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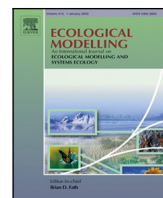
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From formulae, via models to theories: Dynamic Energy Budget theory illustrates requirements

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ABSTRACT

As sciences mature, they transition from observation and description to explanation and prediction. This transition is associated with qualitative changes in the way quantitative mathematical formulations are constructed and interpreted, resulting in a ‘theory’. Such transitions from phenomenology to theory are happening in biology but the heuristic framework involved is rarely articulated. We here describe how the use of models in research sets model requirements, using Dynamic Energy Budget (DEB) theory to illustrate the more elaborate ones. We first make the distinction between mathematical formulae and models based on their relation to the abstract and real worlds. We then explain how the transition from models to theory affects model construction and parameter estimation, and discuss the concept of parameter estimation-in-context using the database Add_my_Pet on animal energetics. The transition comes with the need to develop auxiliary and meta- theory and to work with multiple datasets, implying constraints for the loss function that is used for parameter estimation. Finally, we discuss the extra requirements for general explanatory models: they need to be explicit on relevant general principles and to be embedded in a wider scientific context. We also discuss how we see theory’s relationship to observation and prediction change in the future as we use it to deal with theoretical and applied problems in biology.

1. Introduction

Mathematical models find an increasing variety of applications in science, and each application comes with its own set of requirements for model properties (see also Jakeman et al., 2024, this issue). Descriptive models, often referred to as phenomenological models, can only extrapolate responses to no-analog environments with large uncertainty (Veloz et al., 2012; Buckley et al., 2010; Evans et al., 2015), and have low structural robustness (Aldebert et al., 2018). When models are needed to predict responses to environmental change, they should

do more than just describe relationships between variables. Ideally, the models should derive from a theory about how the variables are related. There is an emerging view that we have a crisis in how theories are used in biology, akin to that in the psychological literature (Nakagawa et al., 2024; Purgar et al., 2022, 2024). It is thus critical that biologists become more conversant with the link between models, theory and data in the empirical cycle (Fig. 1).

This paper discusses how model application conditions model requirements, i.e. how they should be constructed and their parameters

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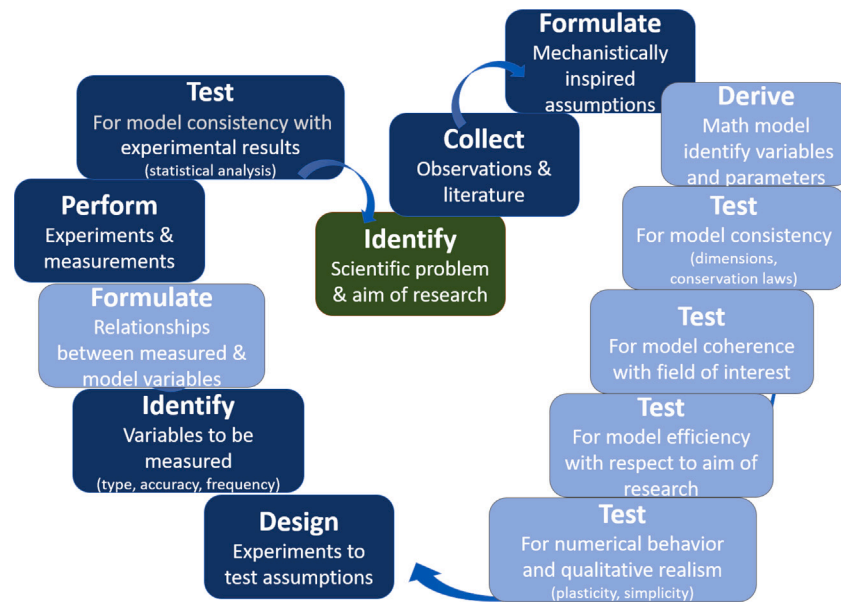


Fig. 1. The empirical cycle for building a theory. Although “perform experiments and measurements” occupies a single box, it might involve a lot of work. Many model-attempts will not reach that stage, since they failed already in an earlier one. This is why modelling might involve a lot of work as well.

Source: Modified from Kooijman (2018).

estimated from data. It is the use of models in research that sets the requirements for these models. The more intellectual work models have to do, the more elaborate become their requirements. Given how a particular model is constructed, it can function well in one phase of research, but can lose its function when the research program further develops, typically from describing to understanding. We here try to capture this spectrum of use-and-requirements in four steps.

The requirements for formulae (Section 2) are covered by the rules of mathematics. Requirements for descriptive mathematical models (Section 3) involve a small set of basic elements of the philosophy of science. Explanatory models (Section 4) involve more subtle and challenging philosophical issues. General explanatory models (Section 5) need to consider a basic set of topic-specific general principles and be embedded in its scientific context. To avoid that the discussion becomes really abstract, we use examples from Dynamic Energy Budget (DEB) theory to illustrate the more advanced steps in the methodology. For explanatory models other specific models could have been selected as well for illustration. In this way, the material serves as introduction of requirements for a general explanatory models (Section 5), where general principles are discussed that need to be considered in any theory on metabolism, in this case. This section is topic-specific by necessity, but we think that general explanatory models on other topics have parallel requirements.

An innovative aspect of the development of DEB theory is that it couples general theory to a large database. This coupling comes with the need to become detailed on data, parameter estimation and supporting code. The database plays a key role in parameter estimation-in-context, as we will explain; the processes of theory development and theory application become intertwined. This innovation fuels the development of what we call meta-theory: theory about covariation of parameter values.

DEB theory is about metabolic organization, which is fundamental to life. Life is hard to define, but proceeds in time, which makes time a natural variable in the theory and makes dynamical systems theory and stochastic processes natural mathematical contexts. The primary focus of DEB theory is on life cycles of individuals of all forms of life (micro-organisms, plants, animals) in dynamic environments (mostly regarding temperature and resource availability). The theory includes consequences of environmental perturbations and supra- or sub-organismal interactions for individuals, populations, ecosystems, and System Earth.

Environmental responses involve interactions (i) between individuals (e.g. predator/prey (Kooijman et al., 2004), host/pathogen (Hall et al., 2007, 2009), symbiosis on the basis of syntrophy (Muller et al., 2009; Mariño et al., 2019)), and (ii) within individuals (e.g. host-mitochondria interactions Kooijman and Segel, 2005, allocation to organs Kooijman, 2010 including tumours Leeuwen et al., 2003; Terranova et al., 2018, biochemical modules in central metabolism Kooijman and Troost, 2007), in an evolutionary context. This broad scope calls for a multi-disciplinary approach, involving biology, physics, chemistry, geology and computer sciences. The common language for uniting these diverse disciplines is mathematics.

2. Formulae and equations: a skill

Strong mathematical literacy has historically not been a prerequisite for biological sciences, so many biologists struggle with (and sometimes mistrust) mathematical formulations. A practical problem is that mathematics is a huge field that developed over millennia. Once a mathematical statement is proven, it remains true forever. By contrast, new insights in natural sciences tend to replace previous ones, although good knowledge of the history of science facilitates finding the best path forward (Kearney, 2021).

Abstract mathematical thinking requires training, motivation and patience, and excellent books exist to help navigate this large field of knowledge. New developments in mathematics typically requires full-time specialization and a good memory for what has already been done; this is rarely necessary for the use of mathematics in modelling. A survey of mathematical topics that are frequently encountered in work on theoretical biology and relevant references can be found in Kooijman (2011) and here we briefly summarize some of the key concepts required.

