Dynamic energy budgets in population ecotoxicology: applications and outlook

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ABSTRACT

Most of the experimental testing in ecotoxicology takes place at the individual level, but the protection goals for environmental risk assessment are at the population level (or higher). Population modelling can fill this gap, but only models on a mechanistic basis allow for extrapolation beyond the conditions in the experimental tests. The life-history traits of individuals form the basis of population dynamics, and population modelling thus requires a proper understanding of the individual's behaviour. The Dynamic Energy Budget (DEB) theory offers a flexible platform for the development of models at the individual level. Linking DEB models to population models can thus provide a mechanistic basis for extrapolation. Here, we provide a conceptual overview of DEB theory, with emphasis on its applications in ecotoxicology. Furthermore, we briefly review the applications in which a DEB-based individual model has been linked to structured population dynamics. Finally, we discuss some of the most important areas for further research in this context.

Keywords: dynamic energy budget; review; ecotoxicology; TKTD models; population models

1. Introduction

Environmental risk assessment aims to predict the impacts of anthropogenic stressors on populations and communities. However, most of the experimental testing takes place at the individual level. Laboratory testing usually comprises exposure to a constant concentration of a single toxicant, for a pre-defined period of time, under controlled environmental conditions, with *ad libitum* food supply. In the environment, however, multiple stress is the norm,

exposure concentrations vary in time and space, and environmental conditions fluctuate. This huge gap between the simplified conditions of the toxicity tests and the complexity of the field situation can only be covered in an ecologically-relevant way by using population models to extrapolate from individual-level traits to population responses. However, due attention should be given to the extrapolation of traits from the experimental test to the same traits under the environmental conditions experienced in the field. This requires mechanistic models at the individual level.

Models at the individual level can be of great assistance in designing toxicity tests, interpreting the individual's response to stress, and to extrapolate that response to untested conditions (Ashauer and Escher, 2010; Jager et al., 2006). For a model to be useful at the individual level, it should explain life-history traits (feeding, survival, growth and reproduction) over the life cycle of the organism, as a function of the environment (e.g., food availability, temperature), and the presence of stressors (e.g., toxicants). The model should allow educated extrapolation from the response in controlled environments (e.g., laboratory toxicity tests) to field conditions, where populations are to be protected. The model should be as generic as possible regarding the species, chemicals, and environmental conditions that it can cover; we simply cannot build a dedicated model for each combination. Finally, the model output should allow its coupling to population models of different levels of complexity (e.g., matrix models or individual-based models), since the most appropriate population-level strategy may well depend on the risk-assessment question.

What strategy should we apply to develop mechanistic models at the individual level? Clearly, modelling every individual process at the molecular level is unlikely to yield practically-useful models. Processes at this level are also rather specific for each stressor, and each species. Fortunately, we can invoke some general biological principles to structure our modelling efforts. Every living organism takes up resources from its environment, and uses these resources to build and maintain their own bodies, and to create offspring. In doing so, they must adhere to the conservation laws for mass and energy. Models that operate on these principles are generally called energy budgets. A number of bioenergetic approaches have been proposed in ecology (see discussion in Sibly et al., 2013; Van der Meer, 2006), but the best-tested and most extensive framework in this field is the Dynamic Energy Budget (DEB) theory (Kooijman, 2001; Nisbet et al., 2000; Sousa et al., 2010). At this moment, methods based on DEB theory are the only energy-budget models that have been systematically applied in ecotoxicology, and the only ones that have been included in international risk-assessment guidance for their relevance in analysing ecotoxicity data (ISO, 2006; OECD, 2006). Therefore, we limit ourselves here to a discussion of DEB-based methods.

In this paper, we provide a conceptual overview of DEB theory, and show how it has been applied to ecotoxicological questions. Subsequently, we provide a short review of the applications of DEB theory that address the effects of chemical stressors at the population level (focussing on structured population models), and highlight areas for further research.

2. Theoretical background

2.1. Energy budgets for the individual

Before we can consider toxic effects, we first have to look closer at the general biology of the organism. Toxicant effects are deviations from the situation without toxicants, and therefore, we first need a quantitative model for the unstressed behaviour before we can interpret

toxicant effects. As stated in the introduction, all living organisms take up resources from the environment, and use these resources to maintain their bodies, grow, develop, and reproduce. When a stressor decreases the investment in a trait such as reproduction, we have consider where that energy went: was it never assimilated in the first place (e.g., an effect on the feeding rate), or was it used for other purposes (e.g., to increase the maintenance costs to counteract damage by the toxicant). An energy-budget model can thus be used to quantitatively test various hypotheses for the metabolic mechanism underlying the response to stressors (Alda Álvarez et al., 2006), accounting for the causal links between all traits. Identifying the affected process is essential to extrapolate the individual's response to the toxicant from the laboratory setting to the environment (e.g., with time-varying food or toxicant levels).

