of the scaled functional response $e = f$ and the dynamics of structural length $L = V^{1/3} = (M_V/[M_V])^{1/3}$ simplifies to von Bertalanffy growth for juveniles and adults:

$$\frac{dL}{dt} = \dot{r}_B(L_\infty - L) \quad \text{with } \dot{r}_B = \frac{\dot{k}_M/3}{1 + e/g} = \frac{1}{3/\dot{k}_M + 3fL_m/\dot{v}} \tag{11}$$

where the somatic maintenance rate coefficient $\dot{k}_M$ is given in Table VII. The inverse of the von Bertalanffy growth rate $\dot{r}_B$ is thus linearly increasing with ultimate length, as listed in the stylised empirical facts in Table II.

If allocation of reserve to soma is not sufficient to pay the somatic maintenance costs, structure can shrink:

$$\frac{d}{dt}M_V = -\dot{J}_{VS}\left(1 - \frac{\min(\dot{J}_{ES}, \dot{J}_{EC})}{\dot{J}_{ES}}\right) \quad \text{with } \dot{J}_{VS} = [\dot{J}_{VM}]L^3 + \{\dot{J}_{VT}\}L^2 \tag{12}$$

where the somatic maintenance costs $\dot{J}_{VS}$, if paid from structure, have the same set-up as those paid from reserve (see Eq. 8). A natural simplification is to assume that $\frac{[\dot{J}_{VM}]}{[\dot{J}_{EM}]} = \frac{\{\dot{J}_{VT}\}}{\{\dot{J}_{ET}\}}$, but this ratio should be larger than one for thermodynamic reasons. Death by starvation occurs if structure, relative to the maximum the individual once had, decreases below a minimum. This minimum fraction is for supply systems typically smaller than for demand systems, but even for demand systems, empirical support for shrinking exists [25]. Most species seem to avoid shrinking, e.g. by using the reproduction buffer to cover the somatic maintenance costs.

In extreme cases species can sport suicide reproduction, and convert part of their structure to gametes before dying.

Maturation and reproduction and initial state of the individual

Maturation is the use of reserve $\dot{J}_{ER}$ to increase the level of maturity, M_H. This level controls qualitative changes in metabolism (life-stage events). The initiation of feeding occurs at birth when $M_H = M_H^b$. The initiation of allocation to reproduction occurs at puberty when $M_H = M_H^p$; it is coupled to the ceasing of maturation. Other life history events, such as cell division, metamorphosis or other stage transitions (e.g. to the pupal stage) occur also at threshold values for M_H.

Multicellular organisms typically have three life stages: embryo, juvenile, adult. At the start of development, age a is set to zero, structure M_V and maturity M_H are zero, $M_V^0 = 0$ and $M_H^0 = 0$, and the initial amount of reserve M_E^0 is such that the reserve density m_E at birth equals that of the mother at egg formation; the maternal effect as listed in the stylised empirical facts in Table II. This fully specifies M_E^0; for an efficient algorithm to obtain M_E^0, see [51]. Dividing unicellulars are treated as juveniles; division of maturity follows that of structure and division occurs if maturation exceeds a threshold.

The allocation to maturity (in embryos and juveniles) or reproduction (in adults) is

$$\dot{J}_{ER} = (1-\kappa)\dot{J}_{EC} - \dot{k}_J M_H \tag{13}$$

The change in maturity (in embryos and juveniles) is given by

$$\frac{d}{dt}M_H = \dot{J}_{ER}\frac{\dot{k}'_J}{\dot{k}_J} \quad \text{if} \quad M_H < M_H^p \tag{14}$$

where $\dot{k}'_J = \dot{k}_J$ if $\dot{J}_{ER} > 0$, but for shrinking maturity (rejuvenation), it is a free constant parameter. Empirical evidence for rejuvenation induced by starvation is presented in [103]. The hazard

rate due to starvation is proportional to the difference between the maximum maturity level that the individual has reached and the actual level.

The reproduction buffer fills at rate $\dot{J}_{ER}$ for $M_H = M_H^p$. The details of the conversion of the reproduction buffer of females to a number of eggs is rather species-specific, typically including requirements on temperature and filling of the buffer; the conversion of the reproduction buffer of males to sperm is typically linked to female reproductive behaviour. The simplest buffer handling rule is to produce an egg as soon as the reproduction buffer allows; this rule involves no new parameters. The conversion of the content of the reproduction buffer to one or more eggs involves an overhead cost of the reproduction process, i.e. a fraction $(1 - \kappa_R)$ of the converted buffer (and so of the reserve allocated to reproduction $\dot{J}_{ER}$) dissipates, and a fraction κ_R is fixed into eggs. The cost per egg equals the initial amount of reserve M_E^0.

