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including and introduction to Ecological Economics"**

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**A CONCEPTUAL INTRODUCTION TO  
DYNAMIC ENERGY BUDGET THEORY**

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# A conceptual introduction to Dynamic Energy Budget theory

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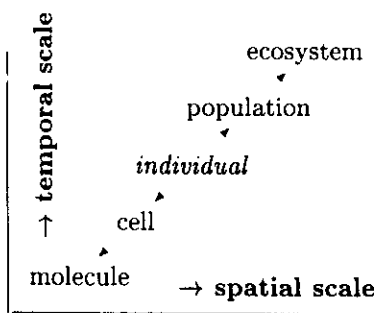
## Abstract

This paper discusses Dynamic Energy Budget (DEB) theory, avoiding mathematical formulations. The theory plays a unifying role in biology, and has firm roots in physics and chemistry. It quantifies how individuals acquire and utilize energy and substrates and applies to all species of organism. It provides constraints on the metabolic organization of sub-cellular processes, which helps to understand these processes quantitatively. Together with rules for interaction between individuals, it also provides a basis to understand population and ecosystem dynamics. The theory, therefore, links various levels of biological organization. It offers explanations to body-size scaling relationships of natural history parameters that are difficult to understand otherwise. The theory constitutes a powerful tool to tackle important problems in science and society.

## 1 Introduction

This summarizing introduction to Dynamic Energy Budget (DEB) theory aims to describe the contents and scope of the theory, avoiding mathematical formulations. Since the theory is a quantitative one, this description has to be sketchy at places, since a more rigorous exposition involves mathematical formulations; these have been given in [27]. The present focus is on arguments to understand why the theory has been set up in the way it is, and how it links specializations in biology that are presently almost independent from each other. The gist of the exercise is an attempt to find rules for the uptake and use of substrates that all organisms seem to have in common, and to capture the impressive biodiversity in differences in parameter values. To this end, individuals are considered as dynamic systems that follow predictable patterns during their life cycle, starting from the very first beginning. Although many additions and modifications are possible to make the theory more detailed, and perhaps more realistic, little room seem to exist to simplify the theory while preserving realism.

## 2 Space-time scales



One aim of theory in natural sciences is to relate processes at different organizational levels in a way that is understood. For biology, the levels are: molecules, cells, organisms, populations, ecosystems and the (planetary) biosphere. This is exactly the aim of the DEB theory for energy and mass fluxes through biota, using physical and chemical arguments only, while refraining from species-specific ones. The aim has also been to keep the theory as simple as possible, with a strong focus on the major patterns.

While moving up in space-time scales, new processes come into a dominating role, while others fade out. Each process has its own range of operation in the space-time domain. Many processes that are important at small space-time scales hardly contribute directly at large ones, but they can contribute indirectly. This is not typical for biology. Knowledge about technical details of engines in autocars is extremely valuable in optimizing design, and reducing air pollution, but it is of little help to fight traffic jams. Similar relationships hold between molecular biology and ecology, these specializations focus on different space-time scales and deal with different processes.

It is our task as scientists to find out how the process of fading in and out works, while moving up and down scales, and how to avoid the situation that a large number of variables and parameters contribute to the processes under study. Such models contribute little to our understanding and are, therefore, less useful. This makes that accessible scales in space and time are linked, and a large spatial scale poorly combines with a small time scale. Simplifying models, while preserving essential features, is a difficult task that requires careful scientific and numerical judgement.

A quantitative theory boils down into the form of a model for a particular situation. It differs from a model by being more general, leading to other models for other situations. It can do so because it is based on a set of assumptions, from which the model can be derived in combination with situation-specific assumptions. The set of assumptions contain the scientific insight, which (hopefully) evolves.

## 3 A weird world at small scales

One approach to the problem of understanding complex systems is to start from the molecular level, to collect all possible information and use it to explain processes at higher organization levels. Although spectacular progress has been booked in the last decades on qualitative aspects of molecular biology, the quantitative ones are substantially more difficult to tackle. Chemical kinetics, and enzyme kinetics, are developed for reactors, not for small cells. The kinetics is based on the assumptions of homogeneous mixing, large numbers of participating molecules and a constant reactor volume. None of these requirements apply to cells' interior. Basic to chemical kinetics is the law of mass action: transformation rates are proportional to meeting frequencies, which are taken proportional to the product of concentrations of substrate. This rests on transport by diffusion (or convection). A few observations might help to reveal that the application of classic chemical kinetics in cellular metabolism is problematic. This even holds for the concept 'concentration' of a

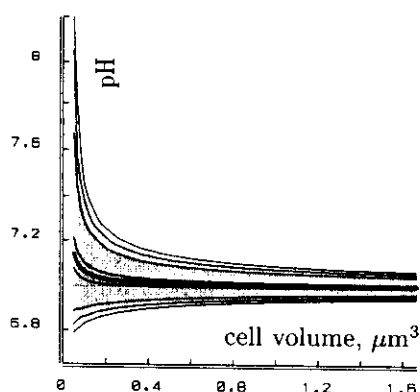


Figure 1: The 95%, 90%, 80% and 60% confidence intervals of pH in cells of pure water with pH 7 as a function of the cell size. They increase dramatically for decreasing cell sizes for cells (or cell compartments) less than  $0.5 \mu\text{m}^3$ . The thick curve represents the mean pH, which goes up sharply for very small cell sizes.

compound inside cells.

Consider, for example, a typical bacterial cell of volume  $0.25 \mu\text{m}^3$  of pH 7. The compartments of eukaryotic cells are not larger. It must have 15 free protons, but random dissociation of water, and random association of protons and hydroxyl ions make this number fluctuate wildly [31]. Figure 1 shows that the (asymptotic) frequency distribution of the number of protons, and so of the pH, dramatically increases in variance for decreasing cell sizes for volumes smaller than  $0.5 \mu\text{m}^3$ . We have to think in terms of pH *distributions* rather than pH *values*. Many chemical properties of compounds depend on the pH, which makes matters really complex.

A water molecule is created by association of a proton and a hydroxyl ion, and is eliminated by dissociation about twice a day at  $25^\circ\text{C}$ . Brownian motion transports a water molecule about 3 cm, while protons and hydroxyl ions are transported some  $3 \mu\text{m}$ , on average. These distances do not fit into a cell (or cell compartment), however, which must lead to the conclusion that undisturbed diffusion does not occur in cells. These expectations are based on pure water, but a more realistic cytoplasm composition does not solve the problem.

Electrical potentials in water decay exponentially as a function of distance, so it is proportional to  $\exp\{-L/L_D\}$ . The parameter, called the DEBYE distance, is about  $L_D = 0.1 \mu\text{m}$  for water at  $25^\circ\text{C}$ , which means the electrical potential of a proton is felt through most of the cell, even if it would not move. Water in very small volumes behaves as a liquid crystal, rather than as a liquid, which has substantial consequences for kinetics.

Many compounds are bound to a transport protein in a cell, and are moved to a site that corresponds with the address label in a way that is poorly understood. The cytomatrix might play a role here. The transformation processes at the time scale of the division interval are further complicated by dilution by growth. Many biochemists try to study the rate of these processes, using a reactor at steady state. Between their observations at the level of the population, and the object of study at the molecular level, is the level of the individual (cells), which follows a cell cycle, so a cyclic pattern.

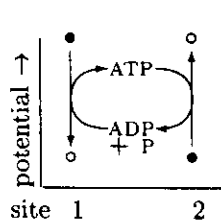
Many transformations are mediated by enzymes that are bound to a membrane. A cell can regulate the rate of transformation by binding enzymes from the cytoplasm to membranes. Regulation by the production of enzymes cannot operate fast because enzyme production is a relatively slow process, while binding to membranes can be fast. Since substrates are acquired from cytoplasm (volume), and amounts of active enzymes are proportional to that of membranes (surface area), the cell has local information about

its size, since the ratio of volume and surface area yields a length measure. Changes in this ratio during the cell cycle affect transformations rates and introduce a morphological argument: shape matters, so do changes in shape during growth.