Every living organism has an energy budget, but different species follow different acquisition and allocation rules. In the remainder of this review, we will focus on animals, as these organisms form, metabolically speaking, a rather homogeneous group. All of them feed on other organisms to obtain their energy and building blocks, which places similar constraints on metabolic organisation. This similarity is for example supported by the observation that growth curves for a wide range of animals are well described by the same curve as long as conditions are constant; the von Bertalanffy growth curve (Kooijman, 2010). In the DEB animal framework, species differ mainly in their parameter values, and only to a lesser extent in model structure (which reflects the metabolic organisation). The level of the energy budget thus presents a relatively species- and stressor-independent platform that can be adapted to any focal species to interpret stressor effects over the life cycle.

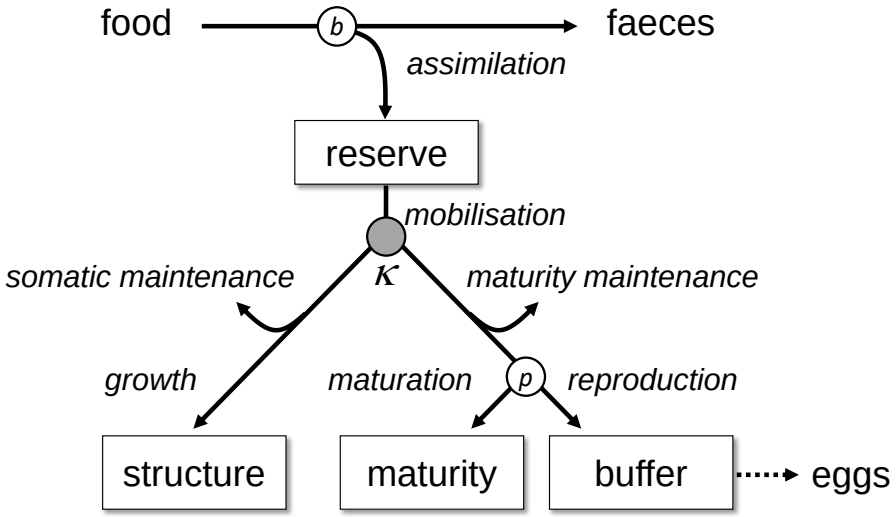

Figure 1. Schematic representation of the standard DEB model for animals. The nodes 'b' and 'p' denote switches at birth (start of feeding) and puberty (start of investment in reproduction), respectively. The mobilisation flux is continuously split (grey circle), with a fraction κ allocated to the soma.

The standard animal DEB model, as presented in Sousa et al. (2010), is the simplest complete DEB model (Figure 1). It deals with an animal that feeds on one food source (with constant composition), does not change in shape (isomorphy), and reproduces via eggs. Biomass is divided into structure (which requires maintenance) and reserve (which can fuel metabolic processes). The state variable, 'maturity', specifies the developmental status of the individual and hence determines the start of investment into reproduction (maturity does not have

associated mass in DEB but is quantified by the amount energy invested in it). Feeding rate is proportional to a surface area of the individual, and thus scales with structural volume to the power 2/3. Food is assimilated into the reserve compartment, from which reserve is mobilised to yield energy and building blocks. A fixed fraction κ of the mobilisation flux is channelled to the soma (somatic maintenance and structural growth). The remaining fraction 1-κ is used for maturation (in juveniles), maturity maintenance (whole life cycle), and reproduction (in adults). Maintenance costs need to be paid from the mobilised reserve first. Somatic maintenance cost is proportional to the volume of structure, whereas maturity maintenance is proportional to the actual level of maturity. The continuous investment in reproduction is first collected in a buffer, from which clutches of eggs are produced. This particular organisation of the metabolic processes is the only one that can match a full set of general empirical patterns observed in animals (Lika and Kooijman, 2011).

Table 1. Three categories of DEB models that have been applied in ecotoxicology: the full animal model and two simplifications. Primary parameters relate directly to metabolic processes, whereas compound parameters are combinations of primary parameters.