The reproduction rate in terms of numbers of eggs per time, is a delta function of time. Ignoring the effect of the reproduction buffer, and treating reproduction as a continuous process, the reproduction rate would amount to $\dot{R} = \kappa_R \dot{J}_{ER}/M_E^0$.

Foetal development is a variation on egg production, where the mother does not fill a reproduction buffer, but directly adds to the reserve of the foetus, bypassing its digestive system. This process can, therefore, not be seen as a feeding process from the foetal perspective.

Three organising fluxes in metabolism

An implication of strong homeostasis is that the different types of aggregated chemical reactions occurring in the organism have constant stoichiometries. These reactions are assimilation ($X \rightarrow E + P$), growth ($E \rightarrow V + P$) and dissipation ($E \rightarrow P$), where dissipation is defined as:

$$\dot{J}_{ED} = \dot{J}_{ES} + \dot{J}_{EJ} + (1 - \kappa_R)\dot{J}_{ER}, \tag{15}$$

and $\kappa_R = 0$ for the embryo and juvenile stages. Thus, metabolic transformation has 3 degrees of freedom; the flow of any compound (e.g. dioxygen), produced or consumed, in the organism is a weighted sum of these three organising flows. The method of indirect calorimetry (see Table III) is a particular case: the flow of heat is a weighted average of the fluxes of carbon dioxide, dioxygen and nitrogenous waste. Since, reserve is key to the ability to delineate these three fluxes (without reserve we would have two), the empirical success of the method of indirect calorimetry gives strong support to the topology of the standard DEB model.

Ageing

The hazard rate $\dot{h}$, i.e., the probability of dying, due to ageing, is taken to be proportional to the density of damage compounds (e.g. modified proteins):

$$\frac{d}{dt}\dot{h} = \ddot{q} - \dot{r}\dot{h}, \tag{16}$$

where $\dot{r}\dot{h}$ is the dilution by growth and $\ddot{q}$ the change in ageing acceleration which is proportional to the density of damage inducing compounds (e.g. changed mitochondrial DNA). Damage compounds are generated by damage inducing compounds at a rate proportional to the metabolic activity measured by the reserve mobilisation rate (see Eq. 3). The production of damage inducing compounds is again taken to be proportional to the reserve mobilisation rate (as quantifier for the respiration rate, excluding contributions from assimilation, which are supposed to have local effects only).

The change in ageing acceleration is given by

$$\frac{d}{dt}\ddot{q} = (\ddot{q}\frac{L^3}{L_m^3}s_G + \ddot{h}_a)e(\frac{\dot{v}}{L} - \dot{r}) - \dot{r}\ddot{q} \tag{17}$$

where $\dot{r}\ddot{q}$ is the dilution by growth and the factor $e(\frac{\dot{v}}{L} - \dot{r})$ is proportional to the mobilisation rate; cf Eq. 3. The proportionality factor $(\ddot{q}\frac{L^3}{L_m^3}s_G + \ddot{h}_a)$ increases linearly with $\ddot{q}$ because damage inducing compounds promote their own production. This expression involves two new parameters, the Weibull ageing acceleration $\ddot{h}_a$ and the Gompertz stress coefficient s_G. The latter parameter is close to zero for most ectotherms, but for endotherms it is typically positive. It can be shown that if the growth period is short relative to the life span, both the Weibull and the Gompertz ageing models result, see Table IV. For further details on ageing see van Leeuwen et al. [64].