Mathematical formulations can have variables and parameters (= constants) but, unlike models (see Section 3), they have no interpretation in the real world. Variables can be stochastic or deterministic. Probability theory deals with stochastic variables, calculus with deterministic ones. Markov processes play an important role in stochastic processes. Ordinary and partial differential equations (ODEs and PDEs) are frequently used to specify changes in variables. If the values of the variables at the start (or some point in time) are specified (together with the values of the variables at the boundaries, in the case of

PDEs), differential equations can be integrated over time to obtain the trajectories of the variables. Sometimes the behaviour in the long run (i.e., asymptotic behaviour) can be of interest, and this behaviour can be quite complex (e.g., limit cycles, chaos). Bifurcation theory can be used to understand the parameter dependence of asymptotic (= long-term) behaviour (Chow and Hale, 1982; Kuznetsov et al., 1998).

Dynamic systems are of special interest in biology. They are defined by a set of variables, named state variables, which are influenced by input variables and may exert an influence on other external systems through output variables. The changes in the state variables of the system only depend on the current state and input variables, given parameter values. Dynamical systems theory was created as a sub-field of mathematics to structure research on the behaviour of dynamic systems. It provides a natural context for the study of life via models (see e.g. Arrowsmith and Place, 1990; Guckenheimer and Holmes, 2013; Strogatz, 2024).

Not all mathematical formulations are explicit. The task of numerical mathematics is to find the most efficient algorithm for solving an implicit mathematical problem with a specified minimum accuracy, such as in root-finding or integration of a set of ODEs or a PDE (see e.g. Stoer, 1972; Wouwer et al., 2014). In this context, “efficient” means involving the least computational effort. Evaluating the accuracy of a numerical method is itself an art. Algorithms for numerical mathematics should have adjustable parameters to set tolerance or accuracy levels; there is frequently a need to overwrite default settings.

3. Models: an interpretation

The big difference between formulae and mathematical models is that variables and parameters of models do have interpretations in the real world; this feature characterizes natural sciences. We must first give variables in formulas an interpretation to estimate parameters from data, which turns a formula into a model; we leave the domain of mathematics and enter the domain of philosophy of science.

Models are a stylized simplification of reality. So, when we look hard enough, it is always possible to find a difference between data and predictions. Models are used for a variety of purposes, one being the description of relationships between variables, another one is understanding these relationships and/or predicting variables in other situations (see Section 4 on theories).

The art of modelling lies in combining an accurate description (i.e., small difference between data and predictions) with as few variables and parameters as possible. Generally, but not always, accuracy increases with the complexity of the model. Adding a parameter might allow a model to express a wider range of processes, but can also reduce the explanatory potential of previously existing parameters while adding uncertainty/potential error in parameter values. Removing a parameter, on the other hand, might reduce the realism in particular applications, but increase generality. The best balance between simplicity and accuracy depends on the aim of the research, making it impossible to formulate general rules.

The first problems to deal with in modelling are those of notation and dimensions. Certainly, when the number of parameters and variables becomes large, there is a need to formulate notation rules explicitly in preparation for dimension checking and coding. The notation of DEB theory links leading symbols to dimension groups (DEBnotation, 2024), so, if two leading symbols are the same and only differ in indices, they have the same dimensions. Variables such as total length, fork length, standard length and snout-to-vent length, or wet weights, dry weights and ash-free dry weights, must all be separated in the notation. Many quantities, such as relative fecundity, are relative rather than absolute, constituting again a notational challenge. Almost all quantities that can be measured have units, but the numerical behaviour of models is frequently best analysed after out-scaling these units. The large number of symbols to work with calls for an advanced notation system, the role of which is more than just administrative; it

has strong conceptual aspects. We think that not only for DEB theory, but generally, it is a good idea to link symbols to dimension groups. This becomes clear in the dimensional analysis of expressions. It is unfortunate that dimension errors occur in many publications on models as authors frequently fail to pay sufficient attention to dimensional consistency. Any paper that deals with models should have a table with symbols, dimensions and descriptions.

A model has mathematical properties, which should be evaluated. It is important to know the properties of all tools used in research, models being no exception. The potential behaviour of a model needs to be known for judging goodness of fit and plasticity (see next paragraph). The reason to formulate a model is to apply it to data, so the next topic to consider is the problem of parameter estimation.

As with formulae, the variables of a model can again be deterministic or stochastic. Since deterministic models do not explain why data may not exactly match model predictions, deterministic models must be considered incomplete. Stochastic models, by contrast, capture the scatter in data, which is key to quantifying the accuracy of parameter estimates. A good fit does not imply accurate parameter estimates, although the reverse is generally correct: a bad fit typically comes with inaccurate parameter estimates, as revealed by the confidence intervals for parameters. The statistical literature on estimation and accuracy of parameters has a strong focus on scatter in data. Maximum likelihood estimation and least squares estimation, for instance, are powerful tools for estimating parameters from data. They assume that data are independently and identically distributed and follow a specified stochastic model, which may become prohibitively complex in cases where trials are not independent. Although accounting for scatter can be important, our experience is that model plasticity dominates parameter identification. Models can be ranked on a spectrum from stiff to plastic for a given parameter. A large change in the parameter value of a stiff model can have a small change in the prediction. The reverse applies for plastic models. Thus, parameters of plastic models are easy to estimate accurately, but a good fit hardly provides scientific support for that model. If the data were different, another parameter combination could fit well. The parameters of stiff models are difficult to estimate, but a good fit gives strong scientific support for the model. If the data were different, the good fit would be lost. So, stiff models are more falsifiable (in the Popperian sense). Kooijman (2018) gives an example of a stiff and a plastic model for biodegradation, both with three parameters. These differences will not be revealed by sensitivity or elasticity coefficients, which have related aims but operate only locally, for a limited range of the independent variable. We developed methods for evaluating the confidence intervals of parameters of deterministic models that are based on this stiffness/plasticity concept (Augustine et al., 2020; Lika and Kooijman, 2024).

Many variables contribute to biological data. Reproduction rate, for instance, not only depends on the size, but also on, e.g., temperature, food, reproduction history, and seasons. This diversity of variables requires the separation of independent from dependent variables in a regression context. Errors, or variation, in independent variables can contribute to deviations of predictions for dependent variables from data - a difficult problem to deal with. The standard statistical way of simply adding noise to deterministic predictions lacks realism. Formalized parameter estimation is based on the minimization of a loss function. For models with a single dependent variable, minimizing the classic least squared deviation between data and predictions typically gives satisfying results. However, we found serious problems (and satisfying solutions) when dealing with cases involving more than one dependent variable (Marques et al., 2019); see next section. For stochastic models with a degenerated dependence structure, the maximum likelihood (ML) criterion is popular with usually satisfying results: minus the log ML function is then treated as a loss function, although it is not a distance measure between predictions and data. Model parameters are typically constant. However, parameters in metabolic models that have time in their dimensions depend on temperature, as

temperature affects the rate of chemical transformations. Temperature might remain (nearly) constant – resulting in constant parameters – but can also vary in time.

