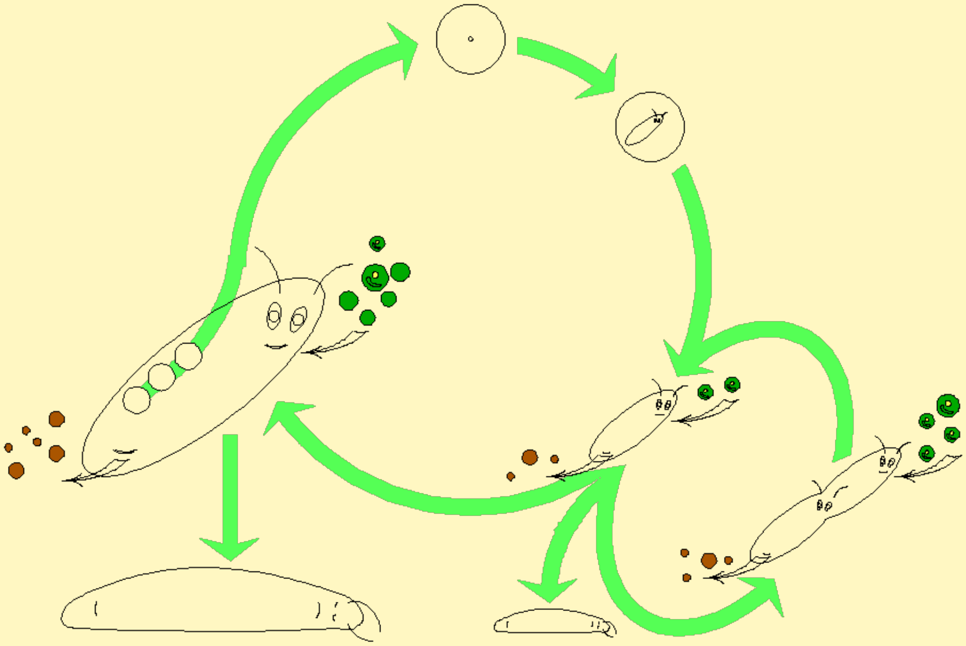
# Trilogy on a case study in Theoretical Biology



**S.A.L.M. Kooijman**

Farewell address VU University Amsterdam

May 2015

# Trilogy on a case study in Theoretische Biology

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## 30 years Theoretical Biology

Farewell address as Professor at VU University Amsterdam
Aula of the VU University Amsterdam 2015/05/08/15:45

## DEB theory: where fascination meets profession

Farewell address upon retiring as Professor of Theoretical Biology
4th DEB symposium, Luminy (Marseille) 2015/04/30/17:10

## Theoretical Biology, a specialisation in integration

Inaugural lecture given at the acceptance of the chair Applied Theoretical Biology at the Faculty of Mathematics and Natural Sciences/ Subfaculty of Biology of VU University Amsterdam at 18 June 1987.

# 30 years Theoretical Biology

**Farewell address as Professor at VU University Amsterdam, 8 May 2015**

Rector

Ladies and gentlemen,

## Evaluation

Now, at the occasion of my farewell after serving for 30 years as professor of Theoretical Biology at VU University Amsterdam, is the perfect moment to evaluate what I have been aiming at and to judge to what extent I achieved my goals.

The standard way of evaluating scientists is by simple statistics. I gave 60 courses on a variety of topics, such as statistics, probability theory, modelling, theoretical biology, ecology, ecotoxicology, ranging from 1 day till 10 weeks, national and international; gave, on average, 5 till 10 lectures per year and graduated 46 students till now, with support from a small group of staff members. I (co)authored 300 publications, including 4 books, an h-index of 43, an i10-index of 164 and a citation rate gradually increasing till now once per 8 hours. My research has been in de form of projects that were all externally financed and we have been able to keep the department in a healthy state, financially, over the full period of 30 years.

Of course you are free to have your own opinion about this, but such statistics have very little meaning to me. Great to give courses, but what did the students actually learn from this and what have they done with that knowledge? Well done to keep your department financially healthy and avoid becoming a problem for your fellow faculty members, but this cannot be an aim in itself. The purpose of science is not writing as many publications as possible. The citation score tells little about the significance of scientific work. At best it is a quantifier for the number of scientists working in that field or for the popularity of the topic. It is easier to boost this score with blunders than with nice results and inserting some mathematics in papers for a biological audience is a great way to plummet the score.

A meaningful evaluation can only be based on a judgement of contents. I first need to provide context for what I wanted to achieve and why.

## Biology as science

For non-biologists, biologists are typically people who are busy with plants and animals. For biologists, however, knowledge of plants and animals species is not popular since long, and in practice very much limited.

My view on biology is pitty wide. For me, medicine, pharmacology, toxicology, agriculture, fisheries, sewage water purification are all examples of applied biology: the science of life. Fields, such as environmental management, climate change and recycling have important biological components. Sociology, psychology and economy would benefit a lot if they would include more biology. Do biologists then play important roles in all these fields? I am very sceptical about this and see the attitude of biologists as main reason for this and what they made of their field up till now.

Biology is traditionally very descriptive, identifying problems, rather than analytic, solving problems. Many biologists experience biological facts as a huge collection of exceptions that hardly allows for a classic physical–chemical analysis, based on general logical principles. A confusing chaos, that can hardly be accessed by non-biologists. On top of that, biology requires a solid background in mathematics, physics, chemistry and geology, while the huge literature and the wide scope of the field force specialisation to the extent that it becomes suffocating. Where physics profits enormously from the possibility to simplify by excluding complicating factors experimentally, biology has to deal with the fact that even the most simple organism is still hopelessly complex. The number of chemical compounds in a living cell is in fact infinitely large, processes are extremely hard to measure quantitatively, due to temporal and spatial scales, and the numbers of molecules of most chemical compounds are frightening small. Cell compartment are that small that classic reaction-diffusion is hardly applicable. We hardly know anything about transport in liquid crystals, which has a much higher relevance for cells, where, on top of that, membrane activity dominates cell physiology.

I see theoretical biology as a specialisation in generalisation in biology, linking specialisations as molecular, cellular, organismal, population, ecosystem and evolution biology. Disciplines as methodology of science, mathematics, physics, chemistry and geology are natural pillars in such an enterprise. Close collaboration with specialists in the various disciplines is a must for any hope of success.

Apart from this task of linking specialisations with theory, theoretical biology also has a task in transforming biological research from empirical to theory-driven. Empirical research has typically no sharp questions or emphasis on quantitative aspects, but collects observations and data in search for patterns that call for explanations. All science started like this, including physics and chemistry. The problem with biology is that the natural next stage in the ontogeny of science is difficult to enter: theory-driven research that builds on empirical research, with sharp questions, strongly quantitative, where mathematical models play a central role. See Figure 1.

## Task

With my background in theoretical biology I set myself a very ambitious, may be even reckless, task: to construct a formal and consistent framework within which it would be possible to do biological research, similar to that in physics and chemistry. The transparently organised framework that emerges would open doors for non-biologists, such as engineers, to enter the biological field and for biologists to work on their societal tasks that I think biologists should have, in collaboration with others. I have a practical character and hate vague wild claims that lead to nothing. I, therefore, have chosen for a specific topic that is central in biology and for the method to build an explicit theory. I called this theory the Dynamic Energy Budget (DEB) theory, which deals with the flows of energy and mass to and from an individual during its entire life cycle, from the start of development till death by ageing. This individual can be uni- or multi-cellular, plant, animal or micro-organism, in short: the theory should be applicable to all live on earth, no exceptions, in a changing environment. Interactions between individuals, such as competition, symbiosis, parasitism and predation, are also included in the theory, which paves the path to population dynamics. Such a theory would be iconic for similar ones in other fields of biology and, in due course, boost biology as a discipline leading to further integration in natural sciences, which I consider to be essential for further progress. The idea was to build a formal theory, i.e. based on explicit assumptions with strong roots in physics and chemistry, which, in combination, uniquely specify a family of related models that can produce quantitative predictions that can be used to test the theory on realism. The assumptions should be free from empirical elements and also of optimization arguments. Such arguments are popular among evolutionary biologists, but with me.

When I hear myself talking like this, I would, without further knowledge, conclude that a lunatic is at work here. Perhaps you have the same idea in mind, and may be you are even correct, but it might less extreme if you allow

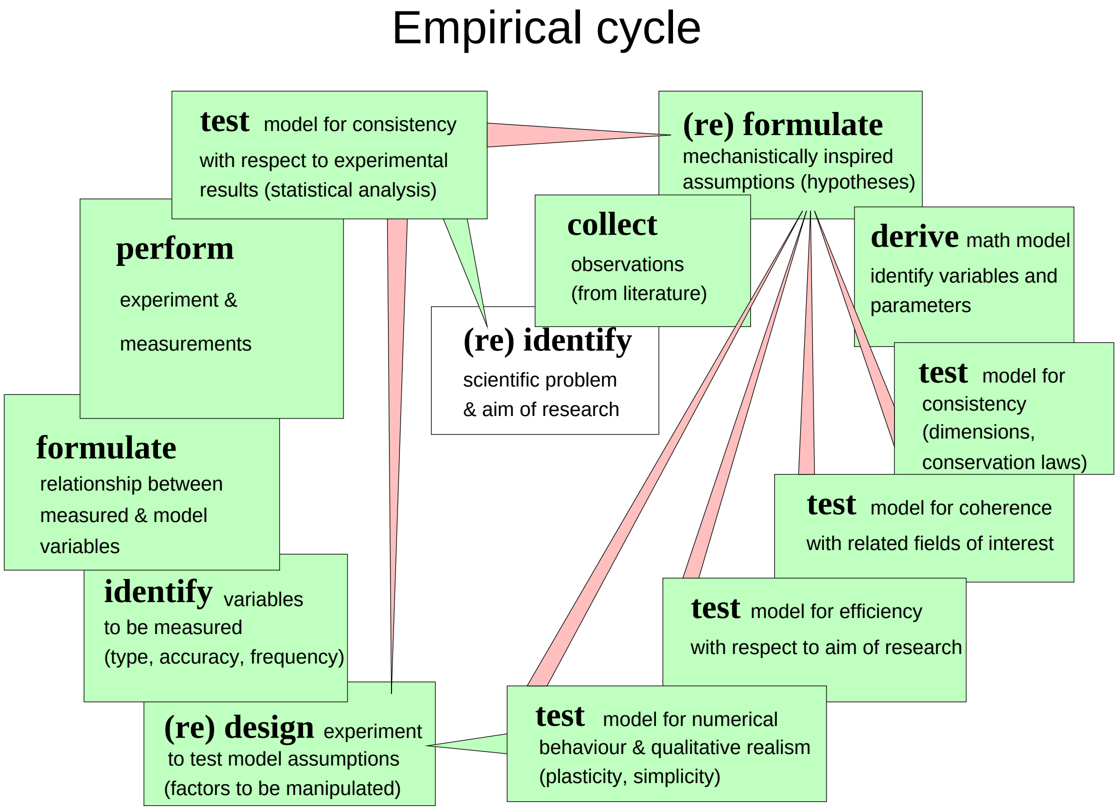


Figure 1: The empirical cycle in the eyes of a theoretician starts with the formulation of the problem, using published work as source of inspiration for assembling a list of assumptions: the red arrows are followed in case of a bad result, the green ones otherwise. While experimentation is here only in one box, this does not mean that it is relatively little amount of work, but its significance fully rests on the rest of the cycle. The role of statistics is confined to the last step in the cycle. Many models don't need to be tested against data, since they already should have failed earlier tests in the cycle. More than half of the models that are published in the biological literature suffer from dimension errors and are, therefore, useless; some 80 % of the manuscripts that I reviewed that were submitted for publication by journals also suffer from this. Given that nonsense models can easily fit data very well if they are sufficiently flexible, fitting data well is not the most important criterion for useful models. If the step from assumptions to the specification of the model is sufficiently lucid, a bad fit should lead to the assumptions that needs replacement. Since the assumptions reflect insight, this can be seen as a step-up and, perhaps, the most useful role of models that are derived from assumptions. Such models are rare, however.

me to provide further context.