Model category	Main features	Reference
Full DEB model	Standard model for animals. Primary parameters and explicit mass balance.	Sousa et al. (2010)
	Scaled standard model; dimension 'energy' scaled out. Mostly compound parameters.	Kooijman et al. (2008)
No maturity	Original DEBtox model. Reserve in steady state. Compound parameters.	Kooijman and Bedaux (1996)
	Several errors in original DEBtox corrected. Reserve in steady state. Compound parameters.	Billoir (2008)
	Reformulated model; different inclusion of chemical stress. Reserve in steady state. Compound parameters.	Muller et al. (2010)
	Revised DEBtox version; all errors corrected. Reserve dynamics added. Compound parameters.	Jager and Zimmer (2012)
No maturity, no reserve	KM-DEB. No maturity maintenance. Compound parameters.	Kooijman and Metz (1984)
	DEBkiss. Maturity maintenance optional. Primary parameters and explicit mass balance.	Jager et al. (2013)

The standard model can be extended in various ways, but it may already be too complex and data hungry for practical applications in ecotoxicology, so simplifications of the standard model are extensively used. In Table 1 we group several of the simplifications in three categories, providing their main features and a reference (where more details on the model are provided). In the 'no maturity' models, the state variable for maturity is removed; the transition from juvenile to adult takes place at a fixed size. Furthermore, primary DEB parameters (with a direct link to metabolic processes) are usually combined into easy-to-interpret compound parameters such as maximum body size. The reserve compartment is included, but is often simplified to a situation of steady state (assuming rapid dynamics of the reserve compartment). The 'no maturity, no reserve' category contains the earliest application of a DEB model to ecotoxicology. Compared to the previous category, it is further simplified by the complete absence of the reserve compartment. Apart from these three categories, a range of DEB-inspired approaches have been used, which include more descriptive elements

(e.g., Ducrot et al., 2010; Péry et al., 2002). For reviewing model approaches, we will however stick to the models that fall into one of the three categories of Table 1.

It must be stressed that there is one DEB theory (Kooijman, 2010), but a range of different DEB models can be derived from it. The most appropriate model obviously depends on the purpose for which it is to be used: more complex versions can include more biological realism, but use more parameters, which places higher demands on the type and quality of the data required to estimate the parameters of the model.

2.2. Including toxic effects in DEB models

A chemical first needs to be taken up into the body before it can produce an effect on the organism's life-history traits. Toxicokinetics (TK) entails the processes of uptake, elimination and transformation. The chemical will reach some target site in the organism, which is linked to one (or more) metabolic processes in the DEB context (Figure 2). The models linking the internal concentration (at the target site) to effects on life-history traits are collectively designated as toxicodynamics (TD). A DEB model can thus be used as the TD component of a TKTD model.

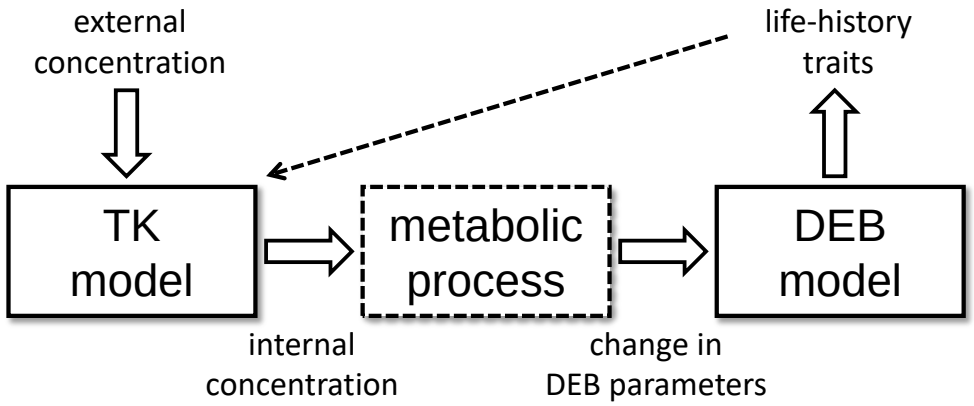

Figure 2. Flowchart for a TKTD model using DEB as a toxicodynamic component. The broken arrow indicates the effect on life-history traits (changes in body size and reproduction) on toxicokinetics.

In principle, any TK model can be linked to a DEB model, although the choice is limited in practice by the amount of information available. In ecotoxicity tests, internal concentrations are not routinely determined, and when they are, it is usually the total concentration in a single animal, or in a number of individuals pooled. Especially for invertebrate test species, their small size precludes more detailed measurements. The simplest useful TK model in this context is the 'scaled one-compartment model' (see Jager and Kooijman, 2009; Jager and Zimmer, 2012). The single remaining TK parameter (i.e., the effective or dominant elimination rate constant) is determined from the development of the toxic effect over time. The scaling allows TKTD modelling in the absence of measured internal concentrations, and thus on the results of typical ecotoxicity tests. Changes in body size can affect TK in two ways: an increase in size dilutes the internal concentration (a decrease in size concentrates it), and an increase in size decreases the exchange rate for the chemical (which is governed by the surface:volume ratio of the organism). In this way, the TK model is closely linked to the DEB model, as the growth rate and the body size affects the kinetics of the toxicant (broken

line in Figure 2). Reproduction may also affect TK, but these effects on the internal concentration are ignored in most applications (see discussion in Section 4.3).

