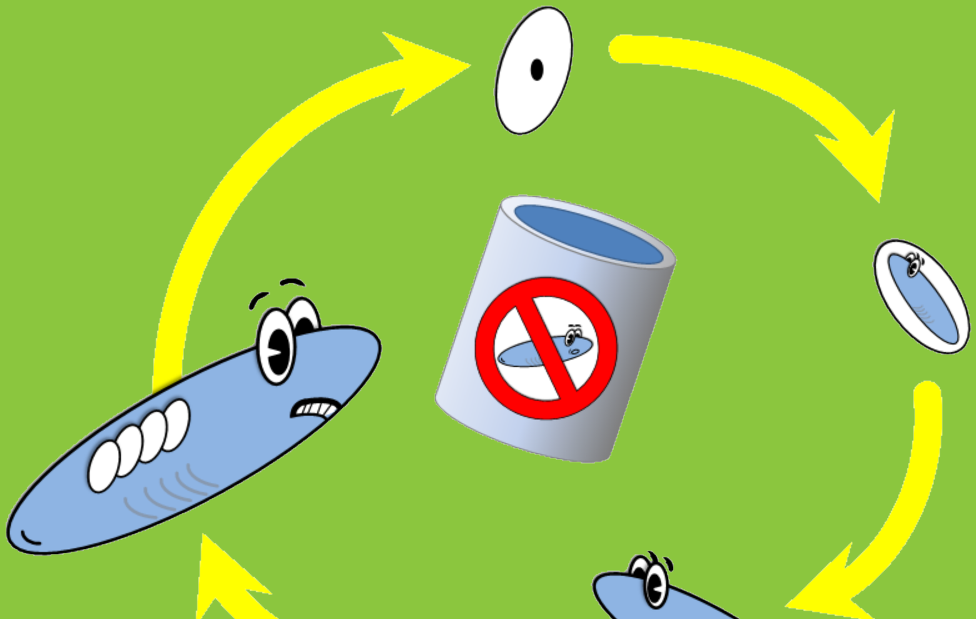
Making Sense of Chemical Stress

Applications of Dynamic Energy Budget Theory in Ecotoxicology and Stress Ecology



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Alternatively, refer to one of the papers in the open literature. E.g., [102] for the general concepts, [114] for toxicants in the standard DEB animal model and mixture toxicity, [115] for the simplified DEBtox model, or [106] for the DEBkiss model.

If you spot errors (spelling, grammar or conceptual), please notify me by email (see address below).

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Preface

Who should read this book?

Have you ever asked yourself why the effects of toxic chemicals depend on the exposure time? Or asked why stress effects on growth and reproduction are so different in the same organism, even though these responses must be linked in some causal way? Did you ever wish to *understand* toxic effects, so that you can make an educated prediction of effects under other conditions? Or do you want to understand why toxic effects depend on the presence of other factors such as temperature, food density, and life stage? This book offers a framework to address those questions by taking a radically different approach than what is common in ecotoxicology and stress ecology: by simplifying biological reality to an enormous extent. In this book, I will present a 'mechanistic' treatment of chemical effects. The main focus lies on one particularly useful framework for the interpretation of toxic effects, namely Dynamic Energy Budget (DEB) theory, and more specifically, the formulation by Bas Kooijman in 2010 [125]. Even if you are not convinced that this theory is the way to go for your particular problem, knowledge of the concepts behind it allows you to examine your (and other people's) data and models more critically.

This is not a cookbook with recipes for how to derive *the* toxicity of a chemical from your test data. First and foremost, it is an open invitation to start thinking about toxic effects on organisms as the result of underlying processes; processes in time. Furthermore, it is an invitation to focus on the generalities that link all species and all toxicants, instead of losing ourselves in the details that make them unique. Recognising and understanding the dominant processes governing the toxic response is invaluable for understanding the effects of toxicants in a laboratory test. This understanding, in turn, is crucial to compare effects between species and between chemicals, and to make science-based predictions for the real environment, under conditions far removed from those in the laboratory. However, I also want to show you how stress in general (and toxicants in particular) can help to provide insight into the basic structure of metabolic organisation in organisms.

This book covers a lot of fields: biology, (eco)toxicology, chemistry, modelling and statistics. I will not dive into any of these fields in great depth; the message is in their interconnection. There is, as far as I know, no education to properly prepare you for a multi-disciplinary arena such as this. For this reason, I attempted to write this book for a broad audience, assuming no specific background knowledge, and keeping it math-free. However, training in science and in abstract thinking is needed to fully appreciate all of the concepts presented (and some knowledge of ecotoxicology and general biology would help).

Why a book?