The classic view in the natural sciences is still widely held that everything should be explained from lower levels of organisation. In the end all should be explained from nuclear physics. I believe that this view is not correct, certainly not in biology, and also not productive. Interactions between levels of organisation need to be taken into account: emerging properties. Based on this view, the classic approach to cellular energetics is the biochemical one. As said before, an organism consists of an infinite number of chemical compounds and attempts to follow compounds comes with the need to select a small number of important compounds, implying that the rest is unimportant. The implication is that important principles, such as energy and mass conservation, cannot be exploited and it becomes very hard to exploit thermodynamic constraints, which are based on these conservation laws. An alternative is to partition the individual into metabolic pools that can change in size, but not in chemical composition, a principle that is called homeostasis. The general idea is to continue partitioning till realism is approximated. The next step is to specify the dynamics of these pools: a miraculous process that cannot be discussed here in detail. It would take too long. The two different approaches don't exclude each other and are in a sense complementary: bottom-up versus top-down. If applied in combination, this greatly restricts freedom to model intermediary levels of organisation; a powerful research strategy. One possibility is, for simplicity's sake, to delineate only a single metabolic pool in an individual, which could be called biomass. The implication is that this cannot change in chemical composition and that the individual does not have metabolic memory. This would be very unrealistic, because biomass does change in composition in response to the nutritional status and the metabolic behaviour of individuals is very sensitive to food uptake in the recent past. We, therefore, should delineate at least two pools in an individual, which I called reserve and structure. Reserve serves the function of metabolic memory, which I consider to be the most important cornerstone of DEB theory, which set DEB theory apart from other theories on the metabolic behaviour of individuals that I know of. After 35 years of research, it turned out that many aspects of animal energetics are well captured with thus two pools. For plants and microorganisms we need more pools for reasons that follow form the theory itself.

## What has been achieved?

35 years of work on DEB theory by an increasing number of co-workers across the globe is hard to summarize in a few sentences. In an early stage of the development of DEB theory, I laid down the quantitative foundation that stood

the test of time, despite the intensive testing program that is still going on. Judging to what extent the theory can capture effects of toxic compounds has been part of the testing program is. The general idea was that each toxic compound perturbates the metabolic machinery in its own way, and, examining many toxic compounds, these perturbations reveal the underlying organisation. A paper of Jan Baas will appear this year that links the sensitivity of toxic compounds to one of the DEB parameters, which crowns the theory in my opinion.

The theory was constructed in modules and fit into a lean skeleton. Each application, such as isotope dynamics, mother-foetus and parasite-host interactions, growth of tumours and microbial flocks in sewage treatment plants, requires its own details that can be organised in modules. The modules can be removed again when these details are not required, keeping the applications always rather lean. Scales in space and time are important criteria for including and excluding particular modules.

I found an alternative for enzyme kinetics, which I called the dynamics of Synthesizing Units (SUs). Enzyme kinetics quantifies enzyme-mediated chemical transformations; all transformations in living cells fall in this category. My alternative works with fluxes particles, molecules if you like, and avoids the use of the concept concentration, which is key to enzyme kinetics. Concentrations are problematic to work with when space becomes really small and structured, which is the case in cell compartments, so does the number of molecules. This concept only works well if space is homogeneous and the number of particles is large. You will not find this in cells, however. DEB theory makes use of SU dynamics at several places; phenomena such as co-metabolism and adaptation are hard to capture otherwise, but Bernd Brandt was very successful with SU dynamics. This dynamics also find fruitful application in modelling the behaviour of individuals, where the individual plays the role of an enzyme molecule. Behaviour is here meant in the wide sense, including selection of food types, coupled to the state of the individual, the exchange of products in symbiotic relationships and in mitochondria cytosol interactions. This type of syntrophic exchange has relevance for the dynamics of firms in an economical context. SU-dynamics is basically stochastic, and the random effects become more important with the decrease of fluxes. Randomness dominates (animal) behaviour, including feeding behaviour, fuelling individual's metabolism. If the input into a system is stochastic all the rest of the system behaves stochastically as well, but in a very special way. This is of importance for the statistical analysis of metabolic data. I expect that SU dynamics will, in due time, out-compete enzyme dynamics in modelling living systems

Continued research resulted in a better understanding of metabolic dynamics and it became increasingly clear to me why the original skeleton stood the test of time. A powerful element in this context a set of co-variation rules for parameter values, when different species of animals are compared. These rules follow from dimension analysis and do not involve any empirical argument. I had to invest quite some effort to understand why assumptions that are inspired by the logic of the underlying processes actually have implications for parameter values. Many properties of species, such the maximum body weight, reproduction rate, length of embryonic and juvenile stages, life span, maximum growth rate, can be written, in the context of DEB theory, as functions of parameter values, so also as function of one of them: maximum body weight. Libraries full of papers plot these quantities log-log against maximum body weight; a hobby that became known as body size scaling relationships. DEB theory continued to produce the correct predictions, now for some 40 different quantities. The big difference with the empirical approach is that we now understand why. I also found similar co-variation rules for the exchange of chemical compounds between individual and the environment. This is of importance to understand how different species react on chemical compounds, a hot topic in ecotoxicology and pharmacology.

Something that I did not expect after such a long period of working on DEB theory is that each year there was a new development that I experienced as a break-through. Happy enough for me, because I don't consider myself to be a patient person and without these repetitive stimuli, I would have ceased this line of research much earlier.

More than 30 very different popular empirical models in biology turned out to follow mathematically for DEB theory, either exactly, or by a very good numerical approximation. Since they now follow from theory, we now know under what conditions these models can expect to produce useful predictions. The oldest model, that of indirect calorimetry, goes back to Lavoisier 1780. This model states that dissipating heat from an animal is a weighted sum of dioxygen consumption, and carbon dioxide and urine production. The most famous model is possibly that of Kleiber 1932, which states that dioxygen consumption is proportional to body weight to the power 3/4. Textbooks on animal physiology state that this law is best known and documented, but least understood, and to understand the law is key to animal physiology. Indeed, a very large number of scientists have tried to understand this law, but all eventually in vain, except DEB theory, which has a simple explanation since 1986. Apart from the deep satisfaction that these formal reconstructions of empirical models gave me, the empirical support of these models also support DEB theory.

Every application of quantitative theory comes with the need to know parameter values. This is one of the reasons why the DEB course that I organised over the years has a module where the student can complete a data template for the species of his choice during the tele-part of the course, and during the practical part we help and teach him how to estimate the parameters. So after the course he/she is directly able to apply DEB theory for that species. To facilitate all this I wrote a powerful software package of more that 1000 routines, to compute the various predictions of the theory. In this way we now have a collection of some 400 species from almost all phyla, and for chordates all orders. The goodness of fit is generally very high, and the number of papers on striking evolutionary and ecological patterns in now rapidly increasing. The curators of the collection are presently in the process of revision on the collection and code, which might become a frequently used data base.

This data base, in combination with the list of implied empirical models and all the other testing research that we did over the years, I can now conclude the DEB theory is the best tested quantitative theory in biology. Despite this huge amount of work that has been done, the development of DEB theory is still in its juvenile stage. Not a surprising conclusion, given the ambitions. Biological research that took a descriptive route during centuries, cannot change direction within 30 years based on work of a small group. Moreover, each door that opens gives view on several new closed ones; a basic principle in science.

## Impact

With respect to impact of this work, I arrive at a mixed conclusion. There is hardly any impact at all at VU University where I worked. But, happy enough, nation wide this is better and internationally much better. With more than 120 participants of the international DEB course that ended last week, 4 DEB symposia, 5 special DEB issues of journal, 500 publications in which DEB theory plays an important role, DEB theory leaves competition behind. By the way, I don't know other theoretical attempts with comparable generalisation on a formal basis, a bit to my amazement and regret. It is, therefore, not that difficult leaving competition behind. My honourable degree in Marseille and membership of the Dutch Academy of Sciences can be viewed as signs of recognition, but they tell little about impact. That DEB based methods to evaluate the toxicity of chemicals found their way into the OECD and ISO guidelines does say something about impact. I cannot be proud of a list of prices, but a number of people around me can, on the basis of DEB research. What for me is much more important is that an increasing number of former students found jobs because of the knowledge of DEB theory, and several institutes came to the insight that DEB theory has the potential to couple seemingly different projects and this way increasing their internal coherence and boosting team building internally. It is promising that a number of universities now teach DEB theory in the obligatory part of their biological or engineering program. Although DEB research and theoretical biology now ceased at VU University, I happily observe that it continues elsewhere due to effort of others and the upcoming DEB course 2017 will be organised from Tromsø, thanks to Starrlight Augustine.

The most important critical notes on DEB theory, up till now, is its supposed complexity. I did not meet critics on contents, such as on the assumptions that the theory makes. Although I do understand this critics, I think the DEB theory is a very simple theory about a very complex network of interacting phenomena. A lot of people confuse, I think, the problem of complexity with the fact that quite a few different disciplines meet in the theory, and most are new to them. This does not concern the content of the theory, but their first exposure to different disciplines. I directly admit that to work with the theory requires a substantial effort investment. This certainly not helps a fast and broad acceptance within science, but to what extent should this be a concern?

If you study physics and relativity theory is of relevance to you, everybody fully accepts that it takes half a year to master and nobody complains. My question to biologists would be: Why, you think, is it that physicists feel the need to develop complex theories for simple phenomena and biologists think that simple theory will work for complex phenomena? Do they take their field seriously or did they give up all hope that biology once can become a rigorous science?

The requirement to invest substantial effort comes with the need to generate enough motivation to make such investments. I think that it can only be done via sufficiently convincing applications of the theory. The pile of such convincing applications is steadily growing and in due course the pile will be sufficiently large to motivate many. The time is takes to reach that point is much larger than I expected in my naivety. I see promising developments, but not necessarily within biology, and also not in the Netherlands.