The internal concentration might be linked directly to a metabolic process in a DEB model, or via an additional TD process (e.g., detailed receptor kinetics or a state of 'damage'). Primary parameters (such as the maintenance costs per unit of structure) are associated with metabolic processes. An effect on each of the primary parameters will yield a unique pattern of effects on the life-history traits over time: a physiological or metabolic mode of action (Alda Álvarez et al., 2006). In practice, we can thus use the observed effect pattern on the traits to deduce the most likely affected DEB parameter. Kooijman and Bedaux (1996) proposed a linear-with-threshold relationship between the internal concentration and the value of a DEB parameter. The concept of a threshold is not only helpful for environmental risk assessment, but also of practical elegance. Even in a laboratory setting, there are always hundreds of chemicals present in the test system (nutrients, waste products, metabolites, minerals, etc.). If we can assume that the concentration of these chemicals remains below their respective thresholds, we can ignore them, and focus on the test compound as the driver for the toxic effects.

An up-to-date list of all of the papers using DEB theory in ecotoxicology (that we are aware of) can be found at http://www.debtox.info/papers_debtox.php. An extensive conceptual introduction into DEB theory and its application in ecotoxicology is provided in Jager (2012).

3. Applications of DEB models in population ecotoxicology

DEB models have been extensively used to extrapolate responses from individuals to populations by integrative coupling to demographic models. For this brief overview, we focus on the coupling to structured population models for animals, and applications in ecotoxicology, thus involving a chemical stressor.

Before going into specific approaches, it is good to distinguish between different types of output from population models. For ecotoxicological application, a simple and meaningful output is the population multiplication factor (λ) or the associated intrinsic rate of population increase (r). These asymptotic statistics specify the exponential increase of the population under unlimited conditions in a constant environment, and a decrease of such a statistic due to toxic stress can thus be seen as a relevant measure of ecological impact (Forbes and Calow, 1999). Even though natural populations will not show prolonged exponential growth, the resulting statistic is a fitness measure for the species, i.e., a measure of the intrinsic ability of the population to express a healthy population growth rate. Of course, population models can yield other outputs, such as population trajectories over time, age or size distributions, or extinction probability (e.g., Biron et al., 2012). However, in the studies that we have evaluated, the asymptotic growth statistics are by far the most popular.

3.1. Coupling to matrix models (discrete states, discrete time)

In matrix models, individuals are assigned to discrete classes based on age, size or developmental stage, and the population is simulated in discrete time steps. The population matrix contains the probabilities to move from one class to the next and the fecundity for individuals in each class (the vital rates). A DEB model, calibrated to data for individuals, can be used to derive estimates for the vital rates for each class, providing a solid basis for the derivation, and thereby reducing bias due to deviating observations. Furthermore, the DEB

model can be used to extrapolate vital rates from one set of environmental conditions to the next. An extensive discussion on the integration of DEB with matrix models is provided by Klanjscek et al. (2006).

A DEB model from the 'no maturity, no reserve' category (Table 1) was linked to matrix models by Klok and co-workers in a series of papers on the population-level effects of metals on earthworms (e.g., Klok and De Roos, 1996; Klok et al., 2007). The demographic model was a stage-structured matrix with four classes, corresponding to the developmental stages. Toxicokinetics was ignored in these studies: it was assumed that the external concentration is instantly related to a change in DEB parameters. This simplifying assumption of instantaneous steady state was able to provide an adequate description of the effect patterns in this case.

A model from the 'no maturity' category was applied by Ducrot et al (2007), combined with a two-stage matrix approach (summarised into a characteristic equation), to predict the population-level effects of zinc on the snail *Valvata piscinalis*. Billoir et al. (2009; Billoir et al., 2007) also applied a DEB model from this category to model individual performance of cladocerans (*Daphnia magna* and *Moina micrura*) exposed to stressors (cadmium and toxic cyanobacteria). The modelled survival and reproduction curves over time were used to quantify the vital rates for an age-structured matrix model (with 10 age classes) as a function of exposure concentration. The same DEB model was combined with a more extensive age-structured matrix model (21 age classes) by Biron et al. (2012) to assess effects of uranium over several generations in *Daphnia magna*. This study revealed that parameterising a population model on observations from the first generation only can lead to serious underestimation of effects on subsequent generations. Such issues require vital rates in the matrix model to change across generations, which precludes the estimation of a meaningful population growth rate. All these studies mentioned above focus on the asymptotic population growth (in this case: λ), but Biron and co-workers additionally calculate extinction probability.