Bio-energetics studies the processes of ATP generation and use, because cells use ATP to drive energy requiring transformations. The energy charge, i.e. the ratio

$$\frac{[ATP]}{([AMP] + [ADP] + [ATP])},$$

changes, and therefore the 'energy content' of ATP. This complicates the understanding of slow transformations in terms of generation and use of ATP. These problems hardly affect the slower transformations, however, because of the dominant role of polymers (proteins, lipids and carbohydrates), which do not suffer from fluctuating energy contents.

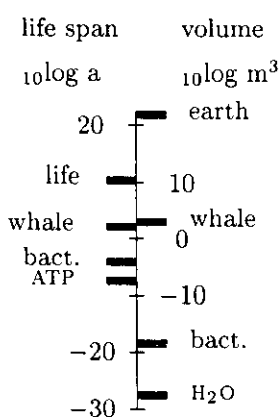


ATP should be seen as a shuttle that transports energy from a site where an energy producing transformation occurs, to a site where an energy requiring transformation occurs. If both transformations would occur at the same place and time, ATP is not required. Variations in the energy content of an ATP molecule affect the speed of the shuttle, but not necessarily the transformation rates.

The strong focus on ATP is not justified for slow processes. A typical lifespan of an ATP molecule is 0.3 second, and the amount of ATP molecules in a cell can drive synthesis for just 2 seconds. These time scales are too short to understand processes that are relevant at the time scale of the division interval. ATP plays the role of purse money, while bank account dynamics is required to understand the changes in cell economics during the cell cycle.

## 4 Individuals

These considerations leads to the conclusion that a direct approach to quantify cellular kinetics is a demanding task. A promising alternative, or complementary approach if you like, is to infer transformation kinetics from the behaviour of the integrated dynamical system in terms of input-output relationships. Even if this behaviour does not fully specify transformation kinetics of its components, it produces valuable constraints for their quantification. This is the approach taken by the DEB theory.



The natural integrated system to study metabolic transformations is the individual. It has to cope with the coupling of energy generating and requiring transformations in a way that meets the energy and mass balances. The explicit use of these balances greatly help the quantitative understanding of the individual as a dynamic system. The individual is also the unit of selection in evolutionary theory, which is essential to understand their similarities and differences. Individuals come in a great diversity and body sizes. Many individuals are unicellular, which makes the link with cellular metabolism rather direct. The ratio between the volumes of a whale and a bacterium is much larger than that of a bacterium and a water molecule; it is even larger than that of the whole earth and a whale.

The DEB theory delineates reserves, apart from structure. Both are taken to be general-

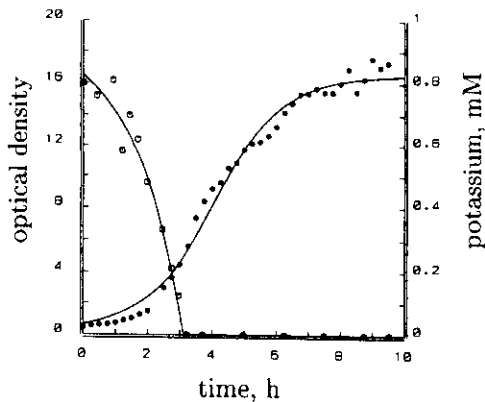


Figure 2: Potassium limited growth of *Escherichia coli* at 30 °C in a batch culture, measured in Optical Density at 540 nm. Data from [34]. The population continues to grow in absence of substrate in the medium, using intracellular reserves. For a small saturation coefficient, and small maintenance costs, the DEB theory predicts exponential growth during substrate presence, and logistic growth during substrate absence. The latter model is a very popular empirical model in population dynamics.

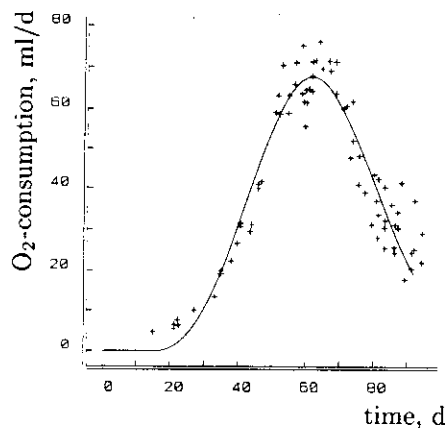
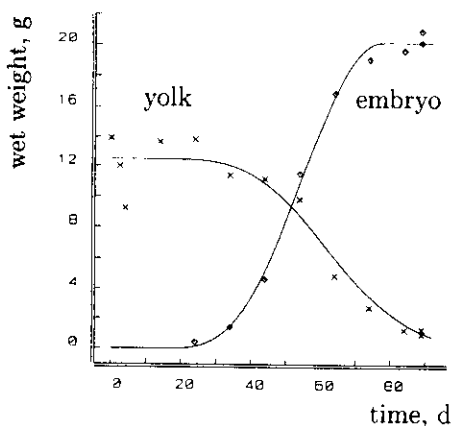


Figure 3: The embryonic development of the New Guinea soft-shelled turtle *Carettochelys insculpta* illustrates that development is at the expense of reserves that do not respire. Data from [43]; the curves are DEB-based expectations, fitted by C. Zonneveld. The respiration rate decreases because of depleting of reserves. These turtles tend to wait for their brothers and sisters to hatch synchronously.

ized compounds, i.e. mixtures of a large number of compounds (carbohydrates, proteins and lipids form the main bulk), which do not change in composition. The latter requirement is called the strong homeostasis assumption. Aiming at the simplest realistic characterization of metabolism, one might wonder if reserves are strictly necessary. Several reasons can be given to include reserves in even the simplest characterizations.

The first reason is to account for metabolic memory, which is important during transient states (shifts up and down in substrate availability as is standard during embryonic development), see Figures 2, 3 and 9.

The second reason is to explain observed respiration patterns, which has a close link with the use of energy. Freshly laid eggs hardly respire, while the developing embryo respire at an increasing rate, while the total egg-mass decreases, see Figure 3. The DEB theory explains this (and other observations) by assuming that structure requires maintenance, while reserves do not.

The third reason is that the composition of biomass depends on growth, which cannot be explained with a single generalized compound. With two components (reserves and

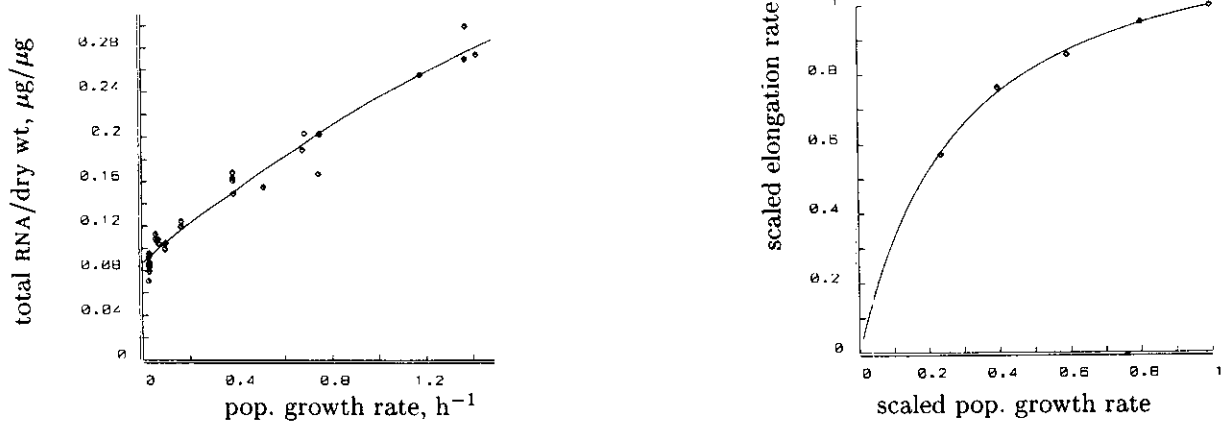


Figure 4: Left: The concentration of ribosomal RNA as a function of the population growth rate in *Escherichia coli*. Data from [23]. Right: The elongation rate as a function of the population growth rate. Data from [7]. Both elongation rate and population growth rate are expressed as fractions of their maximum value of  $1.73 \text{ h}^{-1}$  with an elongation rate of  $21 \text{ aa s}^{-1} \text{ rib}^{-1}$ .

structure) particular changes in composition can be captured. More complex changes require several reserves and structures, as is required for autotrophs. A single reserve (high degree of homeostasis) evolves from a multiple reserves, by coupling of reserves dynamics. This process of coupling is an essential element of the DEB theory.