Not only in the Netherlands, but also in several other countries, I noticed tendencies to trip the biology curriculum at universities from supporting disciplines, such as mathematics and chemistry. The main motivation in the Netherlands is that many students with a taste for biology don't like these disciplines and a strong financial incentive exists to maximize student numbers. I wonder which societal significant problems young doctors then will help solving. I don't have an answer to this and see education in biology slipping down to a recreational setting. My own PhD's rapidly found jobs within their discipline and I was told that it is nowadays very hard to find jobs in ecology in France without sufficient mathematical background. So, I still have some hope. These are, by the way, not easy times for starters in science. Under American lead, scientific research is increasingly organised in 2 or 3 years projects, financed from priority programs. Innovation arguments, with strong political undertones, are used to change priority topics each five years. Under such a regime, it is very difficult for research groups to keep coherence between subsequent projects in longer term programs. Which meaningful scientific problem can, however, be solved in 2 or 3 years? In my opinion this is a very effective way of killing rigorous science and, even more important, of wasting talents. This policy strongly promotes an overwhelming flow useless publications, effectively hiding the few significant ones. The greed for economically promising applications of science let us forget the necessity of first developing a sound scientific basis. Too little distinction is made between technological innovation and scientific research. It translates into an investment on short or long term, which have different priorities. A strong incentive exists to publish a lot, but no reviewers ever ask how much is read. The large number of review reports on submitted manuscripts that I have seen make very clear that the answer to this is: extremely little! Thanks to a number of tricks, I was still able to organise my projects in a coherent program, but I also conclude that this is rapidly becoming more and more difficult, if not impossible. I included my inaugural lecture of 28 years ago now in the trilogy that supports this lecture, to show that I carefully planned the program and also that my view on theoretical biology remained the same. I also included my international farewell address that I presented a week ago on the DEB symposium in Marseille, that has more content on the theory from a personal perspective.

I think it is still too early to make a balanced impact analysis of my work and that of our department. On top of that it is not me who should do this. The future will automatically reveal the impact, but I have positive expectations. These are fed by the assessment that DEB theory concerns problems that are in the core of environmental quality management, food production and medical care. Three fields of problems that will rapidly increase in significance in the near future to the extent that policy makers cannot neglect. I would also be very surprised if DEB theory will have competing alternatives. It remains necessary, however, to further develop the theory for this type of applications and the toolbox that is required should have quite a bit more elements. Anyway, I utterly enjoyed working on the theory as well as the many nice contacts I had all over the globe.

## Acknowledgements

I like to thank VU University for the trust given to me over all these years. Further I first would like to thank my wife, Truus Meijer, for all support she gave in the background in a multitude of contexts. Sometimes you complained that our house more resembled a hotel, but you also enjoyed when our guests

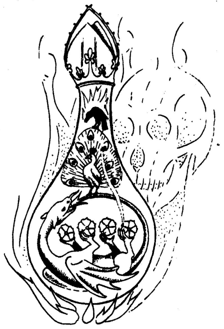
priced your cooking skills, now famous on all continents, and the stories that they brought in with their rich diversity of cultural backgrounds. Thanks to our guests, we now know that Holland is big in poffertjes, stroopwafels and pindakaas, goodies that can better not be translated. To my surprise, walking through Amsterdam forest during lunch as a shock for those who thought that you can only have your lunch while sitting.

I want to thank my colleagues in our group Theoretical Biology for the productive collaboration and for the cosy ambiance that we managed to keep up over the years. In particular I want to mention Bob Kooi and Tjalling Jager, who now help me to entomb Theoretical Biology at VU University. I very much enjoyed interaction with my 50 PhD students and their refreshing criticism that is so essential for a healthy scientific atmosphere. The huge amount of work that has been done during 30 years of Theoretical Biology at VU was only possible thanks to the full support of all.

As mentioned before, theoretical biology is a discipline that can only flourish in close collaboration with others. This has thus be done, not only in the Netherlands, but world wide. I enjoyed this collaboration very much and I would like to thank all collaborators.

I would hate to not-mentioning the supporting staff, administration, financing, beadle and want to mention Karin Uyldert who, long after our department was removed from her duty list, continued to give support and helping hands.

Last, but not least, I want to thank you, audience, for your warm interest and invite you for the reception, also on behalf of my colleague Bob Kooi, for whom this is a farewell as well.



# DEB theory: where fascination meets profession

**Farewell address upon retiring as Professor of Theoretical Biology**
**at 4th DEB symposium, Luminy (Marseille) 30 April 2015**

*Choose a job you love, and you will never have to work a day in your life.*
*Confucius: 551 BC – 479 BC*

## Fascination and profession

Nobody knows or understands why I was born with an intense interest in everything that lives; a mutation in the family that will last till the day I die. I became fully trapped in the interest-knowledge spiral, a most precious gift. Happy enough, my parents and sisters tolerated all my pets, including the many oil-birds from the beach that I tried to clean-up and prepare for a more happy release, the lizards, fish and name it. This interest combines well with hiking, another passion of me, and, with my friend Jacob van Dijk, we visited many remote areas all over the world for more than half of our lives on yearly basis; much more than Darwin could ever do. Apart from utterly enjoying the beauty of nature, these travels are very confronting at the same time. We live on a most gorgeous planet in the universe that took milliards

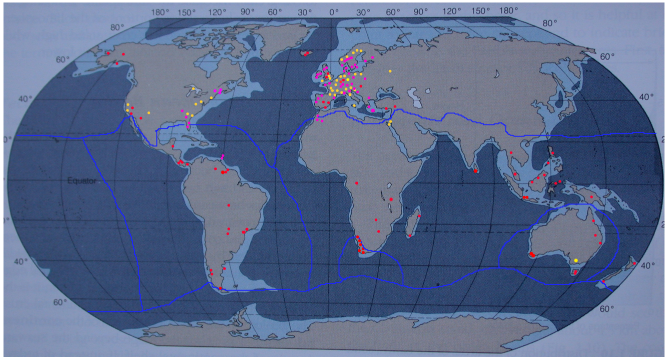


Figure 2: Sites of my extended wilderness hikes

of years to mature and we, as humans, do our utmost to spoil it in a century. I still accumulate pictures of wildlife, now some 150 thousand, which I try to identify in order to learn more about the specific properties. Since most life on earth is very small, I am amazed how few persons take the effort of using a microscope, an interest that was sparked by my friend Jan Parmentier. It is still easy to meet small creatures in your own backyard that is not in any of the books I know, while I have more than 100 meters of books at home. Internet resembles an accumulation of errors about the micro-world and is of little help here; the consequence of being a lonely place.

That I wanted to study biology never has been a point of discussion. Being very dyslectic, I had problems with languages and my older friends who started already, warned me that Latin names of plants they had to learn were not much easier than the French words at high-school. This is why I started to learn them for the plants around me in the summer before the biology study, and why my fellows frequently asked me names, which added to my kick-start at Leiden university.

After 3 years of study it became clear that finding a job in biology would be difficult, so I asked myself the question 'What specialisation is useful but not popular?' to shake-off competition. The obvious answer for me was mathematics; when I saw how ecologists around me used statistics to step from data to conclusions, I thought that it should not be too difficult to improve on that. Moreover my dyslexia here works out as an advantage, rather than a handicap. The strategy was successful for me and I enjoyed giving statistical advices that much that I continued to do this from a student assistantship, during my PhD and my first job at the TNO laboratories in Delft. After talking to people who seek advice, their actual problem frequently differs a lot from the problem they thought they had. I learned a lot from this interaction and helped me to develop an interest in science in general and to see links between seemingly different disciplines. The key value of mathematics is not the handling of symbols or the rules of calculus, but the formalised abstract thinking, which helps in all disciplines.

It took me quite some time to transform my mathematics from a tool to get a job into one to learn more about biology with intrinsic beauty. It came hand-in-hand with a shift in interest in statistical applications: from 'Given assumptions about data, how do I arrive at conclusions?' to 'What am I ready to assume about data and why?'. My interest in the methodology of science was born from practical necessity; it is easy to fool yourself and others with statistics by not paying sufficient attention to the underlying assumptions. Where mathematical reasoning starts and ends in the abstract world, a lot happens during the step from the real to the abstract world and backwards. During my PhD project on the statistical analysis of point patterns in the plane, with applications in vegetation research, I came to the conclusion that patterns themselves have little information; the focus should be on the behaviour of patterns in time: life is a process. This insight helped me to step from statistical analysis to modelling in terms of dynamical systems and stochastic processes.

## Planting the seed

At the TNO laboratories in 1977, we were with very few biologists among a building full of chemists, physicists and engineers in a setting that was very different from my peaceful academic existence at the university with lots of contacts and contracts with chemical industry and governmental institutions. In combination with having to supervise a bunch of young ladies with little patience with me, this was a jump into cold water that eventually worked out very refreshing. We worked on problems in chemical pollution, waste water treatment, environmental risk assessment; from laboratory experiments and mesocosms to environmental monitoring. My additional statistical advice work brought me in all corners of the building, far outside my own field. I learned a lot here and it opened my eyes for the various and complex aspects of environmental quality management.

This was perhaps the least likely setting for planting the seed of Dynamic Energy Budget (DEB) theory in my mind, yet this is how it happened: the combination of two independent questions asked to me: ‘How should we quantify effects of chemical compounds on the reproduction of daphnids in some standardised laboratory experiment?’ and ‘What is the societal significance of a small effect on daphnia reproduction?’. Daphnids are frequently used as test animals in ecotoxicity research and, starting with neonates, they can easily have 600 offspring per female in 3 weeks. I realised that these questions were special cases of a wider question ‘What are the ecosystem effects of a change in the energetics of individuals of some species?’ and that this question has the potential of changing biology as a discipline if approached with sufficient rigour, not respecting any disciplinary boundary. Not only chemical industries can induce such changes, but also environmental conditions in general and evolution. Individuals are the units of evolutionary selection and the link between properties of individuals, via that of populations, and properties of ecosystems are the basis of evolutionary selection. So this question is at the root of evolutionary change and probably at the root of understanding life itself as a biogeochemical process. Moreover, the environment is not only controlling the performance of individuals, but individuals are also effecting the environment, so it is an interaction. This opens the door to systems earth dynamics; Peter Westbroek showed me that this is an exciting field that is in urgent need for ideas how life affects planetary development. In August 1979, lots of population models existed, but none of them accommodated properties of individuals. I went to Hans Metz and Odo Diekmann for help on how to step from unique individuals to populations in an advanced bookkeeping scheme and, in parallel, worked on theory for how an individual interacts with is environment throughout its life cycle. After working on the problem for several years, mostly in spare time, I went to VU University Amsterdam in 1985 to boost progress.

Letting the seed grow in funded research has been a challenge, however, especially during the first 25 years. I had to hide my real aims in 3-year research proposals behind applications that made no reference to it. But finding applications has never been a problem: waste water treatment and biodegradation, global change, ageing and cancer research, fisheries, name it. This diversity of applications inspired international review committees to criticise the lack of coherence in the research program of our group. Only during the last 10 years, DEB theory became sufficiently known to mention it is research proposals. I have been very pleased to see that Roger Nisbet has been able to use the label 'DEB theory' to acquire funds for his research on the toxicity of nano particles. Why I think that the development of theory on the basis of applications is a powerful strategy becomes clear in my philosophical position with respect to theories.