Parameters

Each individual is characterized in DEB theory by a set of primary parameters: the surface-area specific searching rate (feeding) $\{\dot{F}_m\}$, the surface-area specific maximum assimilation rate (assimilation) $\{\dot{J}_{EAm}\}$, the yield of reserve on food (digestion) y_{EX} and of structure on reserve (growth) y_{VE}, the energy conductance (mobilisation of reserve) $\dot{v}$, surface and volume specific somatic maintenance costs $\{\dot{J}_{ET}\}$ and $[\dot{J}_{EM}]$, the specific maturity maintenance $\dot{k}_J$, the fraction of mobilised reserve allocated to soma κ, the reproduction efficiency κ_R, the maturity threshold levels

that trigger the onset of feeding and reproduction M_H^b and M_H^p, the Weibull ageing acceleration $\ddot{h}_a$ and the Gompertz stress coefficient s_G. This amounts to 14 primary parameters including the two ageing parameters and excluding parameters for species-specific handling rules for the reproduction buffer. The details of death by starvation involve another 4 parameters; these can be avoided by letting the individual die upon shrinking or starvation induced rejuvenation. One can argue about the status of the mass-volume coupler $[M_V]$; this parameter relates measurements with no impact on processes.

The standard DEB model is meant to be the simplest in the DEB-family that still has all essential features, a canonical form. Many applications need extensions of various types; the specification of respiration, for instance, requires the elemental composition of various compounds (food, faeces, reserve, structure). We agree with Nisbet and McCauley [74] that some other applications, such as in population and ecosystem dynamics, require simplifications.

Most applications allow setting $\kappa_R = 1$ and $\dot{k}_J = \dot{k}_M$; the latter equality implies that maturity density, M_H/M_V, remains constant and metabolic switches occur at fixed amounts of structure. This means that the maturity thresholds can be replaced by structure thresholds and maturity can be avoided as state variable. If reproduction occurs with one offspring at a time, the reproduction buffer can be avoided as state variable. If investment in heating (or osmosis) is small, we have $\{\dot{J}_{ET}\} = 0$ and $s_G = 0$. Ageing is not always an important cause of death in field situations; the ageing acceleration and the hazard rate can be avoided as state variables under those conditions, and the two ageing parameters are lost. All simplifications together reduce the standard DEB model to 2 state variables (reserve and structure) and 9 parameters, while it still covers a full specification of feeding, digestion, maintenance, development, growth and reproduction over the full life cycle of the individual. This amounts to 9/6 = 1.5 parameter per process; we think a remarkable simplicity. Typical applications involve only a subset of these parameters because they do not involve all processes.

Co-variation of parameter values

A rough estimation of DEB parameters for each species can be made with the scaling relationships, i.e., based only on the species maximum size and a reference species; the accuracy of this estimation increases with the similarity between the species. The design parameters are $\{\dot{J}_{EAm}\}$ and $\ddot{h}_a$, which scale with maximum length, M_H^b and M_H^p, which scale with maximum volume. All

the other primary parameters are independent of size, so also independent of the maximum size of a species. The body-size scaling relationships can also be used partially, making optimal use of all data at hand [52, 59] to detect species-specific deviations from the general trend.

These rules also determine how properties that can be written as functions of the primary parameters depend on maximum length. An example is the respiration rate (i.e. the use of dioxygen). It works out to be approximately proportional to weight to the power 3/4, both inter- and intra-specifically (see the list of stylised facts in Table II), but for very different reasons. The weight-specific respiration rate decreases intra-specifically because growth decreases (and so the contribution of the overhead costs of growth to respiration); it decreases inter-specifically in fully grown adults because reserve density increases with the maximum size of a species and somatic maintenance is only paid for structure. The explanation offered by DEB theory also allows to understand taxon-specific variations in the scaling of respiration, since quite a few parameters contribute to the result and evolutionary adaptations cause deviations of parameters from the mean pattern. Many alternative attempts to explain the scaling of respiration fail to distinguish between intra- and inter-specific comparisons, probably due to the similarity of the numerical behaviour.

Many scaling relationships work out differently for intra- and inter-specific comparisons. Feeding scales with surface intra-specifically, but with volume inter-specifically, while maximum reproduction increases with size intra-specifically but decreases with size inter-specifically.

The remarkable prediction for life span is that it scales with length if the Gompertz stress coefficient is positive (as expected for endotherms), but life span hardly scales with length if it is zero (as expected for ectotherms) which is consistent with empirical data (see table II).

III. CORNERSTONES OF (RESEARCH IN) DEB THEORY

The sub-individual level

The links that DEB theory establishes between the sub- and supra-individual levels give the theory a high explanatory power. This characteristic together with the high amount of throughput data becoming available at the sub-individual level allowed the use, test and development of DEB models at this organization level [64, 77, 109].

