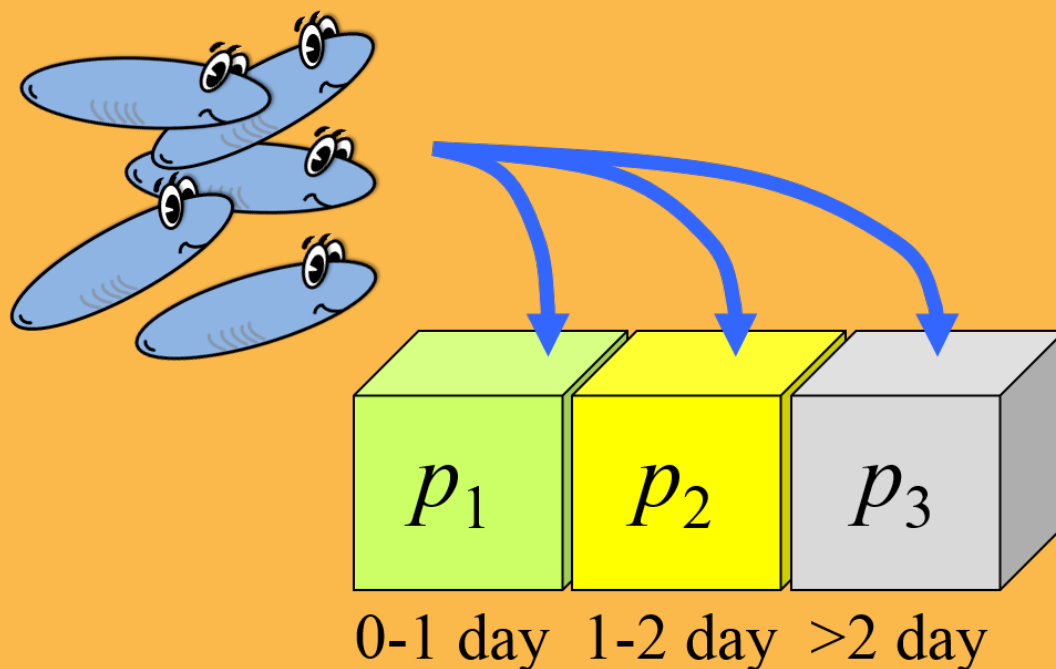


Modelling survival under chemical stress

A COMPREHENSIVE GUIDE
TO THE GUTS FRAMEWORK



Tjalling JAGER and Roman ASHAUER

Modelling survival under chemical stress

A comprehensive guide to the GUTS framework

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Preface

About this book

Stressors, such as toxicants, can cause mortality among organisms. Interestingly, not all individuals will die at the same time in the same exposure treatment, and the number of deaths will change with exposure time. The pattern of mortality will also depend on the exposure profile (e.g., constant versus pulsed exposure), and can be modified by the addition of other stresses (e.g., mixture toxicity). Making sense of these complex issues requires mechanism-based models, known as toxicokinetic-toxicodynamic (TKTD) models. For mortality, almost all published TKTD models can now be viewed as members of an over-arching framework, that we have christened GUTS: the General Unified Threshold model of Survival. GUTS has been published in the scientific literature [95], but a publication is obviously not the place to provide a detailed description of the model or to provide guidance on how to apply the model in practical situations. As the GUTS framework is now gaining broader interest in the scientific, regulatory and industry communities, it is time for a more in-depth treatise.

We decided to publish this book with Leanpub for several reasons. Firstly, this provides us with the opportunity to update our book as frequently as we like. This is not only important to repair errors, but also to include new developments as soon as possible. Secondly, Leanpub allows people to access the book for free. This is important to reach a large audience, but also to allow this book to function as a guidance for the use of GUTS models.

As the users of (results of) GUTS models will have very diverse backgrounds, we only make few assumptions about the reader's knowledge regarding mathematics, statistics and ecotoxicology. Therefore, this book should also be readable for undergraduate students in the natural sciences. In any case, the conceptual basis of the model and its application can be understood without full understanding of the technical details (which we provide as well). At the end of the introduction (Section 1.6), we provide a kind of 'readers guide'.