## Theory for energetics

Theoretical Biology, the name of my chair in Amsterdam that I hold for exactly 30 years now, is a specialisation in integration where biology meets mathematics, computer science and methodology. Chemistry, physics and geology are natural components of such a generalisation in biology. If done properly, theoretical biology connects specialisations in biology and serves the function of cross-fertilisation. The rationale for the existence of this discipline is simple, direct and inescapable. Measurements need interpretation before they get a meaning. This interpretation comes with the need to make assumptions and this then comes with the need to do this in a formalised explicit manner in order to be in control of these assumptions.

A quantitative theory is, for me, a list of consistent and coherent assumptions from which mathematical models follow. Models are formulas that describe the behaviour of quantities. These quantities can frequently not be measured directly, so we need auxiliary theory to link quantities in the model to quantities that can be measured. Wanting to have theory as concrete and applicable as possible, I always have seen DEB theory as a case study to construct theories in biology. Without such a concrete case one runs the risk of becoming vague and useless.

In this view, the value of a model is in the list of assumptions that generates the model. Most models in the literature are not constructed like this, they are just presented, and the reconstruction of the assumption list from a model is rarely possible and even more rarely unique. A model without this list has little value; if one is in need of a curve through a set of points in a graph, this can much easier and more beautifully be done with a pencil rather than a model. So a mathematical model does not necessarily represent a quantitative theory.

Complex models, with lots of variables and quantities, are of less scientific value than simple ones, for several reasons. However complex they might be, they are an extremely simplified abstraction from a much more complex reality. This simplification is essential of the role of models to help our understanding of reality. No wonder that, if we look hard enough, models don't predict reality in all detail, which we can potentially always detect with measurements. I agree with Popper that verification does not work in science, but falsification also has limitations. The philosophical situation is complex indeed and science has, for me, artistic elements. I see the role of theories in science as tools to understand reality and as long as they help us with that, we continue to use them. So the value of a theory is not absolute, but in its practical use; if a theory is not used, it is without value. With the increase of our understanding of reality, we need to adapt or replace theories. Theories, being the building blocks of science, are part of a process. They cannot be judged on their usefulness independent of what we want to understand or predict.

Is it, with this philosophical position, possible to build a theory for the behaviour of an individual, such that, in combination with models for environmental dynamics, properties of individuals can be linked to properties of ecosystems? I think here of individuals of any form of life, including plants, animals, micro-organisms, etc.; no exceptions. Given the overwhelming diversity of life, where it seems easy to find exceptions to any rule you can dream up, most biologists are inclined to answer by a firm 'No!'. With my hobby in natural history, it is easy to see that logic. Yet if you don't try, you will not find such a theory, and how can you be sure, without trying, that it is impossible? Although species share a lot of biochemical machinery, many regulation systems are species-specific. Do we really need such detail to specify what individuals do, or do these regulation systems serve a limited number of particular functions that all species share? I was also not thinking of an overly simple model, because we need sufficient flexibility to accommodate the various life history strategies species do have. When we work hard to trim complexity down, what minimum complexity do we actually need for it?

In the biochemical approach to energetics, chemical compounds are classified into a few that are important and the bulk that is not. Only the few important ones are followed at molecular level, because the number of chemical compounds in an organism is countless. Many individuals are unicellular, which brings for them the molecular and individual levels closer together. For multicellulars we need tissues and organs in addition to ideas about how cells work, but useful models for cells already help a lot in understanding multicellulars. Although many researchers follow this line of reasoning, I see several major problems. First: what makes a chemical compound important or unimportant? Can we really make such a classification in ways that are not species-specific? Second: chemical transformations make that important compounds are synthesized from and decomposed into unimportant ones, which prohibits the use of mass and energy conservation rules since unimportant compounds are not followed. Third: the time scale at which chemical transformation operate is many orders of magnitude smaller than that of growth and division of the cell. It is never a good idea to combine such widely different time scales in one model and leads to hopelessly complex models that do a poor job in helping understanding. We need organisation levels between the molecule and the cell to reduce the huge difference in time scales and reduce complexity. Fourth: the spatial scale of cells, or cell compartments, is so small that classic ideas on chemical and enzyme kinetics don't apply. I come back to this point.

If we don't follow particular chemical compounds in an individual, what alternatives do we have? I think that the only answer is to follow the dynamics of pools of metabolites of constant chemical composition, a principle that I call strong homeostasis. Biomass as a whole could be such a pool, but with one pool we cannot capture to notion of metabolic memory nor can we handle changes in composition or help us to go into the direction of lower levels of organisation. So we need more pools. Strong homeostasis is obviously a idealisation that is never satisfied in detail, but still allows the use of mass and energy balances and access entropy. The delineation of pools directly comes with the problem 'How can we access the chemical composition of such pools?'. At least at the level of frequencies of chemical elements this is essential to close the mass and energy balance. I came to the insight that weak homeostasis is essential for this: as long as environmental conditions are constant, biomass as a whole remains of constant composition, even during growth, but possibly after an adaptation period. So the various pools grow in harmony under such conditions. The relative size of pools might depend on environmental conditions and this we can use to access their chemical composition by comparing the effect of different environmental conditions. Weak homeostasis, therefore, restricts the quantitative behaviour of pools and implies strong homeostasis, but not vice versa. Although the weak homeostasis principle leaves quite some freedom to further design the behaviour of individual energetics, theoretically, it also substantially restricts the set of all possibilities. Once you accept this principle, it will be hard to escape the further details of DEB theory. You are trapped before you realise it. I think that there will never be alternatives for

Table 1: Empirical models that turn out to be special cases of DEB models, or very good numerical approximations to them.

| author | year | model |
|---|---|---|
| Lavoisier | 1780 | multiple regression of heat against mineral fluxes |
| Gompertz | 1825 | survival probability for ageing |
| Bergmann | 1847 | body size increase toward the poles |
| Arrhenius | 1889 | temperature dependence of physiological rates |
| Huxley | 1891 | allometric growth of body parts |
| Henri | 1902 | Michaelis–Menten kinetics |
| Blackman | 1905 | bilinear functional response |
| Hill | 1910 | Hill's functional response |
| Thornton | 1917 | heat dissipation |
| Pütter | 1920 | von Bertalanffy growth of individuals |
| Pearl | 1927 | logistic population growth |
| Fisher and Tippitt | 1928 | Weibull ageing |
| Kleiber | 1932 | respiration scales with body weight$^{3/4}$ |
| Mayneord | 1932 | cube root growth of tumours |
| Monod | 1942 | growth of bacterial populations |
| Emerson | 1950 | cube root growth of bacterial colonies |
| Huggett and Widdas | 1951 | foetal growth |
| Weibull | 1951 | survival probability for ageing |
| Best | 1955 | diffusion limitation of uptake |
| Smith | 1957 | embryonic respiration |
| Leudeking and Piret | 1959 | microbial product formation |
| Holling | 1959 | hyperbolic functional response |
| Marr and Pirt | 1962 | maintenance in yields of biomass |
| Droop | 1973 | reserve (cell quota) dynamics |
| Rahn and Ar | 1974 | water loss in bird eggs |
| Hungate | 1975 | digestion |
| Beer and Anderson | 1997 | development of salmonid embryos |

DEB theory with a similar low level of complexity and high level of generality. The alternatives that I know of suffer from major inconsistencies and don't count, for me, as alternatives. I do realise that this is an extreme position and I will try to give it more context in the rest of this lecture. The remark is also meant to stimulate you proving that I am wrong on this point.

My conjecture is partly based on the observation that quite a list of popular and seemingly unrelated empirical models turn out to be special cases of DEB theory. See Table 1. The oldest empirical and widely accepted model in the list is indirect calorimetry of Lavoisier and Laplace in 1780, who presented dissipating heat as a weighted sum of fluxes of dioxygen, carbon dioxide and nitrogen waste. DEB theory gives an explanation for this as well as for the many other models, with the result that it became clear under what conditions these models are likely to apply. DEB theory can be seen as a synthesis of all these models and even if DEB theory will transform in the future to a construct that can hardly be recognized, this synthesis will stay as an intellectual monument. But for me, DEB theory is much more than that and predicts phenomena that none of empirical models capture. In terms of testing against reality this synthesis of empirical models also means that DEB theory is presently the best tested quantitative theory in biology. Apart from the data that are well described by the list of empirical models, the 35 years of research on DEB theory not only developed the theory, but also paid due attention to testing elements of it against data. The add_my_pet collection of data, parameters estimates and code is part of the testing program for the various aspects of animal energetics. It has now over 400 species of most larger phyla and almost all chordate orders, which high marks for goodness of fit. A strong point in this testing program is that the various aspects of energetics are considered simultaneously, which adds to the supportive value of the goodness of fit.

## Ontogeny of DEB theory

The primary aim of DEB theory was to have a quantitative description of feeding, growth, development and reproduction during the full life cycle of an individual. The original version of DEB theory did not have reserve; it took me 2 years to discover that we badly need that concept for embryo development and to compare different food levels. My ambitions with the theory were originally modest, only thinking of reproduction of daphnia in routine toxicity tests. But that changed radically, within a week, when I made two discoveries.

The first one was on embryo development. My assumption was that an embryo only differed from a juvenile by not eating. This gives a particular pattern of embryo growth and respiration, but I had no idea about data. This was not available for daphnids but, so I thought, probably was available for chicken. I went to the veterinarian library in Utrecht, took a random volume of a random journal on a random page and saw the qualitatively same graphs with data for pelicans that were in my pocket as predictions for daphnia.

The second was on respiration, comparing different species. I was rather nervous about Kleiber's law which states that respiration is proportional to body weight$^{3/4}$. If my model was inconsistent with this generally accepted empirical rule, I could expect problems at ecosystem level, were a large range in body sizes exists. I suddenly saw what I presently call the co-variation rules for DEB parameters: Maximum structural length depends on just 3 parameters, while 2 of them were intensive, meaning that size is irrelevant. So