In matrix models, individuals are divided into discrete classes and follow discrete time steps. This discretisation introduces errors, but a more severe limitation of matrix models lies in their application to time-varying conditions. In simple matrix models (like the ones reviewed above), the status of an individual is only represented by a single state variable (such as size or age). When environmental conditions change rapidly in time, one state may not suffice and we require additional states for e.g., internal concentration, reserve and maturity. Additionally, formulating a matrix model based on an individual model with continuous states in continuous time (such as DEB models) can be rather complicated (see De Roos, 2008).

In matrix models, the sensitivity of the population growth rate to quantitative changes in vital rates (often termed elasticities) can be assessed. Elasticity analysis is a valuable tool to investigate how population growth is affected by particular traits. In linking a DEB model to a matrix model, the idea of elasticity analysis needs some rethinking. The vital rates (e.g., the egg production in each class) cannot be independent, as they are linked by the energy budget. It therefore makes more sense to calculate the influence of changes in primary DEB parameters on the population growth rate.

3.2. Coupling to the Euler-Lotka equation (continuous states, continuous time)

There is a range of population models that deal with multiple continuous state variables for the individual and with continuous time. Such models are, however, much tougher to analyse than matrix models. In a constant environment, all populations will eventually grow exponentially, and it is this growth rate that we can easily calculate with the Euler-Lotka equation (see e.g., De Roos, 2008). The approach thus makes an *a priori* assumption for a constant environment, and a stable age distribution. A further assumption is that each individual in every generation follows the same life history, thus excluding maternal (or trans-generational) effects. The Euler-Lotka equation might be viewed as the solution for the dominant eigenvalue of an age-structure matrix model, in which the time steps are infinitely small and the number of classes infinitely large. The intrinsic rate of population increase (r) is calculated by solving an implicit equation containing survival and reproduction as continuous functions of age. Because this is exactly the output of the DEB models for the individual, no additional recalculation is needed, and there is no limit to the number of state variables for the DEB model of the individual.

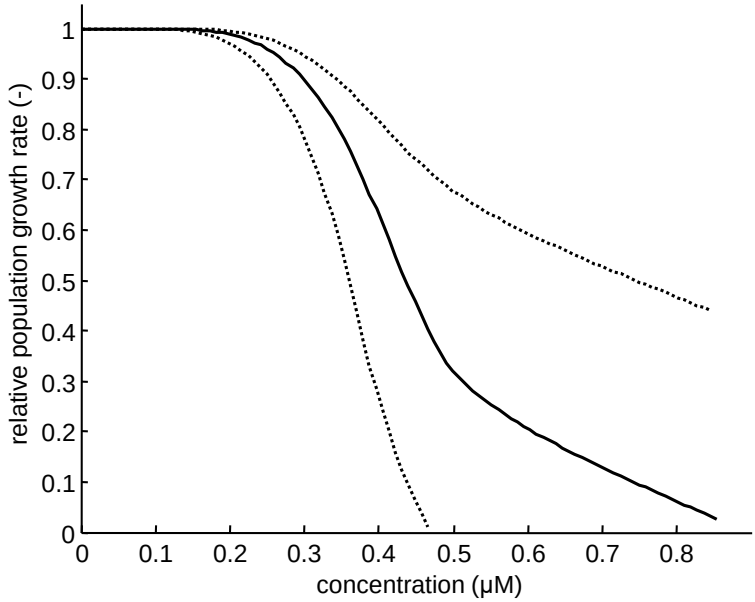

Fig. 3. Population growth rate (intrinsic rate of increase) for *Daphnia magna* exposed to fluoranthene, with 95% credible intervals on the model curve. Population growth rate is normalised to the value in the control for each sample from the posterior distribution. Figure taken from Jager and Zimmer (2012) with permission.

To derive the growth rate r, we must integrate a function (containing the survival and reproduction functions) over the entire potential lifetime of an individual, starting from the freshly-laid egg, until infinity. In practice, the function is often integrated over the duration of the experiment. For a correct calculation, one would however have to start integration at egg formation, and stop at the age where the last animal has died or has stopped reproducing. Therefore, one would often require an extrapolation beyond the test duration. The upper boundary for integration is, however, less important as the growth rate is dominated by the offspring that are produced early in life due to the principle of compound interest: the early young also rapidly produce young themselves, and thus contribute more to the population growth rate than the young produced later in life. We can plot r (with its associated uncertainty) as a function of the exposure concentration (see Fig. 3). The DEB model allows us to interpolate (and even extrapolate) to untested concentrations, so it is possible to plot r as a continuous curve. We can also easily extrapolate to different (constant) food levels (Jager et al., 2004; Muller et al., 2010) or different temperatures (Alda Álvarez et al., 2006).