The goodness of fit of models is frequently quantified as the mean relative error (MRE). A problem of the MRE is that the role of data and predictions is not symmetric, meaning that they cannot be interchanged without affecting the resulting value. So, under- and over-estimation have different impacts on the MRE. Most applications would try to avoid both of them; only some applications will have a preference for either over- or under-estimation. For this reason, the repository *Add_my_Pet* (AmP), for data on energetics and life history and DEB parameters and traits, works with several error quantifiers (AmP, 2024).

4. Theories: an explanation

When models need to do more than just describe relationships between variables, and the understanding of how and why they vary is important, an extra layer of requirements comes into play; the step from models to (quantitative) theory must be made. But first, what is a theory? We follow the definition by Nagel (1961): “A theory is a set of assumptions and propositions that are logically connected and that provide a framework for understanding and explaining phenomena, from which specific models can be derived”. This derivation should be a series of mathematical steps, without introducing new “hidden” assumptions. One must be clear which objects and/or processes the assumptions pertain to; ideally this should follow from explicit criteria.

A (quantitative) theory takes, in practice, the form of a collection of models that follow from the list of consistent assumptions. An example for a list of assumptions can be found in Kooijman (2010, 2020b) for the standard (std) DEB model. This model-collection typically has more than one member if several measured variables are involved. These models usually share some parameters, which requires the simultaneous estimation of parameters from data. For example, predictions for the two data points for maximum weight and maximum reproduction rate share parameters, for the simple reason that reproduction rate increases with body weight.

This sharing of parameters implies strong constraints on the loss function (Marques et al., 2019). The classic weighted sum of squared deviations between data and predictions no longer satisfies. Dimensional issues prevent the straightforward extension of this symmetric loss function to multiple datasets if the datasets differ in units. Attempts to solve these problems via weight coefficients by taking the inverse of the variance associated with each data point can only be done if multiple data-points are available for all values of independent variables; this is rarely the case. We proposed an attractive alternative: the symmetric bounded (sb) loss function which does not increase the number of parameters and retains symmetry (Marques et al., 2019). The function is a dimensionless distance measure between the data and the model predictions, i.e., the distance from predictions to data equals that from data to predictions, is non-negative, is zero if predictions equal data, and obeys the triangle inequality. The fact that the sb loss function is a distance measure helps in the comparison of local minima and it is also used in multi-dimensional scaling, which requires distances. Both aspects are detailed in Section 5.

Predictions for dependent data can depend on parameters and independent data (forcing variables), but not on other dependent data. This clearly separates the roles of independent and dependent variables in the more complex situation of parameter estimation using multiple datasets simultaneously. We call data that consists of a single data point “zero-variate” data, which qualifies as a value for a dependent variable, and can have several associated independent data, such as temperature, food availability or body size. Zero-variate data is specific for multiple datasets (i.e. when combined with other zero-variate data of different types) and, therefore, is rarely discussed in the literature. Single data points can rarely be used in isolation, but if available for different types of quantities, they are very useful for parameter estimation. The predictions of such data points are functions of parameters, so each removes one degree of freedom in a multi-parameter situation.

4.1. Auxiliary theory

A problem in quantitative theory is that variables that play a role in the assumptions can rarely be measured directly. This calls for auxiliary theory: a set of rules that link variables in the assumptions (core theory) to variables that can be measured. DEB theory works, for instance, with the concept of “structure” as a metabolic pool (see Section 5.2). Structure has mass, volume and potential energy, but can hardly be separated physically from “reserve”, another metabolic pool, for (direct) measurement. RNA, especially rRNA, has been proposed as marker for reserve and DNA for structure (Kooijman, 2010), but we feel that their usefulness in practice needs more experimental underpinning. An alternative assumption of auxiliary theory is that structural length, i.e. the cubic root of structural volume, is proportional to some well-chosen physical length. Since length depends on shape, there are many possibilities. The best choice for length depends on the list of assumptions (core theory). The wings of birds, for instance, only become functional later in development when they start to grow, so wing-length has a complex relationship with structure. Sometimes it is better to avoid the use of lengths and work with weights instead. But the contribution of structure to weight involves parameters, to determine the contribution of reserve (and the reproduction buffer) to weight. This is not a problem in itself, but shows that the relationship between parameters and measurements can be rather complex.

The rules in auxiliary theory are used in practice to convert independent data to values of (state) variables. For length-weight data, for instance, physical length is first converted to structural length (i.e., the cubic root of structural volume) to predict weight. When the match with data falls short, it does not automatically mean that one or more core assumptions need revision. It might also mean that a rule in the auxiliary theory should be revised. We see the duo “core and auxiliary theory” as a stratified set of assumptions, where a change in the rules of auxiliary theory has fewer consequences than a change in the assumptions of core theory, due to the restrictions of consistency and coherence that apply to core, but not to auxiliary theory. While core theory concerns mechanisms, independent of measurements, auxiliary theory depends on what is measured and is independent of ideas on mechanisms. We, therefore, use the label “rules” for auxiliary theory, rather than “assumptions”.

This combination of a core set of assumptions and auxiliary theory corresponds to a “research programme” in the sense of the philosophy of science of Lakatos (1970); the concept of a research programme expands on the simpler version of falsificationism by Popper, considering that scientific theories are not rejected based on a simple falsification (Chalmers, 2013).

4.2. Parameter estimation-in-context

In Section 3, a model was deemed good if it was simple, in terms of number of variables and parameters, and if its goodness of fit was high (small error of predictions for data). Models that represent a theory, however, can suffer from the problem of a good fit for the wrong reasons. So the estimation of parameters is more complex and involves more than just achieving a good fit; we call this “estimation-in-context”.

DEB theory assumes that parameter values are individual-specific and are determined by genetic, phenotypic and environmental factors. This is to capture evolutionary change in parameter values, via the principles of variation and selection. Inter-individual parameter variation is supposed to be small enough to talk meaningfully about mean values that are characteristic for a species (or a population).

Parameter estimation-in-context for DEB theory exploits the taxonomic coherence of parameter values among species. The volume-specific somatic maintenance, for instance, shows a huge scatter among all animal species, which can be understood in the context of the waste-to-hurry strategy (Kooijman, 2013), but within an order or family,

the scatter is much less. So far, we found five different patterns in parameter values for animals (Lika et al., 2023), four of which are empirical.

The dominant pattern is caused by the physical co-variation rules (Kooijman, 1986a), which classify all parameters either as intensive (= size independent) or extensive (= size dependent), solely based on their physical interpretation. No empirical argument is involved in this classification. Appropriate ratios of extensive parameters turn out to be intensive, and all intensive (functions of) parameters are assumed to have the same (mean) value among species. This simple rule already implies the standard body-size scaling relationships (some 35 different traits), as known in the eco-physiological literature, e.g. Calder, III (1984), Peters (1983), Schmidt-Nielsen (1983), including the famous 3/4-law of Kleiber (1932). Because ultimate body size itself is also considered to be a function of DEB parameters (Lika et al., 2019), it is more natural to talk about co-variation of parameters, rather than body size scaling relationships. The correct prediction for how traits depend on maximum body size thus counts as strong empirical support for DEB theory, as it does not involve any curve-fitting.

The way in which these co-variation rules are used in DEB parameter estimation is via pseudo-data (Lika et al., 2011a,b): a small set of intensive parameters that is treated as data (so predictions for them can deviate) and given small weight coefficients, compared to real data; the values of pseudo-data are based on (a precursor of) the AmP collection. The primary function of pseudo-data is to avoid parameter estimates that make no physiological sense and to better fix parameters that are poorly determined by the data.