Table 2: The DEB calender

| | |
|---|---|
| **1977** | Effects of toxicants on survival depend in internal concentrations;<br>one compartment model as basic transport model |
| **1978** | No Effect Concentration (NEC) as parameter |
| **1979** | Start of DEB work with Holling, von Bertalanffy, Arrhenius and the $\kappa$-rule;<br>start of work on structured population dynamics with Hans Metz & Odo |
| **1980** | Sublethal effects of toxicants as changes in parameter values |
| **1981** | Reserve on the basis of Droop |
| **1982** | Embryos are juvenile that don't eat;<br>costs of eggs & maternal effects;<br>maturity as state variable |
| **1983** | co-variation rules of DEB parameters;<br>Bacterial populations as juveniles |
| **1984** | Maturity maintenance as energy sink |
| **1985** | Shape correction function;<br>bacteria as static mixtures between V0- and V1-morphs |
| **1986** | The name DEB was chosen on instigation by Joost Joosse;<br>microbial product formation & fermentation |
| **1987** | Mass as conserved quantity in combination with energy;<br>respiration as in indirect calorimetry |
| **1988** | Reconstruction of food uptake from growth |
| **1989** | Ageing as accumulation of damage compounds in 2 steps;<br>Weibull ageing rate;<br>microbial food chains with Bob Kooi |
| **1990** | Start writing of DEB1;<br>Type $T$ acceleration of metabolism |
| **1991** | Multiple reserve and partitionability of reserve kinetics |
| **1992** | Static generalisations of the $\kappa$-rule |
| **1993** | First local DEB course;<br>Dynamic generalization of the $\kappa$-rule |
| **1994** | Multiple substrates, reserves & structures: plants |
| **1996** | Synthesising Units (SUs) as alternative for enzyme kinetics |
| **1997** | Excretion of reserves in multiple reserve systems |
| **1998** | Start writing of DEB2;<br>symbiosis on the basis of mutual syntrophy |
| **1999** | Toxicity of mixtures of compounds;<br>co-variation rules for parameters one-compartment and film models<br>and for effects of toxicants |
| **2000** | Start of DEBtool in Matlab/Octave;<br>modules for mixotrophy;<br>co-metabolism & inhibition with SUs |
| **2001** | First tele course;<br>merging of symbiontic partners into a new individual;<br>effect of ionization on toxico-kinetics |
| **2002** | Ageing acceleration;<br>Gompertz stress coefficient with Ingeborg van Leeuwen |
| **2003** | Generalisations of the $\kappa$-rule |
| **2004** | Handshaking protocols for Synthesizing Units;<br>mitochondria-cytosol interactions |
| **2005** | Stochastic formulations for DEB population dynamics with Johan Grasman & Bob Kooi; Entropy of living individuals with Tânia Sousa |
| **2006** | Isotope dynamics |
| **2007** | Type $\mathcal{M}$ acceleration of metabolism with Laure Pecquerie |
| **2008** | Start writing of DEB3 and of add_my_pet;<br>mergeability of reserve dynamics with Tânia Sousa |
| **2009** | Reserve dynamics as consequence of weak homeostasis;<br>evolution of central metabolism in 5 modules |
| **2010** | Topology of allocation schemes with Dina Lika |
| **2011** | Type $R$ acceleration of maturation with Starrlight Augustine;<br>interactions between photo-synthesis, -respiration & -inhibition |
| **2012** | Bijection between data- and parameter space;<br>quantification of supply-demand spectra |
| **2013** | Waste-to-hurry |
| **2014** | NECs depend on specific somatic maintenance |

the third one, the extensive one, must be proportional to maximum length. Ratios of all other parameters could be formed such that they are intensive, meaning that all parameters could be linked to maximum length in a way that does not make use of any empirical argument. It is all in the structure of the model. Suddenly I had could compare species on the basis of parameter values, while the assumptions only relate to mechanisms. And indeed, respiration of a fully grown adult, being a particular function of parameters, turns out to scale approximately with body weight to the power 3/4 between species. I knew the huge literature with attempts for explanation and all failed. I was very happy in that week. Being naive, I thought that these results would be received enthusiastically by the scientific community. If I knew that publishing it would be a fight for several years and publishing further results a fight for 30 years, I am not sure that I would have brought up the stamina. Later I understood that this experience is typical for science and only shows that the ideas are original.

I started with a focus on energetics as a nice simplification of the household of an individual in 1979. There are many types of masses, but just a single type of energy. With my transfer from TNO to the university in 1985, I started to work with my colleague in microbiology, Ad Stouthamer, and his PhD Paul Hanegraaf. It became clear to me, that this simplification was an illusion. We need both energy and all nutrients simultaneously in order to understand what microbes do. It took me a year to find out how to do this, using conservation laws for chemical elements, and to discover the crucial role of indirect calorimetry in this, which links dissipating heat to three mass fluxes: dioxygen, carbon dioxide and nitrogen waste. It suddenly became clear to me why we have 3 fluxes here; it follows form the structure of DEB theory and, again, reserve plays a crucial role in this. Over the years, masses began to play in increasingly important role in DEB theory. Where I was originally sloppy, easily switching from wet- to dry- to ash-free dry masses and cubed lengths, I stepwise saw the need of becoming better organised on this; the dynamics is water still needs more attention. The notation, an important part of quantitative theory, evolved to accommodate this increasing rigour. Although the model for daphnia and microbes had similarities, they also had differences. During that same period I discovered, working with my PhD student Eric Evers, that these models were actually identical if expressed in surface areas and volumes, rather than lengths, and that daphnia differed from microbes in their surface area to volume relationships. Bacterial cells change in shape during growth, but daphnia hardly so. The original models for microbes could only handle single-nutrient limitations.

Two other milestones were of crucial importance. The **first** one was on the kinetics of chemical transformations, only discovered in 1998 after years of suffering with traditional approaches. Almost all work in quantitative biochemistry is based on enzyme kinetics which links product fluxes to substrate concentrations by delineating two behavioural states of an enzyme molecule: it either can accept a substrate molecule or is busy with handling one for transformation into a product molecule. The idea is known as Michaelis–Menten kinetics, but goes back to Henri 1902. My problem was in the concept 'concentration', which combines poorly with the functioning of membranes, so with spatial structure, especially inside small cells. This spatial structure urges us to replace substrate concentrations by substrate fluxes and consider the proportionality of flux to concentration as just one of the possibilities. This simple step has profound consequences, especially in combination with a simplification of neglecting backward transformations. This is not the best moment to dive into the motivation. It was easy for me to see that the same idea is behind Holling type II model for feeding of individuals as function of food density, where the individual serves the role of an enzyme molecule. It too is in one of two states: searching for prey or handling prey, in the abstract sense of the word. I called the generalized enzyme, which can also be metabolon or an individual, that works on the basis of substrate arrival fluxes, a Synthesizing Unit (SU). Once you have the basic pattern, it is easy to accommodate much more complex ones, such as co-metabolism and inhibition. The first application dealt with multiple reserves in ways that stoichiometric constraints on growth and maintenance are respected. The number of reserves that we need equals the number of essential nutrients or resources that are taken up independently. Since animals live off other organisms, we need just a single reserve because prey has all that the consumer needs. But that does not apply to most bacteria, algae and plants.

SUs dynamics eventually showed me the explanation for reserve dynamics, the engine that drives metabolism. I originally started in 1980 to model reserve dynamics on the basis of the model by Droop of 1973 for nutrient dynamics of algal cells, because of its simplicity in formula and great fit with data. The model links the concentration of a chemical element in biomass to the nutrient-limited growth rate of algal populations in steady states of chemostats. I needed to modify it, because this model was not formulated in terms of systems theory, did not deal with maintenance and did not distinguish surface area from volume. The result worked great in terms of simplicity and fit with data, but I very much disliked the lack of understanding. The first edition of the DEB book of 1993 simply assumed this dynamics, because I was unable to explain it. The second edition of 2000 had a partial understanding, but I still had to include some assumptions that I did not like at all and was approximative only. Only the third edition of 2010 could present a full understanding, and demonstrates that reserve dynamics follows from the weak homeostasis assumption, a key assumption that was already in the list. SU-dynamics plays an important role in the derivation and also shows a possible evolutionary pathway for weak homeostasis. I directly admit that the derivation is perhaps the most complex part of DEB theory, but it would not surprise me if this derivation could be further simplified in the future. Many derivations and discoveries in the scientific literature have the classic structure in being rather complex at first discovery and only much later achieved simplicity, once the reasoning really matured. During this long process of understanding of reserve dynamics, the formulae remained the same, the only thing that changed was how they follow from assumptions. A beautiful illustration of the difference between models and theories.

The **second** milestone was found only very recently: the quantification of the supply-demand spectrum, which reflects where the controls of energetics in animals are, from environmental to internal. Demand-species eat what they need, while supply-species eat what is available. Birds and mammals are examples of demand-species, and, apart from being endotherms, they share a couple of properties that set them apart from most other species, which are supply-species. Although I was aware of this difference right from the start of DEB research, step by step I discovered more and more properties that were associated with demand-properties, such as the ratio between peak and standard metabolism. I also realised that somatic and maturity maintenance have a demand-organisation, since the need is independent of substrate availability, while growth and reproduction have a supply-organisation. Yet I was surprised, and also a bit nervous, that both supply- and demand-species seem to follow the same model. Didn't it matter where the controls of energetics are, in- or external? I expected that the spectrum would be very difficult to quantify; perhaps the good fit with data was for the wrong reasons and classic biologists were right that it is impossible to capture all in one framework. The discovery that this quantification was not difficult at all, and was a simple function of existing parameters, came when I studied to problem of the boundaries of the data and the parameter space with Dina Lika, Starrlight Augustine and Laure Pecquerie.

Many more remarkable steps could be mentioned, such as metabolic acceleration, thanks to work with Laure Pecquerie, or the dynamics of maturation, thanks to work with Starrlight Augustine, or isotope dynamics, thanks to questions by Fred Jean. These are only a few highlights from a much longer list mentioned in the DEB calender, see Table 2. I never lost contact with ecotoxicity, but learned that toxicants not only play a role in environmental protecting issues, but can also be used to change parameters of individuals, a powerful research tool.

After 35 years of development, the result of DEB research is that we now have a sound quantitative description of an individual as a dynamic system with inputs and outputs in changing environments, from the start of development to death by ageing that has the same formal structure for all life on

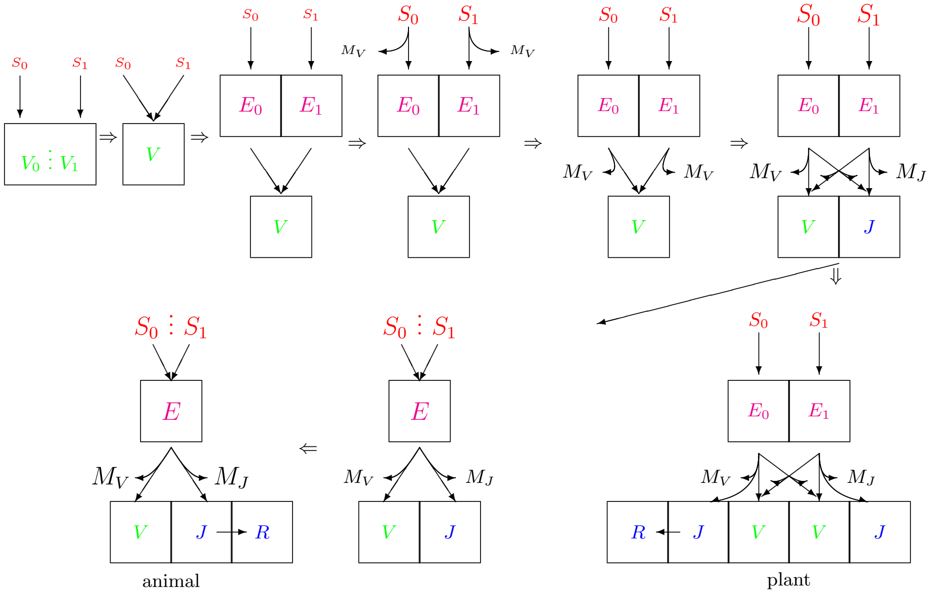


Figure 3: Steps in the evolution of the organisation of metabolism of organisms. Symbols: $S$ substrate, $E$ reserve, $V$ structure, $J$ maturity, $R$ reproduction, $M_V$ somatic maintenance, $M_J$ maturity maintenance. Only two of several possible types of $E$ are shown. Font size reflects relative importance. Stacked dots mean loose coupling. The top row shows the development of a prokaryotic system, which bifurcated in a plant and an animal, line of development.

earth: uni- as well as multi-cellular, auto- as well as hetero-trophic, aerobic as well as anaerobic. See Figure 3. It allows for the evaluation of entropy of living organisms, something that is much more complex than the literature suggests and requires full energy and mass balances. We have modules for food selection, social and synthrophic interactions; the latter being the basis of symbiontic relationships, where partners can merge to the extend of forming a single new individual. Species can now be compared on the basis of parameter values; these parameter values are individual-specific to allow for evolutionary change. We developed advanced parameter estimation methods, including software, and estimated parameters for quite a few micro-organisms and lots of animals. The parameter values revealed very interesting evolutionary patterns and I expect many more results in the near future. All this is firmly based on conservation laws for time, energy, chemical elements and isotopes, on surface area to volume relationships in an evolutionary setting. Most important for me, it allows for the evolution of life history strategies, which further stimulates my admiration for the wonders of life around me during my hikes.