Vinga et al. [109] use DEB theory for a top-down approach to understand the dynamic behaviour of metabolites. The consistency with the individual level in the DEB context poses con-

straints on the sub-organismal organisation such as the size of the reserve fluxes that are associated with assimilation, dissipation and growth: $\dot{J}_{EA}$, $\dot{J}_{ED}$ and $\dot{J}_{EG}$. This translates into constraints on the overall amount of each aggregated chemical compound and the rates of aggregated chemical reactions. Vinga et al. compare the DEB approach with the Biochemical Systems Theory (BST) in modeling in vivo data of lactic acid bacteria under various conditions. In contrast with DEB theory, BST is a bottom-up approach that models each chemical compound and each chemical reaction explicitly. The complementarity between the two approaches might bring new ideas and insights to unsolved problems such as the mechanisms underlying gene expression or the mechanisms underlying ageing [64].

Pecquerie et al. [77] develop DEB theory further to provide a framework for stable isotope dynamics. The fundamental processes of the standard DEB model - assimilation, dissipation and growth - are further detailed into their anabolic and catabolic transformations to account for the mass balance of stable isotopes. Isotope dynamics reveals features that remain hidden in aggregate mass dynamics: the turnover rate of structure. This turnover process has a catabolic as well as an anabolic component. Since turnover has a substantial contribution to somatic maintenance, it is also of importance to energetics. This DEB module on isotope dynamics will allow for the correct interpretation of the increasing amount of data becoming available on isotope ratios contributing to the identification of trophic web structures, the reconstruction of individual life histories, and the tracking of the flow of elemental matter through ecosystems.

Leeuwen et al. [64] review the DEB-based approaches to ageing and link them to current research at the molecular/cellular level. The authors link alternative ageing DEB-based modelling approaches with different cellular senescence processes. This is a first step towards a fundamental understanding of the link between mechanisms of cellular senescence and the individual level.

The individual level

DEB theory allows for a mass, energy and entropy description of all fluxes. This set-up is most useful to study the internal concentration of specific compounds such as isotopes [77], reactive oxygen species [64] and toxicants [39, 110] that affect the performance of organisms. The mode of action of a compounds is, in the context of DEB theory, defined by the parameters that are affected. When the internal concentration increases, more and more parameters become affected, but at a sufficiently low concentration only a single parameter is affected, but the consequences

might be complex, involving feeding, growth and reproduction. For example, an increase in the specific maintenance rate, $[\dot{J}_{EM}]$, leads directly to a decrease in growth, and ultimately also to a smaller adult that reproduces less. Another toxicant might decrease the efficiency of reproduction, κ_R, which decreases the rate of reproduction [38], but does not affect growth or feeding. Jager and Klok compare several DEB approaches for analysing the toxicity of copper in the earthworm *Dendrobaena octaedra*: the Kooijman-Metz formulation [57] (which has no reserve or maturity), the DEBtox approach [54] (which has no explicit maturity) and the DEB3 approach [52]. Results on mortality and growth rate for the DEBtox and the DEB3 approach were similar. Ducrot et al. use the DEBtox model to assess the toxicity data of diquat on the gastropod *Lymnaea stagnalis*, where they include data on embryo development, making full use of the life-cycle features of DEB theory in variable environments, which is crucial for environmental risk assessment.

The population level

The step from the individual to the population level requires extra rules for the interaction between individuals and for transport of resources in the environment. The simplest interaction rule for the standard DEB model is that individuals only interact via competition. The standard bookkeeping technique to follow the performance of populations as collections of individual are (hyperbolic) partial differential equations (pde's). Diekmann and Metz [11] present a wider mathematical framework that removes some of the shortcomings of pde's in this context. The standard DEB model has some features, however, that still cause mathematical problems including the existence of metabolic events (birth, puberty), the fact that eggs are not infinitesimally small and last but not least, DEB is deterministic (apart from the survival module). Some of these problems can be removed. For example, SU-dynamics (which is used to specify feeding) is stochastic by nature and differences between individuals can be implemented using different parameter values. Including this stochasticity has dramatic effects on population dynamics [55].