Additionally, we can calculate the stable age distribution and perform sensitivity analysis (De Roos, 2008) just as done for matrix models, although this is not common practice.

The individual model that Kooijman and Metz (1984) presented is one that we now consider as a member of the 'no maturity, no reserve' category (Table 1). These authors applied their model to *D. magna*, and linked their individual model to the Euler-Lotka equation, integrating from t=0 (neonate leaves the mother) to infinity. As this species hatches the eggs in a brood pouch, the formation of the eggs (and so the actual energy investment) precedes the time at which the offspring are counted. This source of bias is discussed in Jager and Zimmer (2012). Kooijman and Metz (1984) used their model to demonstrate that the population-level effects will be strongly affected by food availability for some, but not all, affected metabolic processes. Correctly identifying the disturbed metabolic process is thus crucial for a realistic extrapolation beyond the experimental data set.

Two decades later, the Euler-Lotka equation was revisited in a series of publications by Jager and co-workers (among others: Jager et al., 2004; Jager and Zimmer, 2012) and Alda Álvarez and co-workers (Alda Álvarez et al., 2005; Alda Álvarez et al., 2006) . In all these papers, a 'no maturity' approach was applied, and in most, r was calculated from an integration over the duration of the experimental test, thus ignoring the hatching time of the eggs and the contribution of animals surviving longer than the test duration. Whether or not to extend the integration beyond the test duration is a matter of discussion. Any extension would require extrapolation beyond the observations, and is thus associated with uncertainty. Jager and Zimmer (2012), for example, decided to calculate r over twice the duration of the experimental test.

Muller and co-workers (2010) derive a slightly different 'no maturity' model, compared to the studies discussed above. For *D. magna* exposed to two chemicals (tetradifon and pyridine), they plot r from the Euler-Lotka equation as a function of both exposure concentration and food availability, to show the interaction between these factors. These authors provided no details about the boundaries of the integration.

3.3. Coupling with individual-based models

The most natural link between DEB and population models is with individual-based models (IBMs), which explicitly follow all individuals in a population. An essential feature of DEB is thus preserved: the dynamic response of an individual's life history to changes in environment. Running an IBM is extremely calculation intensive, but computers have nowadays progressed to a point where application of these models has become a serious option for predicting population responses to stressors. A more serious limitation is that IBMs offer little possibility to investigate model behaviour analytically; the only possibility is to perform simulations. The interpretation of toxicant impacts on population dynamics is thus not straightforward.

IBMs allow for full flexibility in the model for the individual and how the status of the mother affects the offspring. Indeed, in an IBM, there is no limit to the number of state variables for the individual (apart from practical constraints regarding calculation time), and maternal effects can be included in a straightforward manner. The application of such a population framework is therefore not restricted to constant (or slowly-changing) environments, and the interaction with the food source can be included. Food availability is an essential element, as in DEB, the proportion of energy available for various processes

depends on the environmental conditions. For example, when food is available *ad libitum*, maintenance costs are a relatively small percentage of the mobilised energy, while at low food levels, nearly all mobilized energy will be used for maintenance. Thus, the sensitivity of a metabolic process to toxic stress is resource dependent, and therefore, it is important to consider population response in these dynamic consumer-resource systems.

IBMs can be adapted to model specific laboratory, mesocosm, or environmental scenarios. This is advantageous because a key step for the application of models in risk assessment is validation. For example (Martin et al., 2013a) adapted an individual-based DEB model for *Daphnia* to exactly match the experimental conditions used for a *Daphnia* population experiment. In this study, comparison of the model to data was critical for identifying the scenarios for which the model yields accurate predictions, and also led to identification of areas where model reformulation was needed (especially, size-dependent mortality under low-food conditions).

The DEB-IBM framework (Martin et al., 2012) offers a flexible platform for experimentation with linking DEB to IBMs (it applies the scaled standard model, Table 1). The power of this framework was demonstrated for the effects of 3,4-dichloroaniline on a laboratory population of *D. magna* (Martin et al., 2013b). In this study, the IBM, parameterised with data at the individual level only, was able to accurately predict the observed population responses over time. The only other combination of an IBM with a DEB-inspired model in ecotoxicology is currently the work of Beaudouin et al (2012), studying the effects of uranium on the midge *C. riparius*. However, the individual model in this study does not classify as a DEB model in the sense of the categories in Table 1.