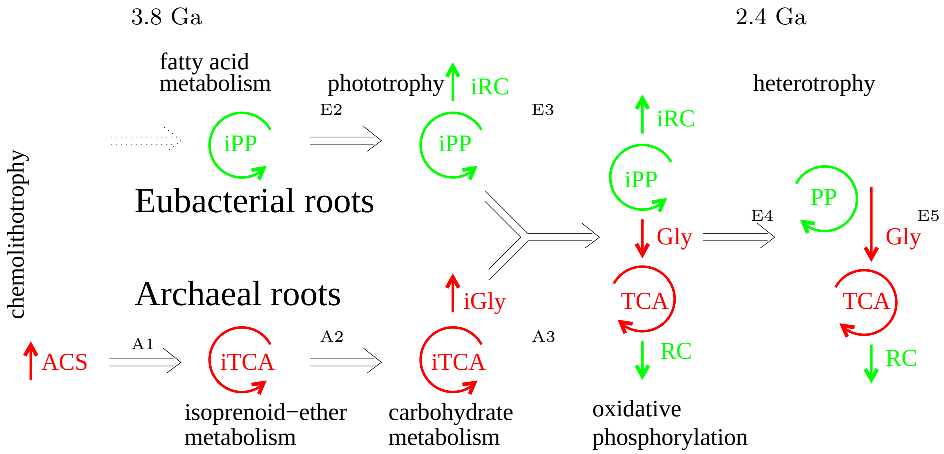


Figure 4: Evolution of central metabolism among prokaryotes that formed the basis of eukaryotic organisation of central metabolism. ACS = acetyl-coenzyme A synthase pathway, iPP = inverse pentose phosphate cycle (= Calvin cycle), PP = pentose phosphate cycle, iTCA = inverse tricarboxylic acid cycle, TCA = tricarboxylic acid cycle (= Krebs cycle), iGly = inverse glycolysis, Gly = glycolysis, iRC = inverse respiratory chain, RC = respiratory chain. The arrows indicate the directions of synthesis to show where they reversed; all four main components of eukaryote's heterotrophic central metabolism originally ran in the reverse direction to store energy and to synthesise metabolites. The approximate time-scale is indicated above the scheme (i.e. the origin of life, and that of cyanobacteria and eukaryotes). Contemporary models: A1 *Methanococcus*; A2 *Thermoproteus*; A3 *Sulfolobus*; E2 *Nitrosomonas*; E3 *Chloroflexus*; E4 *Prochlorococcus*; E5 *Escherichia*.

We are still some steps away from the original question of how properties of individuals relate to that of ecosystems, which I will briefly discuss in the next section on future developments.

## Future developments

A property of predictions for future scientific developments is that practice always works out differently. But we, humans, are in need for horizons and dreams to motivate us. Although DEB theory is well developed for the interaction of individuals with their environment, in many respects it is just a start and lots remains to be done, both into the direction of sub- and supra-organismal organisation.

For many applications, e.g. in the medicine, pharmacy and behavioural ecology, we need more detail, so shorter time scales, than the standard DEB model offers. Quite a few developments into these directions already exist, but they need to be developed further. I am thinking of modules that can be implemented, but also be taken out again, without affecting the overall behaviour of the model as it now is. This requires advanced modelling skills. The typical time scale of processes to be incorporated should be observed and it makes little sense to include very fast processes, without including relevant slower processes. The steps in times scales should not be too large. So central metabolism, for instance, should not be modelled directly in terms of the dynamics of chemical compounds, but of its 4 modules (pentose phosphate cycle, glycolytic pathway, TCA cycle, respiratory chain). See Figure 4. I imagine these modules as Synthesizing Units (SUs) that interact on the basis of mutual syntrophy and are linked to the rest of metabolism. SUs offer a natural framework for modelling behaviour, where components can be sequential, parallel, or mixed, and linked to functional aspects of behaviour.

We still have quite some work to do into the direction of populations, ecosystems and system earth. Thanks to work by Odo Diekmann, Matz Gyllenberg, Hans Metz, Andree de Roos, Horst Thieme and others, mathematics for structured populations is presently well worked out, as long as food consists of soup. Things become really complicated, however, if structured populations feed on other structured populations. Theory for this just started. The most promising approach seems to me to approximate the dynamics of population structure by a set of ordinary differential equations (ode's) and eliminate detail. I showed that the population growth rates of individuals that change or not change their shape during growth are almost identical functions of food density at steady state, if compared appropriately, and also showed that populations of individuals with surface areas that are proportional to volumes do follow ode's.

Since the dynamics of predator-prey populations depends sensitively on food for prey, the scope of classic population dynamics where just two interacting populations are isolated from a complex system, is very limited. Resource recycling is key to natural populations, but many developments are still weak on transport and environmental chemistry. This field is developing fast, however, and I have good hope that the combination of spatially explicit geochemical models and DEB-based population models will lead to exciting results in the near future. Work by Olivier Maury at IRN on tuna, Laure Pecquerie, Stephan Pouvreau and others at Ifremer on anchovy and oysters and Sophia Saraiva at IST on mussels, are examples of such development in the aquatic environment. Mike Kearney is combining DEB with biophysical modelling to study how micro-climate affect body temperature and water balances in terrestrial environments and already made spectacular progress in the understanding of geographical boundaries of dispersal in insects and lizards.

We have done considerable work on canonical communities, consisting of producers, consumers and decomposers and made some progress in understanding the dynamics of biodiversity. Yet much more work needs to be done to elucidate the role of biodiversity in their dynamics. In parallel to these developments, theory on adaptive dynamics meanwhile matured, with Hans Metz in the lead, where parameter values of individuals are allowed to vary across generations and set interactively with their environment. With Tineke Troost, Bob Kooi and Hans Metz, we made the very first steps in the direction of a mixotroph that grows, divides, specialises and evolves in an environment that is closed for mass, but receiving energy in the form of light.

The step from the ecological to the evolutionary time scale combines nicely with that from communities to system earth, a very inviting and promising field that urgently needs more attention. System earth shares an essential property with individuals: it is relatively easy to set up mass and energy balances, something that is much more difficult at organisation levels in between. Life is confined to a 'membrane' that wraps the earth and, given that it evolved some 3.5 billion years ago and will disappear well before the oceans evaporate within a billion years from now, it completed already more than 80% of its cycle, just like me as a person. I made some small steps into this direction, but so far we made little progress in what I see as priority: to combine transport processes at planetary level with community dynamics. DEB theory can be used in the stoichiometric coupling of nutrient flows, in combination with energy conservation and entropy dissipation. Work with Tânia Sousa and Tiago Domingos showed that the quantification of entropy for living systems involves the energy balance over the life cycle, which is only possible if a full mass balance is available as well. DEB theory is the only one that provides this in a quantitative way. A case study on bacteria revealed large differences with a traditional biochemically-derived quantification of entropy, which neglects the fact that the system lives. I expect that it will take the scientific community considerable time to accept this logic, which is, nonetheless, inescapable. The rapidly growing collection of animal species for which we now know parameter values will facilitate evaluation of entropy dissipation by life on earth. Plans exist to extend the collection to include other organisms as well.

In my fantasy, a single chemolithotrophic bacterial cell could give rise to a full-fetched self-organised ecosystem with food webs and all, just by changing parameter values across generations, where we can study links between ecosystem structure and function (i.e. recycling of mass). DEB theory, in combination with models for physical transport and environmental chemistry and powerful computers, bring such a digital planet within reach. The next step is to add mass sources and sinks and scale up to mimic an artificial planet earth, where we can compare the actual trajectory of evolutionary development with the set of potentially possible trajectories. Then, finally, I can check one of my conjectures: the rate of macro-evolution is controlled by continental drift, which is key to nutrient recycling at planetary scale.

## Acknowledgements

I want to start my acknowledgements with thanking the people who helped in this successful DEB course and symposium. In the first place our host Jean-Christophe Poggiale who also promoted me for a honourable degree at Marseille University and for an invited professorship. But, naturally, this includes the lectures and all who supported the organisation.

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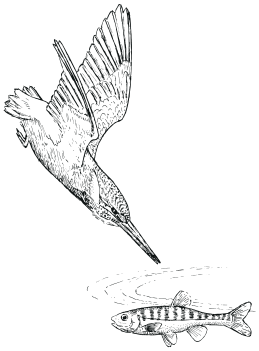
Then lots of colleagues with whom I had stimulating interactions, frequently for many years, such as Roger Nisbet on budget modelling, Hans Metz and Odo Diekmann on population dynamics, Dina Lika, Laure Pecquerie and Starrlight Augustine on DEB theory, Mike Kearney on biophysical ecology. Peter Westbroek stimulated me to consider the planetary level from an geological perspective and promoted me as member for the Dutch Academy of Sciences. He brought me into contact with many discussion groups and gave me a saint-status in one of his books. I very much enjoyed the many discussions with Rob Hengeveld over the years, and he made the first book with Cambridge University Press possible in the background. Seb Lefebvre promoted me for an invited professorship at Lille University; Marianne Alunno-Bruscia took the initiative to create the auqaDEB group, that boosted DEB applications in applied research for 5 years. Tiago Domingos and Tânia Sousa and their crew in Lisbon, with their refreshing engineering perspective, and who helped me setting up the double doctorate program at my university. Evert Meelis who guided me along the first obstacles that biologists meet when learning mathematics and Dick Brandt who stimulated me heading into that direction.

I apologise for any who I did not mention, but still very much enjoyed interaction. I really feel blessed with all this.

## Farewell

I now retire and cease project-work on DEB theory as well as the organisation of courses. It will not surprise you that I am captured by DEB theory and continue working on it. Like Peter Westbroek remarked: retirement is like an everlasting sabbatical. But now I will work with a lot less interaction or the need to publish, relieved from the terror of finding funds or the need to defend my job. It is still an open question for me if DEB theory will change biology, or become forgotten like many other thoughts, but it is also not for me to judge.

I utterly enjoyed working on DEB theory, loved the exchange of ideas with people all over the world and have many reasons to be very happy in all respects. If you choose to continue work in the field of DEB, I wish you an equal amount of satisfaction. To the young researchers I would like to say on the brink: work for interest, not for fame.