Other problems, however, are rather fundamental and call for individual-based approaches or a fully stochastic framework. For example, when feeding on a single resource in homogeneous space, the DEB rules imply that small (young) individuals can rather easily outcompete the large (old) individuals, perhaps to an extend that is not very realistic. There are several DEB solutions to this problem. Nisbet and McCauley [74] consider survival to be maturity-dependent; with this feature they have been able to understand the occurrence of daphnid population oscillations under

particular conditions, using a reduced version of the DEB individual dynamics. They beautifully illustrate that not all details are important under all conditions; if food density is rather constant and different food levels are not compared, reserve and maturity typically play a minor role. Kearney et al. [42], on the contrary, consider that food quality required by the individual depends on size. Large individuals mainly have to cover their maintenance cost (reproduction is low at the carrying capacity, where competition is strongest), which represents work that can be covered by carbohydrates and lipids. Small individuals, however, need to grow; so they need a protein-rich resource.

The step from the individual to the population levels can be done using a variety of schemes, all with there own benefits and problems. Jager and Klok [39] use DEB-structured individuals in matrix and continuous Euler-Lotka population models to extrapolate toxic effects from individuals to populations. Kooi and van der Meer [46] use a physiological structured population to model the dynamics of a population in a semi-chemostat environment where reproduction is a discrete event process. In the case of organisms that reproduce by division, the transition from the individual to the population is simpler, because organisms can be considered as V1-morphs, i.e. individuals that change in shape during growth such that their surface area is proportional to volume. In this case, the population behaves as the individuals lumped together; a population of few big individuals behaves identical to that of many small ones if the sum of their masses match. The individual level completely drops out of the equations. This is the case for the microalgae of Lorena et al. [67] and Poggiale et al. [81], where population performance directly links to sub-cellular physiology.

The ecosystem level

Since DEB theory specifies the interaction between the individual and its environment dynamically, it has no problems with variable environments at all. This volume has a nice collection of examples, where these variations are explicitly used to study the underlying organisation. Ducrot et al. [110] use this feature when analysing the effects of a weed control agent when the concentrations vary in time; they show how DEB-based models can capture observed survival patterns where typical models fail. Lorena et al. [67] model microalgae populations in a chemostat with a variable light regime and study how the biochemical composition of microalgae depends on light. More specifically they discuss the relationship between chlorophyll, biomass and the production of exopolimeric substances; key features in the interpretation of remote sensoring data. Pecquerie

et al. [77] evaluate how variations in isotope concentrations in the environment work out for the organism. They do not make the common assumption that isotope dynamics is at equilibrium, and include the full metabolism in their analysis. Troost et al. [107] adjust DEB individual models for cockles and mussels to a specific site by adjusting the functional response. With this model they detected food preferences in cockles and mussels, inferring about the role of detritus and intra-specific competition under field situations.

Kearney et al. [42] position DEB theory in a wider ecological setting, linking it to the theories of Biophysical Ecology and the Geometric Framework for Nutrition. The combination of these fields stimulates the development of models at their interfaces that can shed more light on the detailed interaction of organisms and their environment. Biophysical Ecology provides a framework for the climatic niche of an organism (distribution limits as constrained by heat and water balances) making use of spatial environmental data while the Geometric Framework for Nutrition provides a way to determine the nutritional niche of an organism (distribution limits as constrained by dietary needs) making use of information on the availability of food. These theories presently make use of allometrically derived static mass and energy budgets. By using DEB theory, these theories can model physiological rates across the life cycle under variable food and climatic environments and establish links between individuals and their functional traits and population. This is an essential step towards the goal of building predictive niche models that can tackle questions such as the impact of climate change on a species distribution.

Synthesizing Units

The kinetics of Synthesizing Units (SUs) [47, 52] is an essential building block for the dynamics of multiple reserve and/or multiple structure organisms. SUs can be conceived as generalized enzymes. Their dynamics is based on classic enzyme kinetics, but with an important modification with far-reaching consequences. Where enzyme-kinetics links the product flux to substrate concentrations, SU-kinetics links it to arrival fluxes of substrate at the enzyme. Concentration is a problematic concept in spatially structured cells and active transport of substrates and products deviates substantially from diffusive transport implied by classic enzyme kinetics. Poggiale et al. [81] interpret the different types of co-limitation in an SU context: the independent nutrient co-limitation (two limiting macro-nutrients) corresponds to the case of parallel complementary substrates, the biogeochemically dependent co-limitation (the ability to acquire a macro-nutrient is

dependent on the supply of a micro-nutrient) corresponds to the case of sequential complementary substrates and the biochemical substitution co-limitation corresponds to the case of substitutable substrates. Poggiale et al. [81] further demonstrate that nutritional details are of importance at the ecosystem level, which illustrates that biology is in great need for coherence across levels of organisation. Lorena et al. [67] use SU-dynamics to model the co-limitation of photosynthesis by light and carbon dioxide and the co-limitation of growth by a carbon and nitrogen reserves. Kearney et al. [42] use SU-dynamics to transform food into separate nutrient reserve pools, and then regulate the assignment of mobilised reserves from each pool into maintenance, structure, maturity maintenance and reproductive output.