The fourth reason is that all mass fluxes turn out to be linear combinations of assimilation, maintenance and growth. If reserves are omitted, these three processes are mutually dependent and actually provide two degrees of freedom, rather than three. This does not provide enough flexibility to capture product formation.

The fifth reason is to allow body size scaling of life history parameters. The specific respiration rate decreases with (maximum) body size between species because large bodied species have relatively more reserve. Many other life history parameters directly or indirectly relate to respiration.

Although the introduction of reserves is unavoidable, it does complicate the empirical application of the theory. All size measures of the individual (volume, wet or dry weight or total carbon) are combinations of reserves and structure, which complicates the measurement of these components. The composition of reserves and of structure can be obtained indirectly only, make using change in biomass composition as a function of the growth rate: Reserve density, i.e. the ratio of the amounts of reserve and structure, increases with the high growth rate, because the use of reserves increases with the reserve density and part of the used reserves are allocated to growth.

Reserves are not meant to be compounds that are set apart for later use, but as a pool of compounds that are synthesized from substrates in the environment for use by the metabolism. This creates a rather constant internal chemical environment, with only an indirect coupling with the environment.

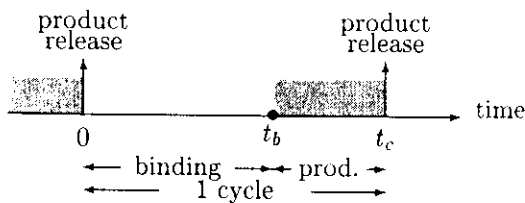
Reserve compounds can have an active role in metabolism. To decide whether or not a particular compound belongs to the reserves and/or to the structure one has to study whether or not its density increases with the growth rate. Figure 4 shows that ribosomal RNA density does increase, which means that at least part of it belongs to the reserves. This has far reaching implications for turnover of ribosomes and elongation rates of peptides, for instance. The latter turn out to be realistic, since the curves in Figure 4 are DEB-



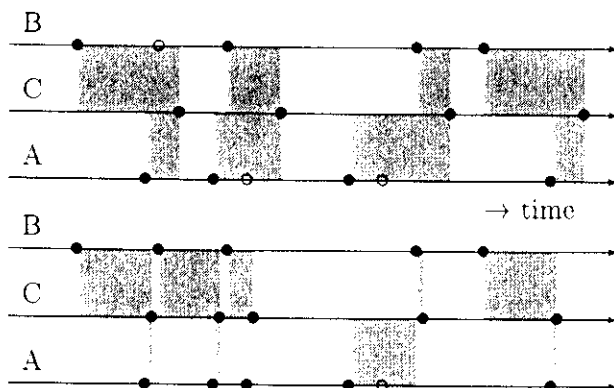
based expectations. Ribosomes that are part of structure or of reserves will probably have the same turnover rate, so part of the (somatic) maintenance requirements are used to drive this turnover. Since ribosomes are part of the machinery involved in synthesis, and synthesis rate has to increase with reserve density, it makes sense for the cell to treat part of its ribosomes as reserves. It can extract energy and building blocks from ribosomes during a shift down in substrate availability. This example illustrates the tight link between macro-economics and molecular processes.

## 5 Flux-based kinetics of Synthesizing Units

The section ‘A weird world at small scales’ illustrates some problems of application of classic chemical and enzyme kinetics to cellular metabolism. This leads to the problem to find better alternatives. The construct ‘Synthesizing Unit’ (SU) is an attempt in this direction. It can be conceived as a (generalized) enzyme that behaves according to the association-dissociation rules as prescribed by classic enzyme kinetics, with two modifications: the kinetics is not specified in terms of substrate concentrations, but in terms of arrival fluxes of substrate molecules to the enzyme, and the enzyme-substrate complex does not dissociate (enzymes are only released after transformation of substrate into product). Assuming that arrival is controlled by diffusion (or convection), the arrival rate is proportional to the concentration of substrate. These two modifications have little consequences in simple transformations of a single substrate molecule into a single product molecule; Michaelis-Mention kinetics is still part of the behavioural repertoire of SUs. The significance of the modifications reveals at more complex situations, where the local environment is not well mixed, or the transformations are more complex.



The SU goes through a cycle, consisting of a binding phase and a production phase. The production rate is inverse to the cycle time.



The upper diagram represents a slow SU, the lower diagram a fast one, which both experience the same arrival processes, in the transformation  $A + B \rightarrow C$ . Filled dots stand for acceptance, open ones for rejection. The gray areas indicate periods during which the SU is blocked for the two substrates.

Note that the fast SU still has substantial blocked periods due to the stochasticity of the (Poisson) arrival processes. Thinking in fluxes, rather than concentrations, implies the existence of rejected fluxes that require a destination (allocation).

Liebig's minimum rule has considerable empirical support; it links the production fluxes to the limiting substrate only. The numerical behaviour of a SU closely follows this rule, except for a narrow window of concentrations, where several substrates limit simultane-

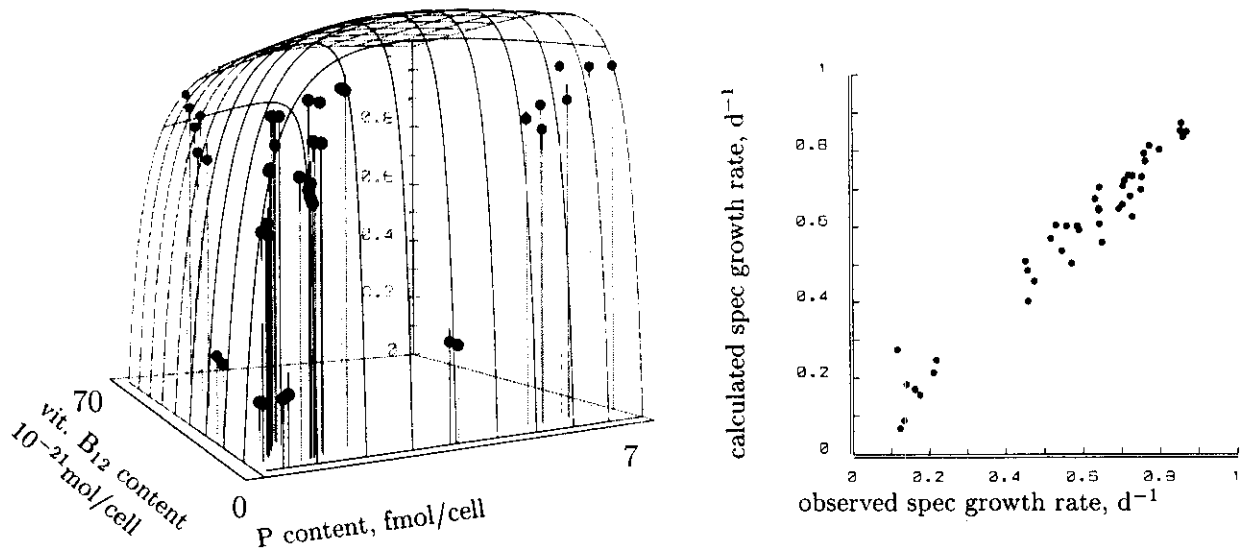


Figure 5: Specific growth rate of haptophyte *Pavlova lutheri* as function of intracellular reserves of phosphorus and vitamin B<sub>12</sub> at 20°C. Data from [10]. The surface area is based on the kinetics of a Synthesizing Unit for two complementary substrates.

ously, see Figure 5. The transition from one limiting substrate to another at changing substrate concentrations in the environment is smooth, however, which is rather essential in combination with reserves; substrates can be absent in the environment, while not (yet) limiting, due to its presence in reserves. This implies complex rules for limitation in varying environments, which can be avoided with SUs.

Another very useful property of SUs is that the stoichiometry of the transformations need not to be known exactly; an increase in stoichiometric requirement almost cancels against an increase in binding efficiency, which allows the description of transformations of generalized compounds, including overheads that are associated with them.