# Theoretical Biology, a specialisation in integration

**Inaugural lecture given at the acceptance of the chair Applied Theoretical Biology at the Faculty of Mathematics and Natural Sciences/ Subfaculty of Biology of VU University Amsterdam at 18 June 1987.**

Rector

Ladies and gentlemen,

When the Subfaculty of Biology of the VU University decided in February 1984 to open a vacancy for the chair Applied Theoretical Biology, I didn't waste time to apply. For me, it was a unique opportunity to help shaping a discipline that biology urgently needed, in my eyes. Before I tell what I have in mind, I first want to introduce the discipline and explain why it deserves extra attention right now. My motivation for this is partly based on the fact that less than 1 on 50 grants of the National Science Foundation for biology is allocated to this discipline and the Groningen University recently decided to reduce their group Theoretical Biology substantially. My conclusion is that, contrary to VU University, many other institutions in the country don't recognize sufficiently what the role of theoretical biology should be.

## The discipline

### What is theoretical biology?

The broad field of biology can be partitioned in experimental and theoretical biology. The many specialisations of experimental biology try to build theories on the basis of experiments and to describe biological processes. Theoretical biology has two levels of activity: to analyse the process of building of theories in biology as well as the creation of biological theories. I hear you asking: yes, but al these biological specialisations, such as genetics, physiology, ecology, etc, are already building their own theories! Yes, indeed, they do; that makes these fields part of science.

Theoretical biology should play an important role in this building process in two ways: The coupling of insights from these different disciplines and the exploitation of knowledge from mathematics, computer sciences and philosophy. Why does it then need a separate discipline? I hope to be able to make that clear by illustrating the discipline, discussing the toolbox of a theoretical biologist. This toolbox is trimmed to serve the most important function of theoretical biology: making the concepts, assumptions and reasoning that are used explicit. This increases the transparency of the results, reveal fake results and leads to a better understanding of the problem.

## No statistics without modelling

The first tool in the box can be statistics, which analyses the link between theory and measurements. Statistics, and especially statistical testing, aims to make objective conclusions from measurements, using theory. After the formulation of assumptions, statistics uses explicit criteria to make optimal use of measurements to select the best hypothesis from given set of alternatives. Inverse reasoning then allows to optimize the measurements and/or experiments. Like many other specialisations in mathematics, statistics evolves rapidly under influence of computer-technology, from an ad hoc recipe approach to a more general and abstract approach. For the applier of statistics in biology this means an extension of the flexibility of the toolbox that increases efficiency for any specific aim.

At this moment it frequently happens in concrete applications of statistics in biology that, without the applier realises this clearly, the real problem is substantially mutilated in the selected statistical recipe. The role of statistics this then crippled to providing an approval stamp on a conclusion that was already made before the testing. The main motivation is that, otherwise, the journal will not publish the result. Although sometimes useful, this is not a use of statistics that promotes insight.

The developments in statistics imply, in a sense, that it becomes easier, since there is no longer a need to choose from a large collection of recipes, but from a limited number of principles. This comes, however, with the consequence that practical application becomes more complex. In general this means that biologists need to consult a statistical specialist. I see meaningful applications for so-called expert-systems.

Another consequence of the increase in flexibility is that the underlying assumptions receive more emphasis, so do the ideas of the researcher on the matter.

## Modelling, a way of thinking

The most explicit way to determine a vision, is in the form of a mathematical model. This is the most important function of modelling in biology. I think that it is fundamentally impossible to do research without using some model. Even those who are adverse of any application of mathematics make in their research a large number of assumptions about the quantities that matter and create a mental picture of how particular mechanisms might operate. Mathematical modelling only makes this picture explicit, such that it can be communicated and criticized. By building a model, the researcher is forced to judge the problem systematically, which reveals gaps in knowledge. This feature links modelling and experimental design in a tight way. Any attempt to separate them cripples the best possible result.

Modelling clearly evolved from a descriptive activity, via a happy playground for specialists, till a powerful tool that helps researchers to acquire knowledge. Models should not be seen as constructs to believe or disbelieve. They represent a vision on some aspect, which always comes with considerable stylisation and simplification of reality. The relevant question isn't therefore: 'are models true or not?', but: 'are they useful or not?'. This involves context and degrades the value of statistical testing concerning the goodness of fit with data. We already know in advance that the fit cannot be perfect. Parameter estimation has in practice more relevance than statistical testing. This part of theory aims to access parameter values of models and their accuracy using explicit criteria.

## The computer, solution to all problems?

' Once a model has been formulated for a certain process, mathematics can be used to analyse its properties and to predict quantities. This allows for a substantial distance between the observational level and the level at which predictions can be made; much larger than would ever be possible without models. We can picture mathematics as a running train that makes no errors. We board with the translation of biological reality to mathematical formality and when we get out in the correct way, new biological consequences reveal. We need to know, however, the schedule of the train, to know where we are when to get out.

Due to the non-linear character of most biologically meaningful models, they typically are too complex to analyse mathematically. In such cases it is still possible to use computer simulation studies to analyse model properties. This makes the computer an essential tool in the toolbox of theoretical biologists. The fast development in the possibilities of computers will, I expect, soon become apparent in biology and in particular in theoretical biology.

It is essential, for computer simulation studies, to know the values of all model parameters. It is typically not clear at all how sensitive simulations are for the specific choices of values. If the model has few parameters, we can try different values, but if it has a large number of parameters it is no longer possible to do this systematically. We need to find adequate sensitivity methods in combination with mathematical analysis and simulation methods. This is an important task for theoretical biology.

## Ecosystem-analysis on the basis of quantum mechanics?

Some models, today mostly confined to the behaviour of ecosystems, have a very large number of variables and parameters. The predictive power of such models is typically very small, as is their contribution of providing more insight. Uncertainties in parameter values and in model structure contribute to this. A stepwise simplification of modules, such that the number of parameter values remains restricted after merging the modules into the model for the whole seems a more productive and attractive approach. Information gets lost in this way, but it becomes more clear which processes dominate the whole. This strategy of modelling strongly promotes its construction in the form of modules and enhances the transparency of the model. It should be mentioned, in this context, that information is only information if it is recognised as such. The strong preference for deductive reasoning of modern science leads to lower levels of organisation. This let us almost forget that inductive reasoning might reveal insights that can be equally important for insight into the problem. It is remarkable how little ecologists and biochemists use each other results. What essential issues are missed this way? The coherence of levels of organisation, and how to deal with this in practice, is key to theoretical biology.

## Cause and consequence as chicken and egg

After having presented some functions of modelling, I now want to illustrate how models can lead to better insight, using two examples from my own work.

Many physiological textbooks describe that we, humans, and similar animals cease growth because cartilage is replaced by bone in our skeleton. It is, however, possible to construct growth models, that fit our growth pattern very well but also that of animal species that do not have this feature at all. This strongly suggests that other reasons must exist to cease growing, and that cartilage is replaced it improve bone structure.

The second example concerns the diffusion of dioxygen through the egg shell, which is generally seen as a rate-limiting factor in the development of bird eggs. This idea rests on the observation of a strongly negative correlation between maximum dioxygen consumption and diffusion resistance of the egg shell. Models show, however, that energy use, that corresponds with the use of dioxygen of the embryo, develops similar to that of the neonate. This suggests that the limiting factor for development has a very different nature and the diffusion resistance of the egg shell matches the need of the embryo.

I could list many other examples to demonstrate that it is hard to draw correct conclusions in a field where everything seems to depend on everything else. This problem is further amplified by the fact that many concepts in biology, the science of life, are far from exact and well defined. After all, what is the definition of life? No surprise that methodology of science is an important component of theoretical biology, which combines well with a modelling approach.

## Collaboration is essential

The previous should have made clear that the context of each (biological) research problem is very important and the collaboration between a biologist and the mathematician who don't no anything about each others field is bound to fail. Because I had the opportunity to be part of different research groups, it is clear to me that this situation is certainly not restricted to biology. Multidisciplinary scientific research can only be really successful if a wide overlap in expertise exists among the group members. The task of linking disciplines is natural for a theoretical biologist.

The contemporary pressure on scientists to publish a lot and fast, in combination with a shortening of the educational program and the apparent decline in the level of education are strong incentives for extreme specialisation. This is the only way in which people feel confidence in their field, but in a way that is narrow minded. The disastrous effects of this will only become visible in a couple of years, since the employability of a specialised researcher in a team is very limited and the time in which a scholastic could show up with brilliant results after a long period of solitary imprisonment is long gone. Due to technological innovations it is nowadays hardly possible for solitary individuals to contribute significantly. Academic education programs could pay more attention to these changing societal and scientific needs.

## Information, une mer à boire

Ten years ago, I could advance the proposition in my dissertation that 'science will drown in the sea of publications'. This process of drowning is already clearly visible at several places. Even within a narrow specialisation it is very difficult to find enough time to remain updated on new developments, given the additional task of finding grants for research proposals. The question how many times the wheel can be re-invented becomes more and more pressing.

The balance between searching the literature for certain information, or neglect it and acquire it yourself more and more shifts to the latter. This means on the one hand that new forms of information exchange are required, on the other that researcher should write less, better accessible and better argued. In other words: more work per publication. Although this problem concerns all specialisations, the consequences of being incompletely informed are worse if one aims for generalisation. This is a major problem for theoretical biology and the flip-side of a wide scope.

This general introduction is successful for me if it is now clear why the further development of biology requires, apart from specialised experimental biologists, also more than a few general theoretical biologists who have to deal with their own problems that require a specialisation in itself. In my opinion, this specialisation now requires extra attention, which I would like to explain why.

## Why the application of mathematics stayed behind ...

The last years showed a clear shift in biology from qualitative to quantitative aspects in almost all specialisations. Mathematics provides, as stated before, the natural framework the capture quantitative relationships. There is presently an rapidly increasing demand for adequate mathematical methods. This is because the application of mathematics in biology did not yet reach an advanced level. This in contrast to the situation in chemistry and, especially, physics. The differences now become rapidly smaller. There are two causes for why the developments delayed in biology. The first one is psychological, those who are naturally attracted to biology are likely to have a distaste for mathematics. The two talents seem to exclude each other. The reason for why the delay is now rapidly diminishing is the inflow of non-biologists into biology. So this does not mean a change in attitude of a typical biologist with respect to applications of mathematics.

The second cause for the delay of the development of mathematical applications in biology is the simple mathematics is not sufficient; only rather advanced techniques really help biology. This is because the environment is very important for the understanding of the various biological processes. With this I mean that, for instance, the quantitative aspects of enzyme-mediated chemical transformations can only be understood in the context of the functioning of whole cell. This, on this turn, can only be understood in the context of the functioning of the whole organism, and this again in the context of the environment in which it lives. Since this role of the environment is so typical for biological processes, I want to discuss it in a somewhat more abstract setting.

## System theory, a general framework with problematic application

System theory provides a natural framework to capture the quantitative behaviour of biological processes. It requires the specification of state variables of the system. These are quantities that, in combination, fully define the state of the system. Subsequently we need to specify how this state changes in response to inputs to the system, given the state of the system. The general idea is that, given initial state of the system and the input as function of time, we can evaluate the state of the system as function of time, as well as any outputs of the system. The system communicates with the environment via its input and output.