A recently developed tool in DEB parameter estimation-in-context is the use of augmented loss functions (Lika et al., 2020), where parameters of several species are estimated simultaneously. Constraints on parameter values are then included as an extra term in the loss function, such as the squared coefficient of variation (variance over squared mean) of one or more parameters among the species. Such a parameter can vary between species, but not that much, depending on the choice of weight coefficients. A high weight coefficient for the squared coefficient of variation term of a parameter leads to the parameter being equal for all species; a weight of zero removes the restriction completely.

Another tool for estimation-in-context lies in the comparison of estimated parameters for (subsets of) the 4900 species in the AmP collection (AmP, 2024). When a taxon is close to “complete” in terms of literature with adequate data, a review is written for that taxon in which the distributions of many traits and relationships between pairs of traits are evaluated, e.g. for fish (Augustine et al., 2022; Kooijman and Lika, 2014; Lika et al., 2022), petrels and penguins (Kooijman, 2020a), cephalopods (Kooijman and Augustine, 2022b), turtles and crocodiles (Marn and Kooijman, 2022), carnivores and pangolins (Kooijman and Augustine, 2022a), and branchiopods (Kooijman, 2024b). Outliers are then revisited to check if the data really support their outlier position.

Several of these reviews also contain a multi-dimensional scaling (mds) analysis for a set of traits (Kooijman et al., 2021); this provides another check on outliers, but now on combinations of traits, rather than on single traits. The scaling is done on a distance matrix between a set of traits (the AmP collection has values for hundreds of traits for each species) for a set of species, using the symmetric bounded loss function as a distance measure. Mds has sometimes spectacular results, such as the complete separation of the waterfleas from other branchiopods (Kooijman, 2024b); within the waterfleas, the daphnids, which are pelagic, come out separated from the chydorids, which are littoral. This separation is not evident from any single trait in the database. This example illustrates that not only taxonomic but also ecological differences can be of importance for traits, and so for parameter values.

Evolutionary coherence forms the basis of the estimation-in-context methods for DEB theory. Even for many non-biological topics, appropriate contexts can be found based on the interpretation of parameters.

In summary, estimation-in-context augments data with pseudo-data and implements the “context” through the sb loss function. It evaluates its local minima in the knowledge that some local minima of the loss function can be very close to the global one, but the corresponding parameter values might differ a lot in realism. It uses all datasets simultaneously, even for datasets for which ML methods would be applicable, such as survival data. Our experience is that the sb loss function gives comparable or even better results than the ML loss function for survival data (Augustine et al., 2020), and better combines different types of data for which ML are not applicable. We use the Nelder–Mead simplex algorithm to locate the local minima, starting from initial values. This method is slow, but robust.

4.3. Testing for a good fit for the right reasons

More elements of the philosophy of science come into play for modelling of the theory-type; modelling becomes intimately connected with experimental research to assess/appraise if a good fit is for the right reasons. This prompted an explicit view on the empirical cycle, see Fig. 1, where, ideally, each assumption is tested experimentally one by one. In the context of DEB theory for metabolism, however, this is rarely possible in detail, since the variables in metabolism are intimately cross-linked.

Nevertheless, perturbation is a powerful approach to experimentally test assumptions in such complex cases. A natural candidate for perturbation is changing environmental variables - primarily temperature and food availability - but we can also think of chemical perturbations. DEB theory originated in ecotoxicological research and continues to be applied there (Aagaard et al., 2023; EFSA Scientific Committee et al., 2019; Ockelford et al., 2018; Zubrod et al., 2024). The general idea is that as chemical compounds (slowly) enter the body, starting from concentration zero, one or more parameters start to change proportionally to the body concentration of the compound in excess of the no-effect concentration for that compound. The change in parameters affects traits such as feeding, respiration, growth, reproduction, and survival, from which the mode of action of the chemical compound can be derived (Kooijman and Bedaux, 1996; Ashauer and Jager, 2018), i.e. effects on traits reveal what parameters are affected. At low body concentrations only the most sensitive parameter for that compound changes, at higher concentrations more parameters might respond. For this purpose, DEB assumptions need to be augmented with assumptions on toxico-kinetics for the various accumulation and elimination routes, chemical and metabolic transformations, mixtures and the like. This type of research is not only useful for testing DEB assumptions, but also for quantifying toxicity of a compound; a large field, indeed, in the context of environmental risk assessment.

Another powerful concept in testing theories is stylized facts (Souza et al., 2008; Lorena et al., 2010), a concept that originated from economics (Kaldor, 1961). These facts summarize (semi-qualitative) patterns in data, without making the step to modelling, and can serve as touchstone to check implied properties of models. They played a key role in the selection of all possible topological alternatives for the organization of metabolic fluxes in the standard DEB model (Lika and Kooijman, 2011).

4.4. Data completeness

The many processes that are interlinked in metabolism involve more parameters than is convenient for a simple collection of datasets. Several parameters need to be fixed at default values. We score the completeness of data, relative to what is necessary to estimate all model parameters from data, on a scale from 1 to 10 (Lika et al., 2011a). Extension or refinement of the completeness scale is possible, as the presence/absence of data required for estimating thermal response parameters is not scored within the current completeness scale, but is relevant for predicting thermal responses of species under climate

change (Cheng et al., 2025). Reducing the multi-dimensional problem of used data to a scalar obviously has its limitations, but still can be valuable when comparing entries. Most entries in the AmP collection score around 2.5 and the maximum scores at 6, illustrating the need for more data to quantify metabolism in all its aspects.

We studied the link between what data is available and what parameters can be estimated (Kooijman et al., 2008). In many cases, compound parameters, i.e. simple functions of parameters, can be estimated, where parameters themselves cannot. In the extreme case where datasets consist of a single data point, such as maximum reproduction rate, maximum weight, or incubation time at abundant food, it is possible to map data to parameters, and parameters to data, i.e. a bijection exists (Lika et al., 2014); code is available in DEBtool (2024) for up to 9 parameters or data points. A small change in data might give a large change in parameters and vice versa, as quantified by elasticities (Lika et al., 2014). For parameter estimation it is typically better to use more data.

4.5. Generality based on physical conservation laws

Individuals are very open systems in terms of mass and energy. This is why conservation rules for energy and mass (of chemical elements and isotopes) take the form of balance equations. Time is also conserved, constraining the timing of behavioural traits.

The significance of these conservation principles is that an entropy balance is only possible if an energy balance is available, and an energy balance is only possible if a mass balance for chemical elements is available (Sousa et al., 2006). When entropy cannot be quantified, metabolism is not fully specified. The concept of macro-chemical reaction equations, as frequently used in biotechnology, plays an important role in the practical implementation of mass conservation.

DEB theory employs conservation rules explicitly, which allows it to be very general; it is thought to apply to all organisms. Mass conservation is exploited by quantifying respiration in a way that is consistent with the method of indirect calorimetry, without making any direct assumptions about respiration. This method takes dissipating heat proportional to a weighted sum of dioxygen consumption, carbon dioxide and nitrogen-waste production; a notion developed by Lavoisier and Laplace (1780) but, as it seems, largely overlooked in modern ecology. The emergence of respiration from the application of mass conservation in itself constitutes a strong theoretical result, since many metabolic processes contribute to respiration. The resulting interpretation of respiration as a composite outcome of dissipative metabolic processes links up with the traditional physiological view on respiration. It contrasts with a view now common in ecology and evolutionary biology where respiration is equated to metabolic rate and viewed as a driver of metabolism that explains e.g. body size scaling relationships and is a direct target or outcome of natural selection (Nilsson and Nilsson, 2016; Videliier et al., 2021; White et al., 2022).