Note that this book deals with effects on survival, and potentially other 'all-or-nothing' responses (such as immobility). The GUTS framework, however, can *not* deal with effects on graded endpoints such as growth and reproduction (see [10]). For those endpoints, an energy-budget perspective is required, such as offered by Dynamic Energy Budget (DEB) theory (see [100]). For the interested, we advise the dedicated e-book on that topic: https://leanpub.com/debttox_book.

Support on the web

The supporting web page for this book is http://www.debttox.info/book_guts.html, which contains a version (and error) log and information directly relating to the book.

Additional information can be obtained from <http://www.debttox.info> (maintained by Tjalling) and <http://www.ecotoxmodels.org/> (maintained by Roman). Here, you will find (links to) software to perform GUTS calculations, and (lists of) publications that apply these concepts.

About the authors

Tjalling Jager studied biology at the VU University in Amsterdam, the Netherlands, after which he started to work at the National Institute for Public Health and the Environment (RIVM). Next to his work on risk assessment systems, he wrote a PhD thesis on modelling bioaccumulation in earthworms, in collaboration with the University of Utrecht. After 9 years at RIVM, Tjalling moved to the VU University, where he worked for 13 years as a scientific researcher at the department of Theoretical Biology (led by Prof. Bas Kooijman) on application of DEB theory to stressors. Since 2015, he is self-employed, running the private company DEBtox Research (<http://www.debttox.nl>), and continuing to work on DEB- and GUTS-related topics. Tjalling has (co-)authored over 90 scientific papers, and several e-books and book chapters.



Roman Ashauer studied Geocology at the University of Karlsruhe, Germany, and Environmental Sciences at Trent University, Canada. During his PhD at the University of York, UK, he started working on toxicokinetic-toxicodynamic modelling. Next, he worked as scientist at the Swiss Federal Institute of Aquatic Science and Technology (Eawag) in the Department of Environmental Toxicology. After five years at Eawag, Roman moved back to the UK to take up a Research Lectureship at the University of York where he is now working as a Senior Lecturer (<http://www.ecotoxmodels.org>). In 2017, he also started a company (<http://www.toxicodynamics.com>). Roman has published over 50 scientific papers, and in 2007 he won the SETAC/CEFIC-LRI Innovative Science Award.



Acknowledgements

Firstly, we are indebted to all of the scientists that have worked on advancing our understanding of the survival process over more than a century. Their work has laid the foundation on which GUTS, and this book, are built. In Section 1.5, we attempt to piece together these historical roots. Secondly, we thank CEFIC-LRI for providing us with the funding needed to prepare the first version of this book.¹ This book could not have been written without the broader community of GUTS users and developers, especially the participants of the GUTS workshops in 2010 (Kastanienbaum, Switzerland) and 2015 (Mallorca, Spain). Their inputs, and the intensive discussion at the workshops, have led to the development of GUTS in the first place, and have shaped our ideas that are now coalesced into this book. Furthermore we would like to thank the participants of the GUTS software ring test for their substantial contributions to Chapter 7.

¹Project: <http://cefic-lri.org/projects/eco39-review-ring-test-and-guidance-for-tktd-modelling/>.

Thanks to L^AT_EX for providing the platform to write this book, and thanks to Wikipedia (<http://www.wikipedia.org>) for many useful facts and figures. And finally, a special thanks to Tom Parker for making dedicated drawings for this book (Page 8, 63 and 85).

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Chapter 1

Introduction

1.1 Relevance of survival

Why are we interested in survival in the first place? Survival is a relevant endpoint for many questions related to the effects of chemicals in the environment. Which species, populations and communities are most vulnerable to chemical pollutants? Which chemicals are most likely to pose a risk to the environment? Knowing if a chemical affects the survival of organisms is central to answering these questions. Furthermore, survival is easy to measure in short toxicity tests, which are often termed acute toxicity tests, and has a clear and unambiguous relation with population dynamics of a species. Often, the organism's sensitivity to lethal effects is used as a proxy for toxicity in general, and acute toxicity data are required in virtually every framework for chemical risk assessment [144, 172]. Therefore, acute toxicity tests have been, and still are, routinely carried out for thousands of chemicals, for example using fish or water flea as the test organism. Clearly, it is imperative to make the best use of this data and the information contained in it, and model analysis is the only way to achieve that. Finally, the knowledge that we gain, and the concepts that we advance, through modelling survival can later be transferred to modelling other kinds of data.