3.4. Selecting the appropriate model

To study the importance of model choice, Jager and Klok (2010) compared several DEB models (one from each category in Table 1) with two population approaches (a stage-structured matrix model and the continuous Euler-Lotka equation), for one data set (copper in the earthworm *Dendrobaena octaedra*). These authors included (estimated) hatching time in the Euler-Lotka calculation, as well as two options for the termination of the Euler-Lotka integration (end of the test and ten times the test duration). The population growth rate from the stage-structured matrix models represents the asymptotic situation, and indeed was most comparable to the Euler-Lotka integration for the longer duration. When both population approaches are compared using comparable assumptions, the results are very similar. Furthermore, the conclusions for the effects on the population growth rate did not strongly depend on the type of DEB model applied, at least in this specific case. Simpler DEB models should therefore not automatically be discarded in favour of more complex ones.

For the calculation of the intrinsic population growth rate r, the Euler-Lotka equation is the most appropriate choice in conjunction with a DEB model. The link to the individual-level model is straightforward and the continuous state variables of the DEB model are preserved. Matrix models allow to model transient behaviour: starting far away from the stable age/stage distribution. In principle, matrix models can deal with time-varying environmental conditions although the possibilities are, in practice, limited (see Section 3.1). IBMs offer full flexibility in terms of DEB model and the ability to simulate dynamic environments, but are calculation intensive, and less straightforward to interpret.

3.5. Lessons from population modelling with DEB

Linking DEB and population models in ecotoxicology has demonstrated that we can indeed extrapolate laboratory toxicity data at the individual level to population growth rates. The main contribution of DEB into this process has been to smooth noisy experimental data (i.e., reduce the impact of outliers in the observations), to interpolate (or even extrapolate) to untested exposure levels, and to extrapolate to untested constant environmental conditions (i.e., food availability and temperature). These last extrapolations depend critically upon the physiological mode of action of the contaminants (the affected metabolic processes).

Admittedly, the benefits of DEB theory have not been fully exploited in most of the studies that we review in this paper. In fact, rather similar population predictions could have been produced by a descriptive analysis of the individual-level observations on survival and reproduction (see comparison in Alda Álvarez et al., 2006; Jager and Klok, 2010). The advantages of DEB theory are most pronounced when extrapolating to other environmental conditions, and especially highly dynamic ones (which would require an IBM approach). Furthermore, the power of the theory can be used to extrapolate between chemicals and between species. Even though such extrapolations are theoretically plausible, and indicated in preliminary studies, the predictive power still needs to be further demonstrated in practice (see Section 4.5).

4. Areas for further research in DEB models

Several areas of DEB theory, and its application to ecotoxicology, require further attention in the context of the linkage to population models. In this section, we will outline the most important ones. Most of these issues require a close collaboration between modellers and experimental scientists.

4.1. Starvation response

Field populations never experience constant food levels for long, and periodic starvation is common. In the standard DEB animal model, starvation occurs when the fraction κ of the mobilisation from the reserves is insufficient to pay somatic maintenance costs (see Fig. 1). For a fully-grown adult, the total flux allocated to growth and maintenance, is already used for the latter process (which is why growth has ceased in the first place). As soon as the food availability drops even a little bit, starvation occurs, and the organism has to deviate from the standard allocation rules. At this moment, there are various options to deal with starvation in DEB models, but it is unclear which species follow which set of rules. Martin et al (2013a) show how the choice for the starvation response can actually dominate the population dynamics, stressing the selection of a realistic set of rules for the species of interest.

4.2. Maternal effects

Maternal effects often play a role in stress ecology; the status of the mother can influence the life history of the offspring (Bernardo, 1996). For example, mothers may change the investment per offspring depending on their own status, they might provide ‘information’ which changes the metabolic processes in the offspring (preparing them, as it where, for particular conditions), or a toxicant may be transferred from mother to offspring (discussed in Section 4.3). In DEB theory, there is one type of maternal effect built in; the rule that the investment per egg is such that the offspring will hatch with the same reserve density as the mother had at egg formation. This implies that poorly-fed mothers should produce smaller

eggs, yielding hatchlings with a poorer reserve status. In biological reality, a range of maternal effects has been observed, and the influence of toxicity on investment per offspring is still unclear. At this moment, it is not obvious to what extent maternal effects may affect population dynamics. Although the work of Biron et al (2012) clearly indicates the importance of trans-generational effects, the underlying mechanisms remain unclear.