A standard way to compare and select models in theoretical biology is to replace an assumption by a different one, derive the model that is implied, and see what model fits data best. When this was tried for the assumptions of the standard DEB model, inconsistencies resulted (Kooijman, 2020b). Further research revealed that the conservation rules for energy and chemical elements turn out to restrict the class of possible models substantially. In the end, a 7-step reasoning was found that concludes that no alternative for the standard DEB model exists or will exist with comparable complexity. Kooijman (2020b) invites to find errors in the reasoning; we hope that there are reasoning errors, since we believe that alternatives would help the further development of DEB theory.

4.6. Code support, database and FAIR-ness

It is nowadays unthinkable to develop a theory without providing supporting code for its applications. This especially holds for DEB

theory, where parameter estimation-in-context very much relies on a database. This database needs maintenance and extension and its use requires intensive code support.

The code package DEBtool (around 8000 files in Matlab, including documentation) supports the application of DEB theory in general (DEBtool, 2024); part of it is also translated into R and Julia and is freely available from GitHub, making the code and models Findable, Accessible, Interoperable, and Readable (Wilkinson et al., 2016). The package is used, for instance, to generate predictions for entries in the AmP collection (AmP, 2024), enabling the predict-functions to be concise and parameter estimation to be reproducible.

The code package AmPtool (roughly 10000 files in Matlab, including documentation) supports the analysis, the curation of submissions, and the maintenance of the AmP collection. Half of the files concern the taxonomic tree for animals in the form of lists-of-lists, which is used by selection functions to extract AmP entries. Taxonomy is a dynamic field requiring frequent changes in the lists-of-lists. The lineage from *Homo sapiens* to Animalia has presently 32 taxa, for example. This might change with the growth of the collection; we aim for two members per node in the tree.

AmP collection

DEBtool and AmPtool support the Add_my_Pet collection (AmP, 2024; Kearney et al., 2021; Marques et al., 2018, 2019), the online freely available database of entries that includes the underlying (referenced) data, metadata, and the resulting DEB parameters and traits. It was started in 2009 as a course exercise, but evolved since 2015 into a journal-type format, where anybody can submit entries, which are curated by a team before addition.

The database presently has 4900 animal species from all large animal phyla, which are presented in a large website (presently some 12e4 files) with many search and scanning options. The website has mirrors on 2 servers (at VU, Amsterdam, and IUEM, Brest).

All entries have data with references and predictions, metadata, parameters and traits, and a page on population properties. The metadata includes species classification, eco-codes, data completeness score, list of data-types, author and curator names, dates of submission, modifications, acceptance, links to relevant websites, facts, general and data-specific discussion points, and comments. The MRE is given for each data set and for the entry as a whole. AmPtool contains all functions that have been used to create the AmP website from 4 source files per entry, which are also downloadable. The whole process from data to parameter estimates can be redone in detail using the 4 source files for each entry, if DEBtool and AmPtool are available. See Fig. 2.

Over time, more data is found in the literature, or becomes available by measurement. Our ideas on the best parameter values can change, as a result of our estimation-in-context efforts. These processes invite new updates of existing entries in the AmP collection. We archive “obsolete” entries in the form of a zip-file with the 4 source files; publications might refer to them. The archive presently has 2500+ entries, illustrating the dynamics of the AmP collection. The collection adheres to current FAIR principles (Wilkinson et al., 2016).

The entries differ considerably in the types of data that have been used for parameter estimation, so the entries cannot be compared on the basis of data. Moreover, data differ in temperature and food availability, while comparison is easiest after eliminating such differences. By contrast, DEB parameters and traits enable direct comparisons (Kooijman et al., 2021), especially if the same DEB model was fitted. We see this as an important asset of DEB models.

We are very much aware of the problem that parameter values can be erroneous, but it would be naive to think that data is always correct in values or interpretations. The reported egg and neonate sizes of the ovoviparous Greenland shark, for instance, differ way too much to neglect pre-natal food intake (Augustine et al., 2022). Moreover the reproductive output would be too large if all eggs developed into neonates. So either many eggs are reabsorbed, combined with uterus

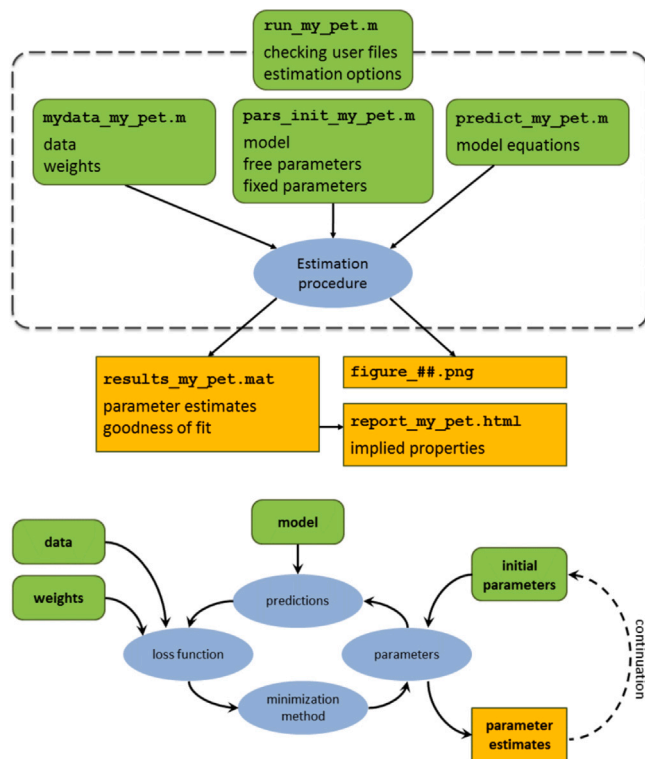


Fig. 2. The workflow for preparing an AmP entry.
Source: From Marques et al. (2018).

milk secretion by the mother, or pre-natal cannibalism among siblings occurs after hatching. The scientific puzzle is that neither option is known in this shark family. DEB theory can be used to detect such problems; another important asset of a database in the context of a well-tested theory. From our curation work we know that checking how models are applied to data is one thing, but checking the data itself is at least as important.

Parameters and traits of all AmP species are collected in two large Matlab structures `allStat` and `popStat`, which can be exported to other programming languages such as R and Python. AmPtool has many functions for selection and representation of parameters and traits from these structures. The selection not only involves the taxonomy, but might also include e.g. eco-physiological characteristics, such as climate and habitat, as specified in AmPeco (2024). Trait values can, naturally, also be used for selection.