SUs can be linked into a metabolic network after specification of the handshaking protocols which specify the rules for exchange of metabolites between the SUs. The open and closed protocols represent extremes, while mixtures are possible. In an open handshaking protocol, the behaviour of the sending SU is independent of the receiving one, while in a closed protocol, the sending SU only releases its product if the receiving one is free for acceptance. (This is only possible if the SUs are bound on a membrane adjacent to each other.) The type of protocol turns out hardly to effect the production of the end (overall) product, but the production of precursors (intermediate products) is very sensitive for the type of handshaking protocol, as is the amount of accepted substrate by the network. Many biochemical modules, such as the TCA cycle, serve the dual role of energy extraction form a resource and the generation of building blocks (as intermediate products).

The application of SU kinetics in the DEB theory is in the assimilation process, which transforms substrates in the environment into reserves, and in the growth process, which transforms reserves into structural mass. Each reserve, and each structure has a single type of SU, thus the basic DEB model has two types of SUs. The flux of substrate that is rejected by the growth-SU is returned to the reserves, or excreted into the environment with a fixed fraction. If all rejected substrate would be returned, no upper boundary for that reserve would exist. The return fraction quantifies the damming up of non-limiting reserves, with the remarkable consequence that the growth rate increases with limiting

	substitutable $y_{CA}A \rightarrow C; y_{CB}B \rightarrow C$	complementary $y_{CA}A + y_{CB}B \rightarrow C$
sequential		
parallel		

Table 1: Interaction of substrates  $A$  and  $B$  in transformations into product  $C$  can be understood on the basis of a classification of substrates into substitutable and complementary, and of binding into sequential or parallel. The symbol  $\theta_{*1*2}$  represents SUs that are bound to the substrates  $*_1$  and  $*_2$ , the dot representing no binding. The schemes can be generalized to more complex transformations without involving new theoretical problems.

reserve density, but decreases with the non-limiting ones.

Thinking in terms of fluxes of substrate allows one to treat photons similar to nutrients, with fixed stoichiometric requirements. Energy extracted from a photon is independent from its wave length, which gives a window for metabolically useful wavelengths of photons. The excess energy dissipates as heat. Flux-based modelling of metabolism links up beautifully with allocation schemes of physiologists, because allocation is basically a partitioning of fluxes to specific destinations.

## 6 Assimilation

The assimilation process is defined as the transformation of substrates in the environment into reserves inside the organism. This involves a transportation process that is linked to a surface area (membranes). The basic DEB formulation takes the relevant surface area proportional to that of the individual, which scales with volume<sup>2/3</sup> for organisms that do not change in shape during growth. Such organisms are called isomorphs.

Changes in shape during growth affect assimilation. If surface area is proportional to (structural) volume, a defining property of V1-morphs, a substantial simplification is possible because maintenance costs are also proportional to volume. If individuals divide into two parts at a certain volume, this simplification is a good numerical approximation, for a wide range of changes in shape. V0-morphs represent another interesting special case, where surface area (at is involved in substrate uptake) does not increase during growth. This occurs in special taxa, such as diatoms and dinoflagellates, in biofilms, and small aquatic individuals that have a relatively thick stagnant water mantle that limits transportation in the environment. Many structures, such as crusts of lichens, and microbial flocs represent dynamic mixtures between V1- and V0 morphs.

Uptake of a single substrate is well quantified on the basis of a fixed handling time of substrate (prey) by the uptake machinery. The time need not be constant, but it

must be independent of substrate density [32, 33]. The handling time not only includes mechanical handling but also metabolic processing. This is why prey eating by predators and transformation rate by enzymes depend in a similar way on substrate (food) density.

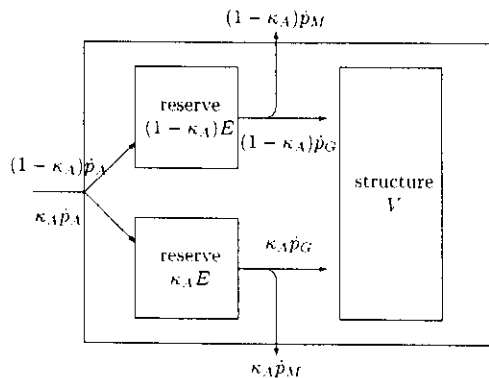
If the mixing rate in the environment is low, and an individual depletes its local environment from substrate (food), the feeding rate becomes limited by diffusion (or convection) of substrate through the environment. This affects the shape of the functional response (i.e. the feeding rate as function of the substrate density), which shifts from a hyperbolic function to a bilinear one (Holling type II to Holling type I).

Table 1 indicates the various modes of interaction of substrates in the uptake processes. Sequential processing has the property that an increase in one substrate density leads to a decrease of the uptake rate of the other, while parallel processing leads to an increase of the uptake rate. Cats feeding on mice and birds represent an example of sequential uptake of substitutable substrates; bacteria feeding on glucose and fructose represent parallel uptake of substitutable substrates, because they use carriers that can handle either glucose or fructose, but not both (while little interaction seems to occur during their processing to reserves).

Photosynthesis, the uptake of photons, and carbon dioxide to form carbohydrates, and the use of carbohydrates and nitrogen compounds to form (generalized) reserves represent a nested parallel uptake of complementary processes. The rejected electrons get lost via the Mehler reaction, while the rejected carbohydrates and nitrogen compounds are stored in two specialized reserves. (The existence of 'excess' electrons has puzzled plant physiologists; the mechanism of SUs implies their existence, however.) Photorespiration can be captured by a competitive binding between carbon dioxide and oxygen, while the net carbohydrate production is proportional to the difference. (The formulas remain simple.)

## 7 Reserve dynamics

The reserve dynamics represents the core of the DEB model because the use of reserves, called the catabolic rate, fuels metabolism. Its specification follows from two requirements: weak homeostasis and partitionability of its kinetics. The weak homeostasis assumption states that biomass (so the combination of reserves and structure) does not change in composition during growth *at constant substrate density*.



The partitionability requirement states that it must be possible to partition reserves into two components (e.g. lipids and non-lipids) such that the kinetics of the reserves is not affected, while the two components follow the same kinetics. This partitioning implies a similar partitioning of the maintenance and growth costs, since these costs are paid from both components. This introduces a special type of additivity of the kinetics.

The result of these two requirements is that the dynamics of reserve density, so the ratio of the amount of reserves and structure, follows a first order process, with a turnover rate is proportional to the surface area/volume ratio. The reserve turnover rate of isomorphs is, therefore, inversely proportional to their volumetric length, while that of V1-morphs

is constant. This kinetics should not be confused with first order kinetics in chemistry, because of the problem ‘dilution by growth’.

The partitionability requirement is essential for the smooth stepwise coupling of several reserves, to behave as a single generalized one.

Weak homeostasis and the partitionability or reserve kinetics also constrain the use of reserves. The fraction that is allocated to somatic maintenance and growth, rather than to maturity maintenance and maturation of reproduction, should not depend on the reserves. It can still be a function of the amount of structure, but the basic model assumes that it is a constant. This property is called the  $\kappa$ -rule for allocation. Both requirements follow from structural homeostasis; a set of rules for the membrane kinetics and action that is not part of the DEB theory itself. These rules provide a mechanistic explanation for the reserve kinetics.

## 8 Budgets and the specification of powers

The DEB theory consists of a set of simple, mechanistically inspired rules for the uptake and use of substrates (nutrients, food) by the individual, see Table 2.

The general assumptions relate energy to mass fluxes. The mineral fluxes of carbon dioxide, water, oxygen and nitrogen waste (frequently ammonia for aquatic organisms) turn out to relate *linearly* to the organic fluxes of food, faeces, reserves and structural mass; these organic fluxes turn out to relate *linearly* to three powers (i.e. energy fluxes): assimilation, dissipation and growth. Dissipation contains maintenance (somatic and maturity) and maturation, in fact all fluxes that are not associated with a net synthesis process.

Somatic maintenance includes protein turnover, maintenance of concentration gradients across membranes, activity and other types of work. The powers relate to allocated powers, not to effective power. So the growth power is larger than the flux that is actually fixed in new tissue. The difference is the overhead costs. These overhead costs might include products that are excreted. Product formation is again a linear function of the three basic powers.