In ecotoxicology, mortality due to chemical stress is an important endpoint, both from a scientific and regulatory perspective. The GUTS framework originated in ecotoxicology, and this is where we currently see most applications. However, we believe that the GUTS framework, and this book, will be of interest to readers from other fields of science as well. Mortality due to chemicals is also of interest in human toxicology and epidemiology [167], pharmacology and medical research [7, 110]. We can further generalise from mortality due to chemical stress to failure or any binary event due to other stressors or external factors. This means that modelling survival, and hence GUTS, becomes relevant and applicable to problems in a diverse range of fields. This includes biological problems [44, 71, 72, 134] and engineering [63], where the survival of mechanical parts is modelled using reliability theory [131], as well as social sciences where the occurrence of certain events is analysed using event history analysis [4, 41, 81]. We believe that GUTS, or elements of it, can help to generate new insights into a wide range of problems. All that is needed is to replace the death of test organisms used as examples throughout this book with the binary event of interest and replacing the toxicant concentration, which is the stressor used here, with the intensity of any other stressor or causative factor.

Table 1.1: Examples of stressors and stressed entities in different fields of inquiry. All of those fields are interested in the analysis of survival (of the stressed entity) over time. In the social sciences it would be more appropriate to talk about influence instead of stress.

Field of inquiry	Stressor examples	Stressed entity	Relevant terms used
Ecotoxicology	Toxicant	Organisms in the environment	Survival analysis, hazard modelling, toxicodynamics
Toxicology	Toxicant	Humans	Survival analysis, hazard modelling, toxicodynamics
Epidemiology	Toxicant, pathogens, environmental factors	Humans	Survival analysis, hazard modelling
Medical research and pharmacology	Toxicant, pharmaceutical, medical treatment (e.g., operation, radiation)	Humans, rats, mice	Survival analysis, event history analysis, pharmacodynamics
Biology	Environmental factors	Organisms in the environment, humans	Reliability theory, mortality, hazard
Actuarial science	Environmental, social and economic factors	Humans	Force of mortality, mortality rate, death rate
Engineering	Mechanical forces, heat, radiation, electricity	Machine parts or products	Reliability theory, failure probability, accelerated life testing
Social sciences	Policy, social & economic factors	Social systems, organizations, human behavior	Event history analysis, transition analysis, duration analysis

1.2 The descriptive approach

Why do organisms die, or better: why don't all individuals die at the same time under the same conditions? Over the years, scientists and professionals interested in the process of mortality (biologists, toxicologists, actuaries, etc.) have generally avoided this question and settled for a description (see Fig. 1.1 for two examples). These descriptions have a number of problems associated with them, all related to the fact that they are used to *describe* the data rather than to *explain* or *understand* them. To focus on (eco)toxicology: in this field, it is common practice to fit a standard curve (such as the log-normal or the log-logistic) to the data for survival versus concentration at a single time point, generally at the end of the experimental test (see right panel of Fig. 1.1). From this curve, one can deduce the concentration at which 50% of the individuals survive, and this concentration is promoted to the status of 'summary statistic': all of the information of the toxicity test is reduced to a single value. This value goes under different names, such as LC50 (when exposure is expressed as a concentration), LD50 (when exposure is expressed as a dose), EC50 (when the effect is not mortality but e.g., immobility), etc. Of course, one can also calculate an LC10 or an LC90, or in general an LC x for any x between 0 and 100%.¹ In toxicology, such summary statistics from a dose-response fit are often referred to as the 'benchmark dose' [51].

It has long been known that LC50s depend on exposure time: under constant exposure, they generally decrease gradually over time, and asymptotically approach a stable value, designated the 'incipient LC50' (see e.g., [170]). Unfortunately, the time needed to achieve this incipient LC50 depends on properties of the chemical (e.g., mode of

¹Generally excluding the boundaries, depending on the curve that is selected to describe the data. For distributions like the log-normal and log-logistic, the LC0 will always be 0, and the LC100 will always be infinite, irrespective of the mean and standard deviation.