Simply because a book like this did not exist. Ecotoxicological textbooks do not address the questions I raised in the beginning of this preface, and if they touch upon these subjects, they stick to descriptions. The DEB book of Bas Kooijman [125] has a chapter on toxicant effects. However, that chapter is a tough read as it contains a lot of detail in a highly condensed form. Furthermore, the book presents DEB theory over its full width of application, which will deter many an ecotoxicologist. There exists a dedicated booklet on 'DEBtox' [128], presenting a DEB-based analysis for standard toxicity tests: acute survival, juvenile fish growth, *Daphnia* reproduction, and algal population growth. However, it is more a collection of scientific papers than a coherent treatise. Furthermore, it presents the equations as such, without paying much attention to explaining the underlying concepts.

Since 2002, I have been working on toxicants in DEB theory, and have tried to explain what I was doing in a considerable number of papers, lectures and courses. I noticed that there is quite a learning curve to DEB theory. Even though the basic concepts of the theory are truly simple, and can be explained in ten minutes, they constitute an extreme abstraction of living systems. Such a level of abstraction is hardly part of the biological scientific tradition, and might lead to feelings of discomfort in the unsuspecting. Furthermore, even though the concepts are simple, following them to their logical consequences is not. Application of the theory almost always requires mathematics, enhancing the feelings of discomfort in many among the audience. Discomfort easily leads to disbelief. In a mathematical model, it is relatively easy to hide a few *ad hoc* factors to get a good fit to a set of data. Of course, all models are simplifications, and thus 'wrong', but how can you be sure that a model is actually useful for some purpose?

Models (at least, all useful ones) follow from assumptions. In fact, they should follow *uniquely* from a set of assumptions. Once you accept these assumptions, and given a correct implementation, you should also accept the model and its implications. If you do not accept the model predictions, it is wise to scrutinise the assumptions. The purpose of this book is thus to clarify the assumptions underlying DEB models for the analysis of toxic effects, with a high level of transparency. Once these assumptions are clear, it will be easier to interpret the model's fit to actual data sets, and the predictions made from them. For most biologists and ecotoxicologists, math is not helpful to explain something, and probably even a hindrance. For this reason, I decided to move all of the technicalities to a separate technical document (where also the derivations of the equations are presented). To apply DEB models in ecotoxicology, you do not need to be good at math, but you do need a firm grip on the concepts and assumptions.

Limitations of this book

To limit the size of this book, and to allow for a more coherent discussion of concepts, I will limit myself to applications involving heterotrophic organisms (mainly animals), and more specifically invertebrates. The reasons to select this group is that I personally have most experience with them, and the data sets that are routinely collected for these organisms are often directly amenable to a DEB-based treatment. I realise that by limiting myself to a selection of organisms, I neglect one of the most important achievements of DEB theory: the unification of all living organisms into a single, coherent, quantitative theory. Certainly, there are very good examples of DEB application to stressor effects in other groups of organisms such as toxicity in algae [133, 33], and tumour induction and growth in mammals [199]. However, a treatment of these developments might distract from the general message that I want to convey.

Support on the web

The supporting website for this book is `http://www.debtox.info`. Here, you will find software (as toolboxes for Matlab) to perform the calculations, lists of publications that apply these concepts, and information on courses. This site also hosts the technical document that presents the mathematical formulations, their derivations, as well as alternative formulations. In addition, I have a version log to keep track of the development of this book.

For more DEB-related information, check out the website of the department of Theoretical Biology: `http://www.bio.vu.nl/thb/deb`. Even though the department no longer exists, the website is still there. More up-to-date information can be obtained from the DEBwiki: `http://www.debtheory.org/wiki/index.php`.

What's that thing on the cover?

The creature on the cover, and in several figures in the book, is a PHylogenetically Indeterminate Life form, or 'Phil' for short. Phil is inspired by the creature that graces the cover of the third edition of the DEB book [125], and is used to illustrate general principles without focusing on specific species. In fact, a cartoon is a model; a simplification of a complex real system, brought back to its essence. Using a cartoon organism instead of a real one thus fits extremely well with the message I want to convey.

Notes for the update to version 2.0

The update to version 2.0 of the book involved a rather major reshuffling of the text. The conceptual switch that was made was to put 'damage' into a central position (whereas this concept has been largely ignored in a DEBtox context so far). This reflects the developments for survival modelling with GUTS [95], which has also already been adopted in DEBkiss [90]. Not only is it a good idea to strive for harmonisation between the different modelling frameworks, I also feel that considering damage is essential for TKTD models in general. The 'old' models are still in there, but they form a special case of the overarching general model. This reshuffling and rewriting mainly affected the old chapters on toxicokinetics and toxicodynamics; the specific modelling context for toxicant effects is now treated in Chapters 3 to 6.

Acknowledgements

Firstly, I am indebted to Bas Kooijman whose work on DEB theory laid the foundation on which this book is built. Furthermore, I would like to thank all of my former colleagues at the department of Theoretical Biology, and the other DEB enthousiasts around the world, for their help and inspiring discussions. Thanks to LaTeX for providing the platform to write this book, and thanks to WikiPedia (`http://www.wikipedia.`

`org`) for many interesting facts. And finally, Marina, I am grateful for your love and support.