The energy balance shows that dissipating heat is also a linear function of the three basic powers, and so of three mineral fluxes: carbon dioxide, oxygen and nitrogen waste. This is because linear functions of linear functions are linear again. The relationship for dissipating heat is discovered empirically by Lavoisier and Laplace in 1780 [28] and used for centuries in the method of indirect calorimetry. It is probably the best empirical support for the general assumptions of the DEB theory.

The specific assumptions quantify the powers. Some, such as the reserve density at birth and the  $\kappa$ -rule can be modified without mayor consequences for the model structure. Most alternative involves extra parameters, which restricts the applicability of the model.

Aging is important in several respects, and provides a mechanism that makes sure that no individual stays forever in the population. The aging process quantifies the memory of a population, and it is essential for population dynamics that it is finite. Linking aging to respiration as in Table 2 directly couples life span to substrate levels. Difference in life span between sexes (of waterfleas) could be explained on the basis of difference in DEBs, rather than in differences of the aging process [26]. Experimental results to demonstrate the genetic basis of aging, by selection of old individuals [40], can also be understood in terms of a selection of a digestive disorder.

Table 2: Assumptions which fully specify the basic DEB model as formulated for reproducing multicellulars and modified for dividing unicellulars.

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**General**, for the specification of mass–energy relationships

- 1 Structural body mass and reserves are the state variables of the individual; they have a constant composition (strong homeostasis).
- 2 Food is converted into faeces, and assimilates derived from food are added to reserves. These fuel all other metabolic processes, which can be classified into three categories: synthesis of structural body mass, synthesis of gametes, and processes that are not associated with synthesis of biomass. Products that leave the organism may be formed in direct association with these three categories of processes, and with the assimilation process.
- 3 If the individual propagates via reproduction (rather than via division), it starts in the embryonic stage that initially has a negligibly small structural body mass (but a substantial amount of reserves).

**Specific**, for the specification of the powers

- 3a The reserve density of the hatchling equals that of the mother at egg formation. Foetuses develop in the same way as embryos in eggs, but at a rate unrestricted by energy reserves.
- 4 The transition from embryo to juvenile initiates feeding, that from juvenile to adult initiates reproduction, which is coupled to the cessation of maturation. The transitions occur when the cumulated energy invested in maturation exceeds certain threshold values. Unicellulars divide when the cumulated energy invested in maturation exceeds a threshold value.
- 5 Somatic and maturity maintenance are proportional to structural body volume, but maturity maintenance does not increase after a given cumulated investment in maturation. Heating costs for endotherms are proportional to surface area.
- 6 The feeding rate is proportional to the surface area of the organism and the food handling time and the digestion efficiency are independent of food density.
- 7 The reserves must be partitionable, such that the dynamics is not affected; the use of reserves does not depend on food density; the reserve density *at steady state* does not depend on structural body mass (weak homeostasis).
- 8 A fixed fraction of energy, utilized from the reserves, is spent on somatic maintenance plus growth, the rest on maturity maintenance plus maturation or reproduction (the  $\kappa$ -rule).
- 9 Under starvation conditions, individuals always give priority to somatic maintenance and follow one of two possible strategies: they do not change the reserve dynamics (so continue to invest in development or reproduction), or cease energy investment in development and reproduction (thus changing reserves dynamics).

**Supplementary**, for the specification of aging

- 1 oxygen causes net DNA damage with a certain efficiency
  - 2 damaged DNA produces ‘wrong’ proteins at constant rate, which cumulate in the body
  - 3 the hazard rate is proportional to the density of ‘wrong’ proteins
-

The basic formulation involves a single reserve and a single structural component, as is appropriate for animals that feed on prey. Prey contains all energy and building blocks that are required by the consumer. Organisms such as algae, which can be limited in their growth by several types of nutrients (and/or light), require more types of reserves. Organisms such as plants, which use different organs for the uptake of different nutrients and light, also require more types of structural biomass. These multivariate extensions with respect to the univariate model for animals, follow naturally from the original set of simple rules, and specify all energy and mass fluxes simultaneously on the basis of the principle of homeostasis, see Figure 6. Since the multivariate extensions delineate more powers, and product formation is a linear function of these powers, product formation, such as wood production, has considerable metabolic flexibility.

Symbionts receive fluxes that the partner cannot use. If a coral polyp has many algal symbionts that excrete a lot of carbohydrates, the polyp uses most of its nitrogen waste itself by converting it, together with the carbohydrates, to reserves. The algae then receive little nitrogen, which reduces the algal density. This is, therefore, a self-regulating system that proves to be very stable, and even follows weak homeostasis under certain constraints. This type of exchange offers a promising basis for modelling cellular metabolic organization in more detail, where the cell is considered to be a symbiosis itself consisting of a number of biochemical units (chloroplasts, mitochondria, Krebs cycle, etc). The model can be used to evaluate the effect of calcification on the performance of the symbiosis, on the assumption that it is associated with the uptake of inorganic carbon from the environment. Some 98 % of the inorganic carbon in the sea occurs as bicarbonate, which has an electrical charge that is balanced in the uptake of calcium; for each two molecules bicarbonate that has been taken up, one is excreted as carbonate, the other is converted to carbon dioxide and metabolically processed.

Plants are notoriously difficult to model because of their great adaptive ability to varying environmental conditions. A lot of these responses can be captured by considering the plant as a symbiosis between root and shoot. This parameter-sparse characterization can respond realistically to changes in environmental conditions, without making use of any optimization argument. A reduction of light induces a larger relative investment into shoot growth; a reduction of water or nutrients induces a larger relative investment of root growth. A seed (embryo) initially consists of generalized reserves; a fixed fraction of its catabolic flux is translocated to the shoot, which behaves in a similar way. The assimilation process is initiated at birth (germination); the root remains in the juvenile phase.

## 8.1 Model formulation and testing

The basic DEB model for the individual amounts to a set of two differential equations that specify the change in amounts of reserve and structure. Inclusion of the aging process requires a third one for cumulated damage. For ecological application it can be useful to include ones for food consumption, faeces and/or nitrogen-waste production etc. These specifications follow directly from the DEB theory. Given the initial values for all variables, these equations describe how they will vary in time.

The basic model can be extended to include several reserves (and structures) to capture growth that is limited by several nutrients (including light) simultaneously.

Testing against experimental data is an ongoing activity that never considered to be complete. It is interesting to note that the DEB theory has several well-known empirical