Parameters

The generality of DEB theory allows the use of more parsimonious models (fewer parameters) to describe accurately experimental data under different environmental conditions. The DEB model for glycolysis in *Lactococcus lactis* uses much less parameters than a comparable BST model [109], while it better catches the differences between growth under aerobic and anaerobic conditions; also the DEB model for microalgae [67] performed better than other published microalgae models.

DEB rate parameters depend on temperature. Van der Veer et al. [108] compare the temperature tolerance (this is the set of temperatures for which the Arrhenius relationship applies) and temperature sensitivity for a variety of marine species. Their results suggest that the width of the temperature tolerance range increases with the optimal growth temperature. Differences in life history strategies of related species translated nicely in differences in parameter values. High optimal growth temperatures, large tolerance ranges and high sensitivities are linked to low specific assimilation rates and low specific maintenance costs.

Although DEB theory does not use any optimisation argument, it remains thought-provoking to study to what extent parameter values, or life history traits, are optimal, or at least could be seen as an outcome of an evolutionary optimisation process. The theory of adaptive dynamics is ideal for this, because there is no need to specify any explicit optimisation criterion. Moreover it includes interactions between organisms and their environment in a natural way and long-term consequences of changes in traits; the outcome depends on the realism of the ecosystem model. Kooi and van der Meer [46] study the handling rules of the reproduction buffer of *Macoma* under

seasonal forcing. They successfully capture the observed spawning behaviour of this iteroparous species, which spawns once a year in spring, but the timing of the spawning is still off (autumn). Application of adaptive dynamics with seasonal forcing is an impressive tour de force; more research is required to understand why *Macoma* spawns in spring. Moreover, Kooi and van der Meer [46] demonstrate that the techniques that they use are a special case of bifurcation theory [106], which can lead to cross-fertilisation.

Although a lot has been done already, the development of DEB theory has only started. Almost all contributions in this volume illustrate this in different ways. Future developments should include, for instance, extensions into the sub- and supra-individual levels. The behavioural time scale is important for animals and humans in particular; behaviour includes food searching, food selection, sleeping, social interaction, parental care, etc. Quite a few behavioural extensions have already been proposed using SU-dynamics; this needs to be explored more systematically using a further formalization of DEB theory, including multiple reserve and multiple structure systems. Detailed studies in plant biology are painfully lacking, while DEB theory has a lot to offer in this field; DEB models for plants have been proposed [52], but not yet tested against data. Contacts with the molecular levels are slowly getting shape, but, again, a lot of work still needs to be done. This also holds for contacts with the planetary level; the development of DEB-based biogeochemical climate models still needs to take shape [50].

IV. CONCLUDING REMARKS

Given the richness of biodiversity on Earth, general explanatory models have to be lean, capturing taxon-specific phenomena in modules that extend the core that is not taxon-specific. For particular applications (e.g. in ecosystem dynamics) the standard DEB model will be too complex, for other applications (e.g. in medicine and molecular biology) not detailed enough. This directly relates to the time scales of interest. Simplifications as well as extensions should be done, respecting a natural order in time scales, where the standard DEB model deals only with the slowest processes at the individual level. It makes little sense to include very fast processes, while slower processes are not included. Extensions should be consistent with the existing assumptions; many have already been developed.

Balancing realism at a detailed level against simplicity (in terms of numbers of parameters and variables) depends on subjective judgement and context. Although the standard DEB model is

simple relative to the complex biological reality, estimating its parameters on the basis of published data is a challenge. Extensions make this problem worse, not easier, and we believe that obtaining accurate estimates for the primary parameters should generally have priority over extensions. We made a systematic start in the add_my_pet program (http://www.bio.vu.nl/thb/deb/deblab) and hope that the collection extends rapidly and improves in quality. We hope that a new generation of scientists will collect data in the light of DEB theory that allow the accurate estimation of its parameters and further critical testing of the underlying assumptions.