Dedicated code

Apart from DEBtool and AmPtool, we have developed a rapidly growing collection of code for special applications, see DEBlab (2024). Examples are the Matlab package DEBtox (Jager, 2011, 2020) that can be used to analyse the results of toxicity tests, supplementing the facilities in DEBtool and AmPtool, and the Julia package DEB-microTrait (Marschmann et al., 2024) that models traits of micro-organisms. Shiny apps produce simulations of trajectories of a selection of energy budget traits interactively, using parameter values from the AmP collection and databases for local environmental conditions. The user can change parameter values to see the effect on the trajectories. These Shiny apps are integrated in a much larger package in R, NicheMapR (Kearney and Porter, 2019; Kearney, 2024), which links models in biophysical ecology with those in the geometric framework for the nutritional niche (Briscoe et al., 2023; Kearney et al., 2010), in which DEB theory plays an important role. NicheMapR has many facilities to link data on local microclimate from large databases to traits derived from DEB theory. We see this as crucial for autecology, e.g. to

understand phenology and behaviour under natural environments and the boundaries of the geographical distribution of species.

These examples illustrate a general rule for DEB applications: few problems can be solved using DEB theory only. Most applications require supplements from other fields, implying the need for a modular approach. DEB theory fits ideally in the modular approach because it follows from explicit assumptions that define the interface with the environment and thus avoids inconsistencies.

5. Metabolic theory based on general principles

So far, we structured modelling requirements depending on the aim of models, stressing the importance of notation and dimensions in all cases. We discussed how the position of models in the stiffness/plasticity spectrum dominates the accuracy of parameter estimates. If models need to be explanatory, they should take the form of a quantitative theory, requiring

- 1 explicit assumptions from which the models follow mathematically
- 2 an integration with experimental work to test assumptions
- 3 parameter estimation-in-context to avoid a good fit for the wrong reasons
- 4 a specification on what objects/processes the theory is supposed to apply to.

This section discusses general explanatory models (i.e. general theories), for which an extra set of requirements applies: they need to be explicit on all relevant general principles, or at least explain why these principles are not that general in the context of the theory. So these models need to address a specified set of topics. They also need to be embedded in a wider scientific context. Since this subject risks becoming meaninglessly abstract, we again use DEB theory as concrete example. But, as stated in the introduction, similar requirements apply to general theories on other topics.

DEB theory is supposed to be very general, beyond the implementation of conservation laws, so there is a need to explain how it can be so and to show how the theory deals with scales in space and time, so how it connects with neighbouring fields in science (final sub-Section 5.7). The underlying idea is that DEB theory can be that general because it is built on a number of general principles. In other words, any general model/theory for metabolism has to deal with these principles in one way or another. So dealing with these principles can be seen as an extra layer of requirements that apply to all general models on metabolism. The first five sub-sections (5.1-5.5) explain how DEB theory meets these requirements. Sub-Section 5.6 gives more background to parameter estimation-in-context and how this provides a basis for developing meta-theory for parameter estimates and traits, i.e. functions of parameters. It has the potential to become a theoretical backbone for evolutionary biology of life history traits, deeply rooted in data and free from optimization speculations (Jusup and Kearney, 2024).

5.1. Forms of homeostasis

DEB theory employs several forms of homeostasis, defined as the ability to run metabolism as independently as possible from the environment.

The implementation of mass conservation comes with the need to delineate metabolic pools that do not change in chemical composition, a concept that we call strong homeostasis.

The concept of weak homeostasis builds on strong homeostasis: In a system with two metabolic pools (reserve and structure, see next subsection), the mass of reserve does (eventually) not change relative to that of structure during growth under constant food conditions. This implies that the contribution of reserve to weight is a fixed fraction, and weight becomes proportional to cubed length for isomorphs (if

the reproduction buffer does not contribute). Hundreds of AmP entries support this finding empirically. It took 25 years to discover that the weak homeostasis assumption fully specifies the mobilization of reserve (Sousa et al., 2008). This assumption is very hard to avoid if the chemical composition of reserve and structure needs to be known. By comparing whole-body concentrations of any compound for different food densities, the fractions in reserve and structure can be assessed if weak homeostasis applies (Kooijman, 2010).

With acquisition homeostasis we mean that food intake hardly depends on food availability, except in extreme cases, of course. It applies only for some taxa and only to some extent. This form of homeostasis is approached for increasing food searching rate, so most time is spent on food processing, while the latter is taken to be independent of food density. Acquisition homeostasis has intimate links with the supply–demand spectrum (Lika et al., 2014, 2023) that exists among animals. The spectrum has strong taxonomic coherence: birds and mammals are close to the demand-end of the spectrum, followed by the other vertebrates, while the invertebrates are near the supply-end of the spectrum. This is fully consistent with the physiological literature on supply/demand, e.g. Withers (1992).

5.2. Metabolic pools and syntrophy

As mentioned before, DEB theory works with two classes of metabolic pools: reserves and structures.

Resources taken up from the environment are first transformed into reserve(s) and then mobilized for use in the rest of metabolism. The number of reserves that need to be delineated equals the number of essential resources (nutrients, light) that are taken up independently and that may limit metabolism. The dynamics, as follows from the list of assumptions, works out such that the non-limiting nutrients do not need to be included explicitly, although they might complicate aspects of mass conservation.

Structures have a quality, called maturity, and require maintenance. The number of structures that need to be delineated depends on the type of organism and the aim of the research. Plants, for instance, minimally require root and shoot as structures. Many aspects of animal metabolism can be understood with a single reserve and a single structure. This is because animals feed on other organisms, which couples all nutrients and compounds that are required for animal metabolism. This broad applicability of a simple DEB scheme invited the setup of the large AmP database for data on animal energetics, the estimated DEB parameters and the large number of traits that follow from these parameters (AmP, 2024). Some applications require particular organs as separate structures.

Assimilation and mobilization drive the turnover of reserves, whereas a part of maintenance is used for the turnover of structures.

Many species are involved in symbiotic interactions, which can typically be captured well by syntrophic exchange of metabolites (Eynaud et al., 2011; Kooijman, 2004; Muller et al., 2009). The quantitative aspects are specified using Synthesizing Units (see next subsection) (Kooijman, 1998; Muller et al., 2019a). Scenarios for the evolutionary development of the pool-structure of DEB models and for the modules of the central metabolism and for symbiogenesis have been worked out in the context of DEB theory (Kooijman, 2004; Kooijman et al., 2003; Kooijman and Hengeveld, 2005; Kooijman and Troost, 2007; Troost et al., 2005). The exchange of metabolites between partners in a symbiosis has a lot in common with the concept of canonical communities of producers, consumers and decomposers (Kooijman, 2010; Meer et al., 2022). These groups of organisms are in fact partners in a syntrophic exchange, like trees, which supply fallen leaves to the soil flora with the latter providing nutrients in return.

A community of mixotrophs and decomposers is an interesting degenerated canonical community, where the roles of producers and consumers are combined (Kooijman et al., 2002; Livanou et al., 2020,

2021; Troost et al., 2005). When mixotrophs live in a homogeneous water column, it is very difficult to let them spontaneously segregate into phototrophs and heterotrophs over generations. But if light extinction in the water column is taken into account, it is very difficult to avoid this segregation, at least partially (Troost et al., 2005).

5.3. Metabolic transformation by synthesizing units

Metabolic transformations are quantified on the basis of flux-based theory, using the concept of Synthesizing Units (SUs). It parallels enzyme kinetics (Kooijman, 1998) but bypasses the notion of concentrations, which is a problematic concept in spatially structured cells. The theory classifies the processing as parallel or sequential, and compounds as substitutable or complementary. They are key to the implementation of the conservation of time in metabolism.