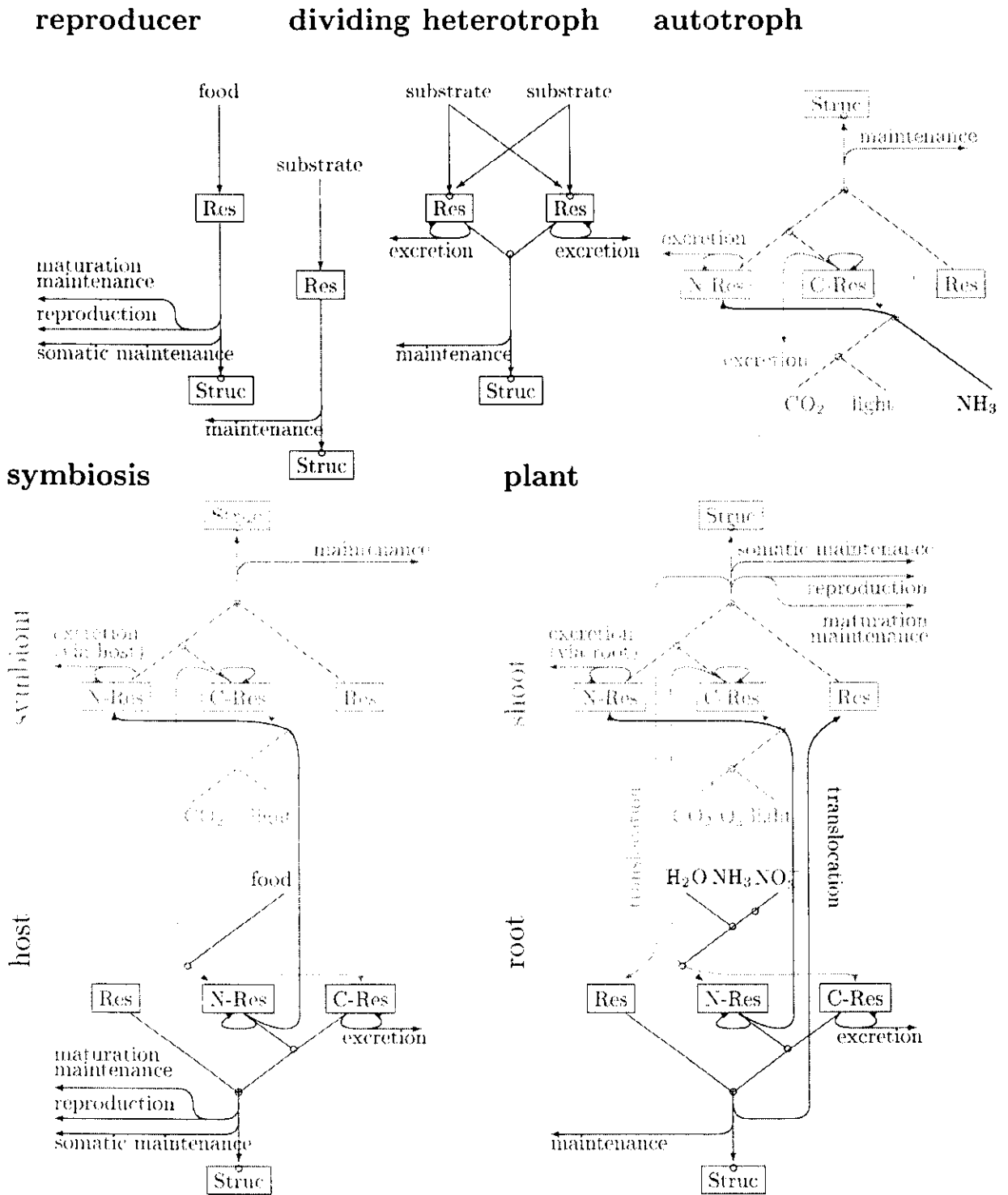


Figure 6: The upper-left diagram shows fluxes as appropriate for a reproducing heterotroph, such as many animals. A simplification is possible for dividing heterotrophs, which remain in the juvenile phase, by combining allocations to somatic and maturity maintenance, and to somatic and maturity growth (second diagram). An extension is required to cope with simultaneous limitation of substrate, which involves excretion (third diagram). Autotrophs require three reserves (a generalized, carbon and nitrogen one; fourth diagram). Symbiotic partners (e.g. in coral) link excretion fluxes, while plants have extra translocation processes between root and shoot.



models as special case:

author	year	ref.	model
Lavoisier	1780	[28]	multiple regression of heat against mineral fluxes
Arrhenius	1889	[14]	temperature dependence of physiological rates
Huxley	1891	[21]	allometric growth of body parts
Henri	1902	[17]	Michaelis–Menten kinetics
Blackman	1905	[3]	bilinear functional response
Pütter	1920	[37]	von Bertalanffy growth of individuals
Pearl	1927	[35]	logistic population growth
Fisher & Tippitt	1928	[13]	Weibull aging
Kleiber	1932	[22]	respiration scales with body weight <sup>3/4</sup>
Mayneord	1932	[30]	cube root growth of tumours
Emerson	1950	[12]	cube root growth of bacterial colonies
Huggett & Widdas	1951	[19]	foetal growth
Weibull	1951	[44]	survival probability for aging
Best	1955	[2]	diffusion limitation of uptake
Smith	1957	[42]	embryonic respiration
Leudeking & Piret	1959	[29]	microbial product formation
Holling	1959	[18]	hyperbolic functional response
Marr & Pirt	1962	[36]	maintenance in yields of biomass
Droop	1973	[9]	reserve (cell quota) dynamics
Rahn & Ar	1974	[38]	water loss in bird eggs
Hungate	1975	[20]	digestion
Beer & Anderson	1997	[1]	development of salmonid embryos

The DEB theory not only shows how and why these models are related, it also specifies the conditions under which these models might be realistic, and it extends the scope from the thermodynamics of subcellular processes to population dynamics.

Most of these models can be obtained mathematically from the DEB model by taking particular parameter values. For instance Droop's model is obtained by focusing on a single nutrient for a V1-morph, and setting the maintenance costs equal to zero; Marr-Pirt's model is obtained for a V1-morph by setting the maximum reserve capacity equal to zero, while Monod's model follows by setting the maintenance costs equal to zero as well. Other models, such as 'Kleibers law', do not follow mathematically, but behave numerically almost identically as the DEB model. (Kleibers law is based on allometry, which suffers from methodological problems.)

In view of the fact that the models in this list are classic because of their ideal combination of simplicity and realism, the DEB theory is the best tested quantitative theory in biology. Many details of the DEB theory are not covered by the models in this list, however. Many additional tests against experimental data are presented in [27], but particular aspects still are in urgent need for tests against realism.

## 9 Covariation of parameter values among species

With respect to physics, biology suffers from the problem that the most simple living creature is still extremely complex. It also has an advantage, however, namely the comparison between different organisms. This is why a model structure can have information about

symbol	dim	interpretation
$X_K$	$\#l^{-3}$	saturation constant
$V_b^{1/3}$	$L$	length at birth
$V_p^{1/3}$	$L$	length at puberty
$\{J_{Xm}\}$	$\#L^{-2}t^{-1}$	max spec ingestion rate
$\{\dot{p}_{Am}\}$	$eL^{-2}t^{-1}$	max spec assimilation rate
$[E_m]$	$eL^{-3}$	max spec reserve capacity
$[\dot{p}_M]$	$eL^{-3}t^{-1}$	spec maintenance costs
$\{\dot{p}_T\}$	$eL^{-2}t^{-1}$	spec heating costs (endotherms)
$[E_G]$	$eL^{-3}$	spec growth costs
$\kappa$	-	partition coeff. catabolic power
$\kappa_R$	-	efficiency reproductive power
$\ddot{h}_a$	$t^{-2}$	ageing acceleration

Table 3: The primary parameters of the basic DEB model classify into intensive parameters that do not depend on asymptotic body size, and extensive ones, that are proportional to volumetric length. Ectotherms do not heat, (so  $\{\dot{p}_T\} = 0$ ), and dividers relate size at birth directly to that at puberty, while reproduction overheads ( $\kappa_R$ ) do not apply, and developmental and somatic allocations can be combined, which eliminate  $\kappa$ ). This gives reductions of 1 or 4 parameters. The aging acceleration transforms into an aging rate for unicellulars.

parameter values, that is to say, about tendencies for covariation of parameters among species. This is because all primary parameters can be classified as intensive or extensive, while ratios of extensive parameters are intensive again (if expressed in the proper units).

All extensive parameters are proportional to the maximum volumetric length that an individual can reach (after a long exposure to a high food density). This necessity reveals by considering the expression for this maximum length, which is a simple function of three parameters: the fraction of energy that is allocated to maintenance plus growth times the ratio of the surface area-specific assimilation power, and the volume-specific maintenance costs. (Growth ceases if all energy allocated to maintenance plus growth is consumed by maintenance.) Since the allocation fraction and the volume-specific maintenance costs are intensive parameters, the surface area-specific assimilation power must be extensive and proportional to maximum volumetric length.

The scaling of the primary parameters defines how any quantity that can be written as a function of these parameters depends on maximum length. These quantities include many physiological and life history parameters, such as life span, length of embryonic and juvenile periods, maximum reproduction rates, etc. Literature gives most attention to respiration rates. The DEB theory predicts that volume-specific respiration rates decrease with body size because large organisms have relatively more reserves. Volume-specific respiration also decreases for a growing individual, but for a totally different reason: its investment into growth decreases with size. Tests against empirical data show that all 35 tested body size scaling relationships are realistic, indeed. Figure 8 shows that the von Bertalanffy growth rate is about inversely proportional to length. This is because the reserve density increase with body size. The respiration is about proportional to volume<sup>3/4</sup> for the same reason, but the coefficient 3/4 varies somewhat in value between the taxa, because of the varying contribution of the maintenance costs in respiration. Ectotherms (mainly birds and mammals) spend a lot on heating, while heat exchange is proportional to surface area. This explains why their scaling parameter is close to 2/3.