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	Stylized Facts	Empirical Evidence
Feeding	During starvation, organisms are able to reproduce	animals [31, 43, 44]
	During starvation, organisms are able to grow	animals [12, 23, 86, 90, 100, 114]
	During starvation, organisms are able to survive for some time	animals [65, 99] bacteria [63]
Growth	The growth of isomorphic organisms at abundant food is well described by the von Bertalanffy growth curve [2, 82]	animals [7, 18, 22, 89, 92, 101]
	For different constant food levels the inverse von Bertalanffy growth rate increases linearly with ultimate length [82]	animals [24, 33, 102, 112] [52, pp.48]
	Many species do not stop growing after reproduction has started, i.e., they exhibit indeterminate growth [29, 61] Holometabolic insects are an exception	animals [41, 94]
	Fetuses increase in weight approximately proportional to cubed time [34]	animals [34, 115]
	The von Bertalanffy growth rate of different species corrected for a common body temperature decreases almost proportional to maximum body length	bacteria [48, pp.276-282] yeasts [48, pp.276-282] animals [48, pp.276-282]
Reproduction	Reproduction increases with size intra-specifically but decreases with size inter-specifically	animals [52, pp69,323][78]
Respiration	Freshly laid eggs do not use dioxygen in significant amounts	animals [5, 79, 87, 113]
	The use of dioxygen increases with decreasing mass in embryos and increases with mass in juveniles and adults	animals [5, 10, 79, 84, 87, 91, 113]
	The use of dioxygen scales approximately with body weight raised to a power close to 0.75 [45]	animals [10, 84, 91]
	Organisms show a transient increase in metabolic rate after ingesting food (heat increment of feeding)	animals [6, 28, 40, 73, 88]
Ageing	Lifespan increases with size for endotherms, but is independent of size in ectotherms	animals [19, 85]

TABLE II: Stylized facts and empirical evidence on feeding, growth, reproduction, respiration and death.

	Stylized Facts	Empirical Evidence
Stoichiometry	Chemical body composition of well- and poorly-fed organisms differ	animals [8, 16, 31, 70] yeasts [27]
	Chemical body composition of organisms growing at constant food density becomes constant	animals [9, 20, 37, 62, 98]
Energy Dissipation	Dissipating heat is a weighted sum of three mass flows: carbon dioxide, dioxygen and nitrogenous waste	animals [93]
Cells	Cells in a tissue are metabolically very similar regardless the size of the organism [72]	

TABLE III: Stylized facts and empirical evidence on stoichiometry, energy dissipation and cells.

Author	**Year**	**Model**
Lavoisier	1780	multiple regression of heat against mineral fluxes
Gompertz	1825	survival probability for ageing [26]
Arrhenius	1889	temperature dependence of physiological rates
Huxley	1891	allometric growth of body parts [36]
Henri	1902	Michaelis Menten kinetics
Blackman	1905	bilinear functional response [4]
Hill	1910	Hill's functional response [30]
Thornton	1917	heat dissipation [104]
Putter	1920	von Bertalanffy growth of individuals [82]
Pearl	1927	logistic population growth [76]
Fisher and Tippitt	1928	Weibull aging [21]
Kleiber	1932	respiration scales with body weight raised to 3/4
Mayneord	1932	cube root growth of tumours [69]
Monod	1942	growth of bacterial populations [71]
Emerson	1950	cube root growth of bacterial colonies [17]
Huggett and Widdas	1951	foetal growth [34]
Weibull	1951	survival probability for aging [111]
Best	1955	difusion limitation of uptake [3]
Smith	1957	embryonic respiration [95]
Leudeking and Piret	1959	microbial product formation [66]
Holling	1959	hyperbolic functional response [32]
Marr and Pirt	1962	maintenance in yields of biomass [68, 80]
Droop	1973	reserve (cell quota) dynamics [13–15]
Rahn and Ar	1974	water loss in bird eggs [83]
Hungate	1975	digestion [35]
Beer and Anderson	1997	development of salmonid embryos [1]

TABLE IV: Empirical models that turn out to be special cases of DEB models, or very good numerical approximations to them.