The concept of SU can also be used for modelling the behaviour of an individual, since it is fully consistent with Markovian processes (Haccou and Meelis, 1992). The conservation of time here becomes explicit when differentiating between sequential and parallel acts. Sleeping, for instance, must be sequential to food searching, but can partly be parallel to food processing (digestion), see Kooijman (2024c). Social interaction, another application of SU dynamics, reduces time that is available for food searching, like sleeping, but in a way that depends on the population size. The latter aspect is important for avoiding competitive exclusion in situations where the number of competing species exceeds the number of resources (the paradox of the plankton) and for avoiding the paradox of enrichment (Kooijman, 2024c).

Complex transformations such as inhibition, co-metabolism, and photosynthesis, which involve elaborate expressions using classic enzyme kinetics, work out to be rather simple in the SU context (Brandt et al., 2003; Brandt and Kooijman, 2000; Kooijman, 2010; Marn et al., 2020; Vinga et al., 2010; Muller et al., 2019a; Muller, 2011). Although DEB theory makes intensive use of SUs, they can be used by any model or theory that deals with chemical enzyme-mediated transformations or behavioural traits.

5.4. Surface area – volume relationships

If an individual does not change in shape during growth, a situation known as isomorphy, surface area (linked to food intake) is proportional to volume (linked to maintenance) to the power 2/3 (Archimedes, 287 BCE). The importance of the surface area-volume interactions was already known to Wallace (1865) and possibly originated from Sarrus and Rameaux (1838). Isomorphy can be seen as a form of homeostasis and is an assumption of the std DEB model, but not of DEB theory in general. The surface area of quite a few animal species is, during a rather short period after birth, proportional to volume. Since assimilation is then proportional to maintenance, growth is exponential, a situation that we call metabolic acceleration. Again, there is a strong taxonomic pattern here, e.g., none of the tetrapods undergo metabolic acceleration and most species with larval stages do, such as molluscs and echinoderms. The surface area of plants typically varies with volume to the power 1, just after germination, then to the power 2/3, and finally, in a closed vegetation, to the power 0 (Kooijman, 2010): they can still increase in mass but not in surface area that is involved in nutrient uptake or light capture, because of their neighbours. Rod-shaped bacteria, which grow in length only, represent a dynamic change of the power value from 0 to 1 (Kooijman, 2010), just the opposite of plants.

Not only organisms, but also the ontogeny of stars and planets is dominated by surface area–volume interactions, e.g., Krauskopf and Beiser (1993). Since many biochemical transformations are catalyzed by enzymes bound to membranes (i.e. surfaces) and their action causes changes in concentrations of substrates and products (linked to volumes), the size of a cell is reflected at the molecular level. Surface

area/volume interactions dominate rates from molecules to the universe, a scale-independent organizational principle of physical transport.

Surface area–volume relationships play an important role in the dynamics of microbial populations (Kooijman et al., 1991), since metabolic acceleration removes the individual structure in a population (one huge individual behaves identically to a large number of small ones), and methods were developed to approximate structured population with unstructured ones. This works especially well for organisms that divide in two parts, so have small size range; the wider the size range during ontogeny, the more significant the difference becomes between structured and unstructured population dynamics models.

The choice of DEB model is typically made at the family or order level, not at the species level. Some taxa have extra life stages, e.g. holometabolic insects have a pupal stage (Llandres et al., 2015), which require extensions of the std model. The DEB model equations are summarized at https://debportal.debtheory.org/docs/Typified_models.html and presented in various contexts in Jager (2020), Jusup et al. (2017), Kearney et al. (2015), Kearney (2021), Kooijman (2001, 2012, 2020b), Ledder (2014), Lika and Kooijman (2011), Meer (2006), Muller et al. (2019b), Sara et al. (2014), Sousa et al. (2006, 2008).

The simplest formulations are deterministic, but processes relating to survival, such as aging, and processes relating to behaviour, such as food searching, are stochastic by nature (Kooijman, 2009a). The comments (Kooijman, 2024a) on section 2.9 of Kooijman (2010) present the stochastic version and a simulation of trajectories, which show that stochastic effects on respiration are huge, explaining why respiration data typically show substantial scatter (section 4.3.1). Stochastic inputs pose a challenge for statistics since the whole behaviour of the system becomes stochastic, but in ways that hamper formulations of likelihood functions for parameter estimation (Marques et al., 2018). Stochasticity has strong implications for population dynamics (Kooijman et al., 2007b).

5.5. Development parallel to growth

Any model for metabolism at individual level needs to specify development, since development structures the life cycle and so life history traits. DEB theory assumes that a fraction of mobilized reserve is allocated to somatic maintenance plus growth (defined as the increase of structure), the rest to maturity maintenance plus maturation (in embryos and juveniles) or reproduction (in adults); so development is parallel to growth. In the simplest DEB models, this fraction κ is taken to be constant, but static and dynamic generalizations have been worked out to capture the differentiated development of organs linked to their workload, such as the hearts of athletes, or tumors (Leeuwen et al., 2003; Tosca et al., 2021, 2020), the development of which very much depends on the state of the host. Life history events, such as birth, i.e. the onset of feeding, or puberty, i.e. the end of further maturation and the onset of allocation to reproduction, are linked to the maturity level; maturity is supposed to have no mass or energy and is quantified as a cumulative investment of reserve that dissipates. Remarkable implications of this so-called κ -rule are that embryo and juvenile development only differ by assimilation (Kooijman, 1986b, 2009b) and that reproductive output is almost proportional to mass, strongly depending on nutrition; these implications are well-supported by AmP data. The ratio of the maturity at birth and puberty is a natural quantifier for precociality (Augustine et al., 2019): how late in the development birth occurs. Staging atlases for development are usually based on size, since time at a particular stage varies too much between individuals, e.g. as result of differences in temperature. Yet, even size at a particular stage varies considerably, since it depends on nutrition. At least part of this variation can be avoided by linking stages to maturity levels (Augustine et al., 2011), allowing for more accurate staging, which is important for the comparison of experimental results in developmental biology. This parallel organization of development

and growth is key to understanding variations in the timing of developmental events, as studied under the label of heterochrony in the literature, and also to capturing a number of stylized facts on growth and reproduction (Lika and Kooijman, 2011).

Although maturation ceases at puberty, metabolic performance can still change until death, even without considering consequences of growth. DEB theory captures these changes, such as post-reproductive periods, as side effects of aging. The theory takes the view that Reactive Oxygen Species (ROS), which are formed by respiration, are partly transformed to damage inducing compounds (i.e. changed mDNA), continuously producing damage compounds (i.e. changed proteins), which accumulate in the body and can lead to changes in parameter values, just like toxic chemical compounds can do. The simplest DEB models only include the effect on the hazard rate, which controls the timing of death in ways that depend on nutrition and temperature. The popular empirical aging models of Gompertz (1825) and Weibull (1951) turn out to be special cases of the aging module of DEB theory, but now linked to metabolism and so to environmental conditions (Kooijman, 2010). The life span of species of many taxa was found to be inverse to the weight-specific respiration at maximum size (Augustine et al., 2022), which further supports this aging implementation. The limitation of life span is essential for feasible population modelling to ensure that the memory of the population-state is limited as well.

In summary, the pre-puberty changes in metabolism are attributed to development, when the accumulation of damage compounds remains limited due to dilution by growth. Conversely, post-puberty changes in metabolism are attributed to side effects of ageing. The overall effect is that metabolism is changing continuously during the full life cycle.