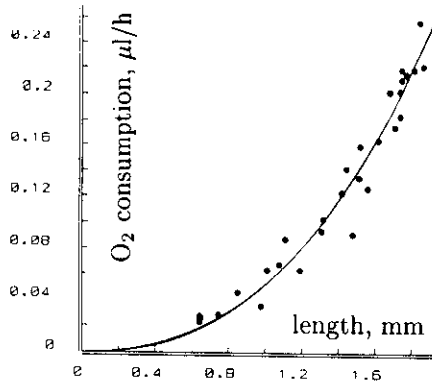
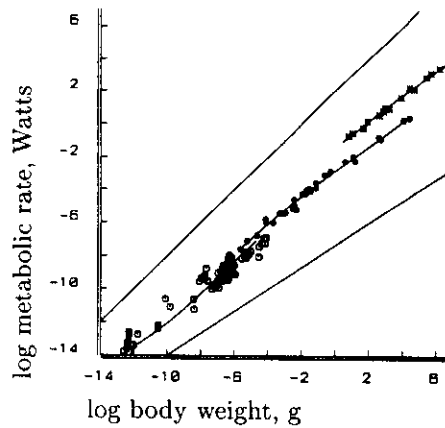


Figure 7: The respiration rate of *Daphnia pulex* with few eggs at 20 °C as a function of length. Data from Richman [39]. The DEB-based curve  $0.0336L^2 + 0.01845L^3$  as well as the standard allometric curve  $0.0516L^{2.437}$  are plotted on top of each other, but they are so similar that this is hardly visible. If you looking hard, you will notice that the line width varies a little. Volume-specific respiration decreases with size because of the decreasing investment in growth.



Specific respiration also decreases with size among fully grown individuals of different species because of the increasing contribution of reserves in body weight. The metabolic rate of unicellulars (○, at 20 °C), ectotherms (●, at 20 °C) and endotherms (\*, at 39 °C) is plotted as a function of body weight. Modified from [11, 16]. The difference between this figure and the many others of the frequently reproduced data set is that the curves relate to DEB-based expectations, and are not allometric regressions. Nonetheless they appear almost as straight lines. The lower line has slope of 2/3, the upper one a slope of 1.

## 10 Evolutionary aspects

Present-day organisms that can be described by a single type of (generalized) reserve probably evolved from organisms with more reserves that gradually became coupled and so increase the degree of homeostasis. The DEB theory has this evolutionary consistency, thanks to the partitionability requirement of reserve dynamics. If all reserves that are rejected by the growth-SU are excreted, and all reserve turnover rates set to an equal value, the reserves can mathematically be combined into a single generalized one. The coupling of reserves is attractive for an organism if the availabilities of nutrients are coupled as well. If food consists of animal prey, this coupling is almost perfect, and the conversion is efficient because the composition of prey resembles that of the consumer. If food consists of plant material, the coupling is still considerable, but, since the compositions of plant and consumer differ more, the conversion is less efficient.

The general picture of the evolution of metabolic systems that emerges is more or less as follows. Initially metabolism became increasingly independent of temporary variations in the nutritional quality of the environment by increasing their storage capacity for the various nutrients; temporary peaks in the availability of a nutrient can only be used if other nutrients are not essential for this uptake, so the number of reserves equals the number of essential nutrients. Then followed a phase where organisms increased their control over the uptake of resources by increasing their taxis, and homeostasis abilities at the same time. It allowed them to use specialized enzymes to catalyse particular transformations,

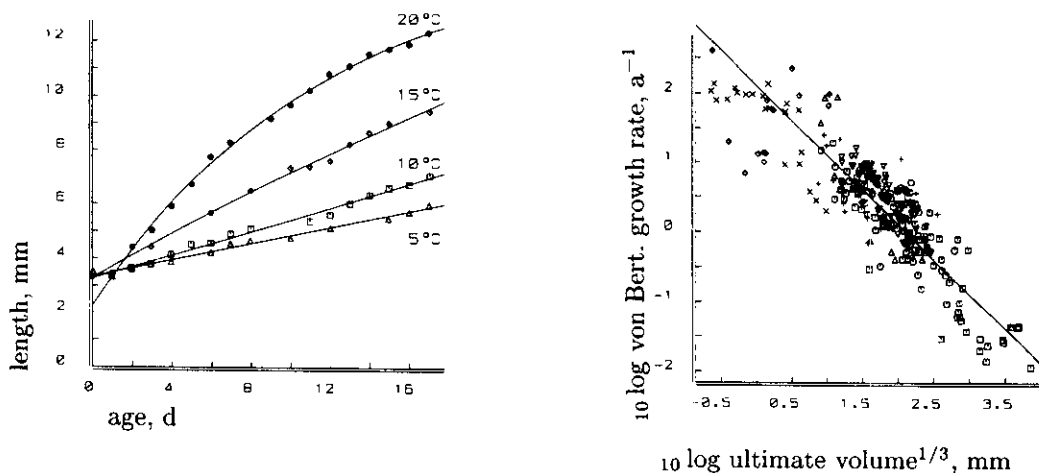


Figure 8: Like many other species of animal, *Pleurobrachia pileus* grows according to the von Bertalanffy growth curve at constant food density and temperature. The von Bertalanffy growth rate quantifies the rate at which the asymptotic size is approximated. Data from [15]. The DEB theory predicts that an isomorph follows the von Bertalanffy growth curve at abundant food and that the von Bertalanffy growth rate is (approximately) inversely proportional to maximum volumetric length. This is shown for data on 261 widely different species, corrected to a body temperature of 25 °C;  $\nabla$  birds,  $\square$  mammals,  $\triangle$  reptiles and amphibians,  $\circ$  fishes,  $\times$  crustaceans,  $+$  molluscs,  $\diamond$  others.

so increasing and regulating the rate of these transformations. The proper functioning of these enzymes requires a steady turnover, and so maintenance costs, which are further increased by the taxis activities. These maintenance requirements have tight links with storage capacities in varying environments to ensure the integrity of the metabolic system.

The animal line of development perfected the control over uptake by feeding on other organisms, which gives an almost perfect coupling of resources. This allowed animals to eliminate many routes of metabolite synthesis, to couple the use of various reserves such that a single generalized reserve emerged, and an almost perfect homeostasis was reached. This specialization came hand in hand with an increase of the taxis abilities, through the development of advanced motor systems and senses, which need a nervous system for information processing and muscle control. They used this nervous system to increase their control over homeostasis as well and the make the transition from supply to demand systems. (The behaviour of a supply system is controlled by substrate abundance, that of a demand system by its needs; production is "pre-programmed" and it eats what it needs.) This more active life style increased the maintenance costs, which is no problem as long as it leads to higher assimilation as well.

The plant line of development specialized in increasing the adaptive abilities. Plants became extremely flexible in morphology, with direct links to the control over uptake of the various nutrients and light (roots versus shoots). They invented the use of products (wood, silica) to solve mechanical problems, and learned to use animals to solve the problem of finding partners in the reproduction process, and of exporting seeds to uncolonized areas, while being confined to a particular site. They also learned to use fungi to capture nutrients that are locked in organic compounds, and some use bacteria to make dinitrogen available to them.

The increase in biodiversity allowed a specialization of functions, which enhanced metabolic versatility, by using other species or their activities; compare mixotrophs with a producer-consumer-decomposer community, for instance. The processes of syntrophy and even more advanced forms of symbiosis developed early in evolution and have been reestablished many times since then, resulting in loose and tight links between virtually all organisms. The eukaryotic cell itself is a symbiotic system, and the DEB rules for mass exchange between the partners, might lead to a understanding of the evolution of homeostasis at the cellular level.

## 11 Population and ecosystem dynamics

Given rules for interaction between individuals, and environmental conditions (supply of nutrient to the system, and/or leak from the system) and initial conditions, the DEB theory predicts population changes. The simplest rule for interaction is competition for the same substrate in a well-mixed environment. Populations in reactors can make to approximate these rules, and the resulting predictions are realistic indeed. This even holds for the dynamics of food chains.

Classic (unstructured) population models only count numbers of individuals or total biomass. Physiologically structured population models take account for differences between individuals, and allow links with evolutionary biology. This is because these models can evaluate how changes in physiological performance of an individual work out in terms of changes in reproduction, and the propagation of its progeny through the population given rules for heredity of physiological characters.