Disclaimer

This book *will* inevitably contain errors. If you spot one, please let me know so that I can include corrections in updates of this book. I do not accept liability or responsibility for any damage or costs incurred as a result of these errors.

Chapter 1

Setting the scene

This is a book about the effects of chemical stress on organisms. It is an attempt to construct a general framework to quantitatively understand, and ultimately predict, the biological effects of chemicals over time. In writing this book, I realised that I need to be more specific about the things I want to discuss. Such a limitation is necessary for me to maintain focus in my discussion (which is difficult enough as it is), and for the reader to understand why it is helpful (in my opinion even inevitable) to work in an energy-budget framework. Different choices in scope would lead (and have already led) to very different books. Even though "effects of chemical stress on organisms" sounds like a well-demarcated research area, I do not think it is.

1.1 Limiting the scope

The world is full of things, and all material things are made of chemicals. Unfortunately, we cannot divide chemicals into toxic and non-toxic ones. Paracelsus (1493-1541) was right on the mark when he wrote: "All things are poison and nothing is without poison, only the dose permits something not to be a poison." Many chemicals are required by organisms for their normal functioning (nutrients). I will not talk about nutrients explicitly, but restrict the discussion to chemicals that are not part of the organism's 'normal' functioning, or are present in levels exceeding the requirements for such functioning. I realise that this definition of 'chemical stress' is a bit vague, but it will have to do for now. Even though the focus lies on chemicals, this book has a lot to offer for researchers interested in non-toxicant environmental stress (e.g., food, temperature, disease or pH stress), because the principles are very similar indeed. Most of the time, I will be talking about the effects of a single toxicant in isolation. However, it is good to realise that organisms are always exposed to a mixture of chemicals; even in an experimental toxicity test, inevitably, other chemicals will be present in the test medium (although usually at non-toxic levels). In the real world, mixture exposure is the norm, although experimental testing and risk assessment mainly focus on single chemicals.

There are many million species of organism, so clearly, I want to restrict myself in the biological scope too. The concepts I present are equally valid for all forms of life on this planet (and likely also on others), but I will only work out the case for animals. More specifically, the focus will be on multi-cellular ectotherms. Even though this group represents only a small fraction of the total number of species on the planet, they have something special. They are popular species in chemical-stress research, they form a group that is homogeneous enough to be described by the same basic model (as I will discuss in Chapter 2), and furthermore, the data sets that are routinely collected for these organisms are often directly amenable to the type of analysis that I will present. The last reason is a personal one: my experience with such critters is greater than the other forms of life, which makes it easier for me to write this book.

Another important set of restrictions is in the organisation levels that I will treat. Chemical effects start at the molecular level, and work their way through to the ecosystem, and even global scale. I will focus on the effects on an individual's life cycle, and thus on life history traits or endpoints[1] such as growth, development, reproduction and survival. The individual level is of key interest as it is possible to work with mass and energy balances, and because individuals are the units of natural selection and the building blocks of populations and ecosystems [89]. I will make some excursions to lower and higher levels of organisation, but the individual will be the basis. This implies that I will not deal (explicitly) with effects at the molecular and tissue level, and not with effects on ecosystems, even though there are clear links with the individual level (in fact, it is the individual level that connects these two worlds). In this book, the focus is on understanding and predicting the effects of chemicals on individual-level traits over time, over the entire life cycle of the individual (in principle, from egg to death).

The final restriction I pose myself is that I want to provide a general framework. That is, not specific for a chemical, species or effect. Making a model that accurately predicts the effects of chemical A on trait B of species C is very nice, but the number of different combinations of A, B and C is quite large. In my opinion, there is a need for generalisation as we cannot ever hope to test all the relevant permutations. The intellectual challenge in this book is to provide a framework that applies to all A, B and C within the restrictions posed above. In the case studies, it will become clear that biology often defies a strict generalisation, and more specific auxiliary assumptions will creep in.

With these restrictions in mind, I hope that the subsequent sections in this chapter, and my observations on current research in fields dealing with chemical stress, can be placed in its proper perspective.

1.2 Many faces of chemicals stress

Chemical stress is not something that humans have invented; it is as old as life itself. The earth's mantle contains a range of compounds that can affect organisms negatively (for example metals and sulphur compounds). The appearance of free oxygen in the atmosphere (produced by photosynthesis in bacteria), some 2.4 billion years ago, is thought to have caused a mass extinction among the anaerobic[2] organisms dominating before that time. Incomplete combustion of organic matter is accompanied by the release of a range of particularly toxic organic chemicals such as polycyclic aromatic hydrocarbons and dioxins. Organisms themselves also produce all kinds of (sometimes very complex) chemical compounds, and put them to cunning use to aid their own survival. In this section, I will put 'chemical stress' in a broad perspective, providing

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[1] In ecotoxicology, the term 'endpoint' is often used to denote a life-history trait that is observed to see if it responds to toxicant exposure.

[2] Anaerobic organisms function without the need for oxygen. For many of them, oxygen is in fact deadly.