4.3. Realistic TK models

Most TK models are validated and calibrated on data for animals that do not grow or reproduce, that do not change in composition (e.g., lipid content), and at concentrations where there is no toxic effect. The reason is that all these factors affect uptake and elimination in a rather complex manner. However, we want to use these TK models in TKTD models for situations that they were not calibrated for. The one-compartment model is usually extended to account for changes in body size (e.g., Jager and Zimmer, 2012), which also takes care of one of the feedback loops in Figure 2 (a toxic effect on growth will affect toxicokinetics, and thereby alter the toxicity). Several TK extensions of DEB models have been explored (e.g., Bodiguel et al., 2009; Van Haren et al., 1994), which include more biological realism in toxicokinetics (see also conceptual discussion in Jager, 2012). These model extensions, however, require some more testing and validation, to see how generally applicable they are. A specific area where more research is needed is in the TK for the embryo. Embryos may be exposed to toxicants that they receive from their mothers through maternal transfer, and the egg may exchange chemicals with the environment.

4.4. Identification of the mechanism of action

In practice, it is often difficult, or even impossible, to identify a unique metabolic mechanism of action (i.e., the DEB parameter that is affected) from toxicity test data. It is, for example, difficult to distinguish between effects on assimilation and maintenance, with observations on body size and reproduction only. Furthermore, it is also possible that more than one metabolic parameter is affected at the same time, which might be mistaken for another mechanism. Identification of the correct mechanism of action is hardly relevant for the characterisation of the response under the test conditions (e.g., to estimate a no-effect concentration), as long as the model fits the data well. Extrapolation beyond the test situation, however, may be seriously affected. The work of Kooijman and Metz (1984) already showed that the interaction between food and toxicants works out differently at the population level for chemicals with a different metabolic mechanism. More work is needed to specify what type of information is needed to identify the various mechanisms of action, and to quantify the importance of a correct choice for the population effects.

4.5. Patterns in effects among chemicals and species

The kind of testing that is needed to identify all DEB model parameters, and the correct mechanism of action, will be unfeasible for each chemical-species combination. However, the power of a DEB-based framework is that the model parameters have a physically meaning. The basic DEB parameters tend to covary between species in a rather predictable way, which can be used to aid their estimation (Lika et al., 2011). The parameters governing the toxic response also seem to vary between chemicals in a particular way (Jager and Kooijman, 2009). In the future, this can lead to the development of powerful estimation routines. However, the work on nematodes shows that the metabolic mechanism of action can

be radically different for the same chemical in two different species (Alda Álvarez et al., 2006). Development of such tools thus requires some systematic testing efforts.

4.7. Multiple stress

In the field, organisms are never exposed to a single stressor in isolation: multiple stress is the norm. Multiple stress is not an issue that can be addressed at the population level; it requires mechanistic modelling at the individual level. Working in a DEB framework provides handles to work with multiple toxicants (Jager et al., 2010) and combinations of a toxicant with a biological stressor (e.g., food limitation, Pieters et al., 2006). Furthermore, such a framework can be used to identify an inappropriate food source in experimental tests (Zimmer et al., 2012), which can bias the interpretation of the toxic response, and thereby the extrapolation to the population level. This is also an area where more systematic experimental testing is needed.

4.8. Differences between individuals

Individuals differ in their basic physiology (and thus in their DEB parameters), and there is inevitable stochasticity in their behaviour (e.g., modifying their exposure to food and toxicants). This topic has not received a lot of attention so far, although Jager (2013) recently presented an approach to analyse toxicity test results in the light of inter-individual variation. Some DEB-based population modelling with individual differences has been performed in an IBM context (Kooijman et al., 1989; Martin et al., 2013a; Martin et al., 2013b). IBMs offer a straightforward way to implement differences between individuals, in contrast to matrix models and the Euler-Lotka equation. However, it is at this moment not clear whether such differences are heritable, and how they will affect the population response to stressors.

5. Outlook

Focussing on the energy budget is a sensible simplification of biology for studying the effects of chemicals (Jager et al., 2006). DEB theory offers a formal framework for building energy-budget models for individual organisms, which can subsequently be linked to population models. The main benefit of using DEB theory lies in the ability to extrapolate the individual's behaviour to untested and dynamic environments, and possibly (in the future) to extrapolate between species and chemicals. Furthermore, we can use the same model structure for a broad range of animals, as animals differ mainly in parameter values and not in model structure. Applications can often rely on relatively simple models derived from the theory. We reviewed most of the papers in which responses to chemical stress are analysed with DEB-based models, and subsequently translated to effects to the population level. As always, the most appropriate tool depends on the question that must be addressed. Unfortunately, most authors neither discuss their choice for a particular DEB model, nor their choice for a specific population approach. We hope that this review can help create a greater awareness of the pros and cons of each approach.

DEB theory offers a flexible framework to include biological realism at the individual level. Surely, not every question requires an energy-budget approach, but its strengths make DEB a vital contribution to the population modeller's toolbox. The work on DEB theory and its applications is far from finished, and we hope that the areas for further research that we specified will provide inspiration for future research projects.

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