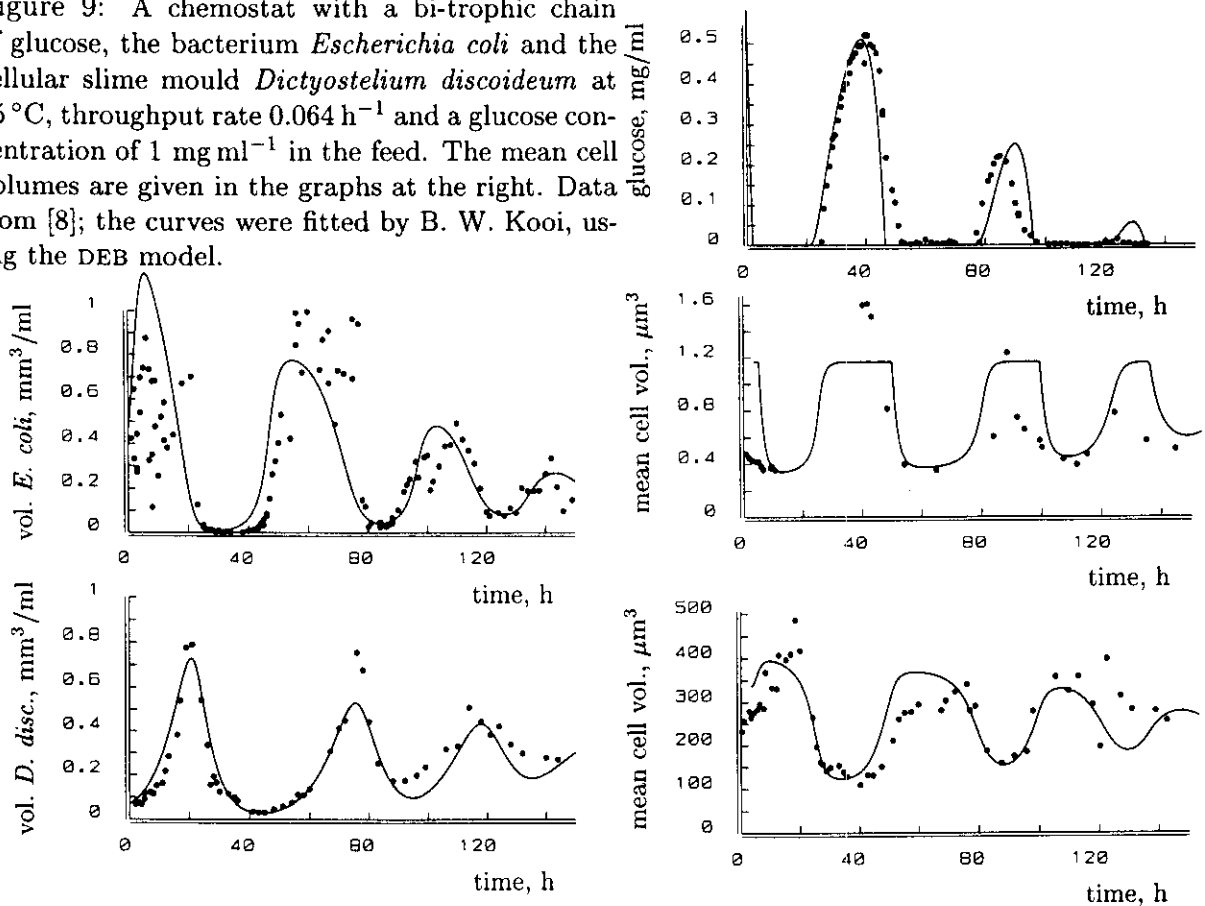
Real world population dynamics is very much complicated by a large number of factors, such as spatial heterogeneity, social interaction etc. When two individuals of slightly different size compete for a food item, the bigger one has a slightly better chance to obtain the item, which enhances the size difference between the individuals. Social interactions have a positive feedback on size difference among individuals that are otherwise similar. The realistic incorporation of such factors frequently involves many parameters and variables, and degrade the generality of the analysis. The main value of population dynamics is in broad expectations, rather than detailed analysis.

Many generally accepted concepts in population biology are based on very simple models for the behaviour of individuals. They do not seem to hold for more realistic models, such as specified by the DEB theory. One example is the competitive exclusion principle, that tells that two predator species cannot co-exist on a single prey species at steady state. Relatively recent results show that the system can oscillate under very particular conditions, such that two predators can co-exist. These results rest, however, on the simplicity of the model, that take prey's biomass composition to be constant.

The DEB theory delineates at least two components in biomass, which allow coexistence of two predators that differ in digestion efficiency of these components. Taking account of faeces production, and a microflora living on it that can be eaten by the predators, it is possible to sustain a substantial biodiversity on a single nutrient. This points to the necessity to think in terms of community metabolism, rather than population dynamics, that links community structure (biomass density over the different biota), and function (nutrient cycling).

Another example that illustrates that DEB-based insights can differ from accepted ones

Figure 9: A chemostat with a bi-trophic chain of glucose, the bacterium *Escherichia coli* and the cellular slime mould *Dictyostelium discoideum* at 25 °C, throughput rate 0.064 h<sup>-1</sup> and a glucose concentration of 1 mg ml<sup>-1</sup> in the feed. The mean cell volumes are given in the graphs at the right. Data from [8]; the curves were fitted by B. W. Kooi, using the DEB model.



in population biology, is the stabilizing effect that invading species of competitors and predators can have on an existing community [25]. Accepted insight is that an increase of diversity comes with a decrease in stability in spatially homogeneous systems. This does no longer seem to hold true for more realistic models.

Predator response on fluctuations of prey density frequently show a delay, as illustrated in Figure 9, where the mean cell sizes of bacteria and slime moulds fluctuate in an opposite way. This has been used to argue that the feeding rate of the slime moulds is a function of prey/predator ratios, rather than of prey densities [41]. The successful application of DEB theory, however, suggest that the delay is due to reserve dynamics.

The asymptotic behaviour of food chains rapidly becomes very complex for increasing chain length. For a length of three species in a chemostat, multiple attractors can occur, some of them of the chaotic type [24, 5, 6]. Recent progress has been made in the systematic analysis of possible asymptotic behaviour [4].

## 12 Applications

DEB theory concerns universal laws for metabolic organization at different levels. Knowledge of such laws is very useful to solve (or reduce) many problems in society that relate to global climate change, environmental problems (chemical pollution, maintenance of biodiversity), biotechnology (production optimization of biomass or bioproducts, sewage purification) and human health.

### *Global change*

Global change problems concern human impact on global phenomena. The response of biota may amplify or compensate this impact. Specific projects concern the emission of dimethyl sulfide from microbial mats, which is relevant for the albedo, and the anorganic carbon flux that is linked to the alga *Emiliana*, which is very abundant in all oceans.

### *Ecotoxicity*

Ecotoxicological problems concern effects of chemical compounds on the energy and nutrient budgets of organisms and their population and ecosystem consequences. Effects can be decomposed into steps: linking external concentrations of toxicants to internal ones, linking internal concentrations to changes in primary DEB parameters, linking changes in these parameters to endpoints (survival, reproductive output), and linking changes in individual performance to that of populations. The quantification of biodegradation of xenobiotic compounds makes the link with biotechnology and bioavailability studies.

### *Biotechnology*

Biotechnological problems concern the optimization of product formation by microorganisms and the treatment of sewage water such that the production of sludge is minimized.

## 13 Future challenges

Further development of the DEB theory towards the molecular and ecosystem levels can contribute a great deal to our understanding of quantitative aspects of biology.

The understanding of different forms of homeostasis is a central topic at the molecular level. This includes the role of regulation systems, and the nervous system in animals. Extension of the symbiotic argument looks promising, and links up with a modular approach to cell's metabolism

The understanding of ecosystem metabolism could benefit from explicit energy and mass balances, and exclude unrealistic behaviour. The DEB theory provides the rules for constructing these dynamic balances, but considerable effort must still be invested in aggregation methods that allow substantial simplifications. Nutritional links between species span a range between tight (flux-based) and loose, using varying pools in the abiotic environment. The quantitative characterization might resemble that of cells, from an abstract point of view.

Insight in ecosystem metabolism will contribute to our understanding of the role of life in the planetary system. Although some qualitative effects of biota on global climate are known, quantitative aspects are still elusive.

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