	Compound		**Process**
X	Substrate (food)	X	Feeding
E	Reserve	A	Assimilation
V	Structure	C	Mobilisation
P	Products	M	Somatic maintenance (volume related)
M_i	Mineral compound i	T	Somatic maintenance (surface related)
		S	Somatic maintenance (total)
		J	Maturity maintenance
		G	Growth
		R	Reproduction or maturation

TABLE V: List of symbols of compounds and processes.

State Variable	**Dimensions**	**Interpretation**
$M_V = [M_V]V; E_V = \mu_V M_V; V = L^3$	$\#, e, L^3$	Structure
$M_E; E = \mu_E M_E$	$\#, e$	Non-allocated reserve
$M_{ER}; E_{ER} = \mu_E M_{ER}$	$\#, e$	Reserve in reproduction buffer
M_H	$\#$	Cumulated reserve allocated to maturation
$\ddot{q}$	T^{-2}	Ageing acceleration
$\dot{h}$	T^{-1}	Hazard rate

Variable	**Dimensions**	**Interpretation**
t	T	time
X	$\# L^{-3}$	Substrate density
m_E	$\# \#^{-1}$	Reserve density
$e = \frac{m_E}{m_{Em}}$	–	Scaled reserve density
L	L	Volumetric structural length $V^{1/3}$
f	–	Scaled functional response
$\dot{J}_{\theta\phi}$	$\# T^{-1}$	Mass flow associated with process ϕ and compound θ
$\dot{R}$	eggs T^{-1}	Reproduction rate

TABLE VI: List of symbols of variables. Dimensions: – dimensionless; T time; L length; $\#$ mass in moles or C-moles; Symbols with $\{\cdot\}$ are per unit surface area, $[\cdot]$ are per unit of structural volume and dots above are per unit time. $\phi = A, C, S, T, M, J, G, R$ and $\theta = X, E, V$.

Parameter	**Dimensions**	**Interpretation**
$\{\dot{F}_m\}$	$l^3\, L^{-2}\, T^{-1}$	Surface-specific maximum searching rate
$\{\dot{J}_{EAm}\}$	$\#\, L^{-2}\, T^{-1}$	Surface-specific maximum assimilation rate
$[M_{Em}] = \{\dot{J}_{EAm}\}\, \dot{v}^{-1}$	$\#\, L^{-3}$	Maximum reserve density
$m_{Em} = [M_{Em}]\, [M_V]^{-1}$	$\#\, \#^{-1}$	Maximum molar reserve density
$[\dot{J}_{EM}]$, $[\dot{J}_{VM}]$	$\#\, L^{-3}\, T^{-1}$	Volume-specific maintenance rate
$\{\dot{J}_{ET}\}$, $\{\dot{J}_{VT}\} = \{\dot{J}_{ET}\}\frac{[\dot{J}_{VM}]}{[\dot{J}_{EM}]}$	$\#\, L^{-2}\, T^{-1}$	Surface-specific maintenance rate
y_{EX}	$\#\, \#^{-1}$	Yield of reserve on substrate (food)
y_{VE}	$\#\, \#^{-1}$	Yield of structure on reserve
$\dot{v}$	$L\, T^{-1}$	Energy conductance
κ	–	Fraction of mobilised reserve allocated to soma
κ_R	–	Fraction of reserve allocated to reproduction that is fixed in eggs
$g = \frac{\dot{v}[M_V]}{\kappa\{\dot{J}_{EAm}\}y_{VE}}$	–	Investment ratio
$\dot{k}_M = \frac{y_{VE}[\dot{J}_{EM}]}{[M_V]}$	T^{-1}	Somatic maintenance rate coefficient
$\dot{k}_J$, $\dot{k}'_J$	T^{-1}	Maturity maintenance rate coefficient
$L_m = \kappa\frac{\{\dot{J}_{EAm}\}}{[\dot{J}_{EM}]}$	L	Maximum length
$L_T = \frac{\{\dot{J}_{ET}\}}{[\dot{J}_{EM}]}$	L	Heating length
M_H^b	$\#$	Threshold of maturity at birth
M_H^p	$\#$	Threshold of maturity at puberty
M_E^0	$\#$	Initial amount of reserve

TABLE VII: List of parameters. Dimensions: – dimensionless; T time; l environmental length; L structural length; $\#$ moles or C-moles; Symbols with $\{\cdot\}$ are per unit surface area, $[\cdot]$ are per unit of structural volume and dots above are per unit time. Chemical compound and process specifiers appear as subscripts to other variables.