5.6. Meta-theory

The assumptions underlying DEB theory have no direct implications for parameter values. This is why we call patterns in parameter values and their explanations meta-theory. This pattern-searching can be done, in principle, with any metabolic theory that applies to all species, although we presently do not know examples other than DEB theory. As described before, the physical co-variation rules form the backbone of the patterns found so far. We have developed a very similar reasoning for toxico-dynamic and toxico-kinetic parameters (Jager and Kooijman, 2009; Kooijman et al., 2007a), based on the one-compartment transport model for chemicals and its relatives (e.g. film-models). It is an (and possibly *the*) explanation for the popular empirical Quantitative Structure-Activity Relationships (QSARs) for how effects/toxicity depend on chemical properties, such as octanol-water partition coefficients. This transport model is independent of DEB models, but our reasoning suggests deep connections between both models, which we understand only partly, and also that the reasoning may be applicable to a wider class of models. We think that surface area-volume relationships play a key role here; we already identified already them as a universal organizational principle.

Our primary aim with the AmP collection is to develop meta-theory for DEB theory: finding patterns in parameters and traits and try to understand these patterns in an eco-evolutionary context. As described above, we found five different patterns so far (Lika et al., 2023). The understanding of patterns does provide strong (indirect) support for DEB theory because of evolution. Apart from effects of temperature and some other special situations (Kooijman, 2014), DEB parameter values can typically be treated as constant for an individual during its life cycle. The differences between parameter values among species are the result of eco-evolutionary adaptations, which occur at a much longer time scale than the life cycle of individuals and provides taxonomic coherence of parameter values. This coherence is exploited by our estimation-in-context methods.

5.7. Embedding of theory: time-space scales

As mentioned before, DEB theory originated in ecotoxicological research. Apart from quantifying how chemical compounds affect traits of test organisms during exposure under controlled laboratory conditions, many other aspects of environmental risk assessment are relevant. One example is how effects observed in the laboratory during short exposure translate to expected effects in the environment during long-term exposure at varying environmental conditions. Some issues become important such as exposure, transport, transformation, (bio)degradation and last, but not least: how effects on individuals work out at population and ecosystem levels (Kooijman and Metz, 1984; Kooijman, 1985; Nisbet et al., 2000; Martin et al., 2013).

Techniques like time-scale separation are frequently applied and are basic to SU dynamics. Metabolite exchange based on syntrophy and surface area/volume relationships are additional tools to link modules across scales. The general idea is that the importance of processes is scale-dependent and that unimportant processes should be removed via simplification and approximation to reduce the number of variables and parameters.

The simple assumption that individuals follow the standard DEB model and only interact by competition for food in a homogeneous environment leads to unrealistic properties at the population level, despite being well-tested for individuals. The problems include juvenile-driven cycles, the paradox of enrichment and competitive exclusion (Kooijman, 2024c; Meer, 2016); none of which seen in reality. These problems can all be solved in realistic ways, but point to the fact that models can be too simple to be useful.

The context determines the level of detail of the theory that is required, and urges us to think in terms of families of models, where modules (= sub-models) can be inserted in or removed.

6. Discussion

This paper shows that mathematical methods are essential for quantitative models, but are free from many problems associated with models. This is because the interpretation of parameters and variables is not involved in mathematical methods and parameter estimation is not an issue. The models require the interpretation step, which comes with a set of complications that have no direct relationship with mathematics but instead relate to methodology and philosophy of science. Statistics covers only part of these complications, but does not address e.g. deterministic models and the concept of model plasticity.

Although quantitative theories take the form of models in practice, not all models represent theories according to the criteria discussed in this paper. Whether they do depends on their generality and how they are constructed: models that represent theories should follow from a list of explicit assumptions. The process of splitting up modelling to (re)construct a list of underlying assumptions has a lot of similarities with the art of coding and requires training. General theories come again with an extended set of requirements: they need to be explicit about a number of general principles which has implications for the topics in list of assumptions. We see this as a next step in the sequence formula, descriptive model, explanatory model (= quantitative theory) to general theory. It helps to become aware of all (previously implicit) assumptions that are made. This list again involves complications, dominated by the issues of coherence and consistency, and more elements of the philosophy of science are important for theories, compared to models. Parameter estimation then must be conducted within a scientific context that lies beyond the reach of statistics alone, necessitating the integration of modelling with experimental research.

What we see as our main contribution to good modelling practice is our plea to integrate thinking about explanatory models fully with scientific methods in general, not making modelling an art in itself, but to stimulate model-based thinking as part of experimental design and data acquisition in general. Following this practice will automatically

result in compliance with most of the recommendations by Jakeman et al. (2024, this issue).

Mathematical statements are either wrong or follow from assumptions. But the reasoning steps that show how statements follow from assumptions can be many and complex, making the statements all but self-evident. DEB theory illustrates this notion; the steps from assumptions to models that are used for predictions of traits can involve quite a few reasoning steps. As with any advanced tool, users should know how it functions to avoid mistakes. This does not mean that there is a need to understand all derivations in detail, in the same way that driving a car safely can be done without detailed technical knowledge.

A theory is a tool, rather than an endpoint of science, and the usefulness of theories lies in the applications. With the progress of science, theories can lose their application, but may still be valuable for developing new theories. This process not only depends on the concepts or the mathematical structure of the theory, but also on technology for new types or quantities of data. The enormous size of the rapidly growing literature forms an increasing problem for the progress of science, motivating many workers to pursue extreme forms of specialization. Stand-alone models are likely to have a short lifetime in active science, which motivated us to work on a broad and coherent field (Sousa et al., 2010).

Similarly, stand-alone data (sets) are likely to have limited impact on science; DEB theory exemplifies how disparate stand-alone data can be integrated into a coherent framework with wide-ranging impacts. This motivated us to create a large database, which hopefully will cover a large part of published data on animal eco-energetics, including the old (but valuable) literature. We hope that this new data is measured by scientists with DEB theory in mind, which would facilitate parameter estimation and lead to more accurate parameter values.

Compared to physics and chemistry, biology still lags behind in quantitative theories. Many biologists do not see the scope for quantitative theories in biology with its bewildering species diversity. Yet, we think that if one does not try, biology will remain a descriptive science, unable to support research on how to deal with environmental change and degradation. Our experience thus far in developing DEB theory convinces us that there is a scope for quantitative biological theories that are consistent with thermodynamics to meet this challenge.

CRedit authorship contribution statement

Sebastiaan A.L.M. Kooijman: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Michael R. Kearney:** Writing – review & editing, Software, Methodology, Data curation, Conceptualization. **Nina Marn:** Writing – review & editing, Software, Data curation. **Tânia Sousa:** Writing – review & editing, Methodology, Conceptualization. **Tiago Domingos:** Writing – review & editing, Conceptualization. **Romain Lavaud:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Charlotte Récapet:** Writing – review & editing, Conceptualization. **Tin Klanjšček:** Writing – review & editing, Conceptualization. **Tan T. Yeuw:** Writing – review & editing, Data curation, Conceptualization. **Gonçalo M. Marques:** Writing – review & editing, Software, Data curation, Conceptualization. **Laure Pecquerie:** Writing – review & editing, Software, Data curation, Methodology. **Konstadia Lika:** Writing – review & editing, Data curation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare to have no conflict of interest.

Data availability

No data was used for the research described in the article.

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