System theory is widely applied in physics and engineering sciences. In biology, however, application is frequently problematic. The nature of the problems can be described as follows. Equations that specify changes of state have a number, and sometimes a large number, of parameters. Generally these parameters are supposed to have a certain constant value. In many biological systems, however, the environment can effect these parameters, meaning that they are not longer constant.

Think, for instance of temperature, which affects the rate of almost all biological processes. Depending on the reason for why these parameters change, we should include more state variables, which makes the system more complex. Think, fore instance, of situations where the system itself affects its temperature. The reason for doing this all was, however, to obtain insight by representing the system in a simple way. This aim is not always best served by maximizing realism. An additional complication is that living systems are typically highly non-linear. Although we know a lot about the possible behaviour of linear systems, or knowledge about non-linear systems is still very limited. Physics also suffers from this problem.

## Diversity, not a problem, but a pillar

Having listed two causes for why the application of mathematics in biology stayed behind, I now want to discuss for a moment why a frequently mentioned other cause, the overwhelming biodiversity, does not belong in the list. The biological literature is full of suggestions that biodiversity is the reason why biology is a science of exceptions, defeating all generality. It is true that biologists frequently select a particular species with the motivation that particular properties set it apart from all other species.

For the sake of the further development of biology I would like to advocate using biodiversity in a somewhat different way, especially with respect to eco-fysiology: it can be used to identify commonalities among organisms. The idea is to combine a detailed case study on a species that is suitable for experimentation with a wider comparative study involving a variety of species. The differences between species can guide to identify what they have in common on the basis of the exclusion principle. I see knowledge on diversity as essential for the identification of generalities. For this reason I think that biologists should give priority to develop substantial active knowledge of biodiversity. Modern biology has, however, the strong tendency to neglect biodiversity. The strong incentive to apply knowledge rapidly, developing a profound knowledge in biodiversity is no longer popular among biologists. An essential component is then missed. I would like to motivate taxonomists the pay more attention to facilitation of identification of species, especially for non-specialists. This should help biologists substantially.

## Program and plans

### What needs to be done now ..

This review on why application of mathematics stayed behind and the role of biodiversity in biology completed my general introduction to theoretical biology. I now want to sketch my plans and wishes for the near future. You will not be surprised to learn that I don't plan to retreat in my room to work solitary, but, on the contrary, would like to involve many. The reason for having this inaugural lecture that late is that I did not want the confront my co-workers with my plans at this occasion, while this lecture is a suitable opportunity to present my plans. Discussions within the group Theoretical Biology, the department, the faculty, other universities and with TNO convinced me that these plans are by and large feasible. I am very satisfied with this and want to thank all involved in advance.

### Education, an investment in the future

Each biologist should have, I think, substantial and practical knowledge of supporting fields. As leader of the work-group, I feel responsible for education in mathematics, computer science and philosophy. I noticed with some concern that knowledge of mathematics among students starting to study biology at university level has a large range in size and in topics. It is not that easy to build on such an initial condition. In view of the developments in high-school teaching, all education programs in science at university level should have a basic part that is the same all over the country, followed by a part that differentiates between universities and links up with their research programs. Also the basic module should be given by people practically involved in research. Basis biology taught as a collection of facts without an essential scientific context hampers, rather than helps, further scientific training. Learning to live with uncertainty, which characterizes science, cannot be exercised early enough.

It is of importance, in my opinion, that basic education in mathematics and computer science in biology is harmonized country wide in the form of a book, not least because this adds to the scope and employability of fresh biologists. Apart from the basic 'tricks', some of which not belonging to the standard-package of the mathematician or computer scientist, emphasis should be given to applications in biology. In this context, I would like to point to differences in requirements between designers and users of tools. Knowledge of each other views, scope and restrictions, among designers and users, is essential for optimal tools. I took the initiative to interest my fellow theoretical biologists in the country in such a book project, and met support in Leiden, Groningen, Amsterdam and in this university. I hope that we soon complete a first draft to polish. Apart as textbook for basic education, which should ease exchange of students between universities, it should also help late arrivals at the playground. Students typically learn to appreciate the significance of experimental design, data analysis and evaluation in biological research only when confronted with the practical need. Improvement of knowledge of mathematics, computer science and methodology of science is not only essential for experimental, but also for theoretical biology. This is my primary aim in teaching. My secondary aim is to teach for a specialisation in theoretical biology, with close links to the research program I am going to present.

## Advice, a source of scientific contacts

An important task that the group Theoretical Biology traditionally had is providing advice on behalf of fellow faculty staff members. From the groups point of view, this advice work is especially productive as source of scientific contacts and problems to work on in an existing research program. This task should be limited in terms of time investment and further reduced, avoiding substantial loss of results, by increasing the efficiency of education in this field. In this context I want to evaluate the use of expert-systems for statistical advice on behalf of biologists. Computer-based libraries now rapidly become available that help reducing this task. Advice-contacts should evolve to research-contacts wherever possible.

## Research, an organisational model

In my ideal of research at this Subfaculty, PhD students of the group Theoretical Biology are co-supervised by some experimental group. Design of theories then find a basis in experimental research, which I see as a strong aspect. Experimental research discipline in the sub-faculty are partitioned to three departments on the basis of level of biological organisation. I would like to see contacts growing with all three departments. By creating a strong link between the selected topics from a theoretical biology perspective, we can expects that PhD students keep contact with each other, without sacrificing the principle of booking results as fast as possible to complete their study within four years. In this way contacts can grow between different departments and links between levels of biological organisation.

I will now present the main research theme and further enlarge on other collaboration and financing.

## What is still missing in evolution theory

Most biologists see evolution theory as the backbone of biology. It should not be seen as a rigid formal theory on the origin of life that is beyond all doubt. More realistically it is a dynamic, rapidly growing, complex of ideas that are more and more quantitative and subject of intensive discussions. Disagreements concern, for instance, the relative strength of selective forces on properties of organisms, the rate at which these properties change or has been changed and the extent of optimality of these properties with respect to some criterion.

An important shortcoming of contemporary evolution theory, is that it concerns some single particular property and that this property is treated as example of a much wider class of properties. A property is only studied in relation to other properties if direct, simple and genetically based links exist. Although we know from eco-physiology that many properties are interlinked, it is presently not possible to study evolutionary processes in coherence and treat individuals as integrated units, due to lack of adequate quantitative models. This lack urgently needs elimination before we can conclude on adaptation and optimality in a satisfactory way.

Population genetics provided important insights in mechanisms that might or might not have played important roles in particular situations. We can, however, not expect further insights from this field as independent discipline with respect to evolution theory. Thanks to developments in molecular biology, it now became clear that the DNA-molecule defines the potential behaviour of a cell, but its concrete properties are controlled by a large number of factors that hardly have simple relationships with the base-configuration of the DNA-molecule. This shifts the research-front on evolution theory to the functioning of cells as integrated units in relation to extinction probabilities of populations of individuals. We need to develop a more accurate and integrated picture of functional aspects of organisms as input-output systems to better understand the origins of life.

## Energy and nutrient metabolism, a topic with a lot of potential

Two fluxes that are important for life are energy and mass fluxes, in the form of nutrients. These fluxes play an essential role on all levels of organisation, from sub-cellular organ, via the individual to the ecosystem. Biology is now ready for modelling these fluxes, such that levels of organisation become connected. I want, very much, to contribute to this, but realise that this task is very ambitious. I am optimistic, however, about the possible success of this enterprise, given the results that were already obtained. I want to sketch some lines of research to further clarify what I have in mind.

The question of how observed effects of toxicants on individuals under laboratory conditions translate expected effects on communities in the environment is key to developing norms for controlling environmental pollution. These effects boil down to changes in some physiological properties of organisms. At TNO in Delft, division of Technology for Society (MT-TNO), I was involved in research that resulted in models for energy budgets of water fleas and algae. In collaboration with the Institute for Theoretical Biology in Leiden and with the Centrum Wiskunde & Informatica (CWI) in Amsterdam, with support of computer simulation studies, we analysed properties of populations of individuals that follow this type of energy budgets. Due to the complexity of this topic, hardly anything is known about properties of population with a relevant physiological structure. Although we still have to cover much ground, we already booked promising results and I have great expectations about the results that still have to be obtained.

The model for energy budgets turns out to be very general, to a level that surprises me. I could predict details of the development of birds eggs and explain relationships between physiological quantities, such as respiration and growth rate, in relation to maximum body weight for the a wide variety of species. Many details of the physiology of pond snails could be predicted accurately. This opens doors for collaboration with the department of Organismal Zoology, that invested some 1000 man-year of research into this species to model hormonal control systems within the context of a model at the level of the individual. This is a new strategy in modelling.

Applied to micro-organisms the energy budget model embraces several frequently used models in the literature for energy limited growth of micro-organisms. In collaboration with the department of Molecular and Cellular biology, and MT-TNO in Delft, we work on the coupling of energy and nutrients budgets for bacteria and algae. A better understanding of this coupling is key to modelling nutrient cycles in communities. Biotechnology can also profit from this effort. The collaboration also concerns growth of micro-organisms in sewage treatment plants. Collaboration with the department of Ecology and Ecotoxicology and MT-TNO is initiated to study the way toxicants affect the mineralisation of leaf litter.

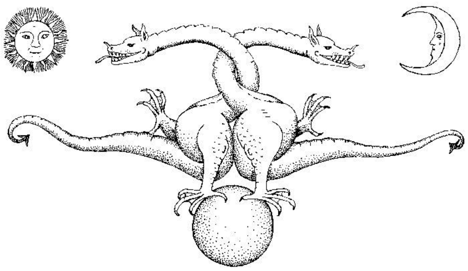
## Closure

### Fundamental or applied research, a choice?

The above-mentioned research is a start which impacts the development of a coherent theory in a broad range within biology. Although this certainly concerns fundamental research, it has lots of applications in ecotoxicology, biotechnology, medicine and agriculture, for instance. Some argue that fundamental research is weak in applications. As long as fundamental research is focussed on mechanisms, I strongly oppose this view. It very much depends on the choice of topics. If the mechanisms of focus are key to important processes, fundamental research always have relevant applications. Applied research that is not focussed on mechanisms, on the contrary, hardly has significance in a wider context and is outdated very soon. Some applications enjoy a financially strong interest, compared to other applications. Given the problems of financing contemporary scientific research, it seems unavoidable that also research in theoretical biology needs to deal with this fact. Together with TNO, I would like to study how to include such applications. I also see tasks for industry in the form of sponsoring high-quality scientific research to safe future generations of researchers. The first phase of the present educational program is not sufficient for a functioning as scientist and the second phase repairs this shortcoming very partly only. Only a few receive further training with support from the National Science Foundations. A sad conclusion in times where society increases demands imposed on researchers.

### Ladies and gentlemen,

with this lecture, I accept the chair Applied Theoretical Biology. I tried to illustrate my view on the field and the expectations and concerns that I have. You can expect that I will do my utmost to train biologists for participation in multidisciplinary research. Thank you for your attention.



## Prof. Dr. S.A.L.M. (Bas) Kooijman (Den Haag, 2 February 1950)

| | |
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| 1967–1974 | Study Biology, Leiden University |
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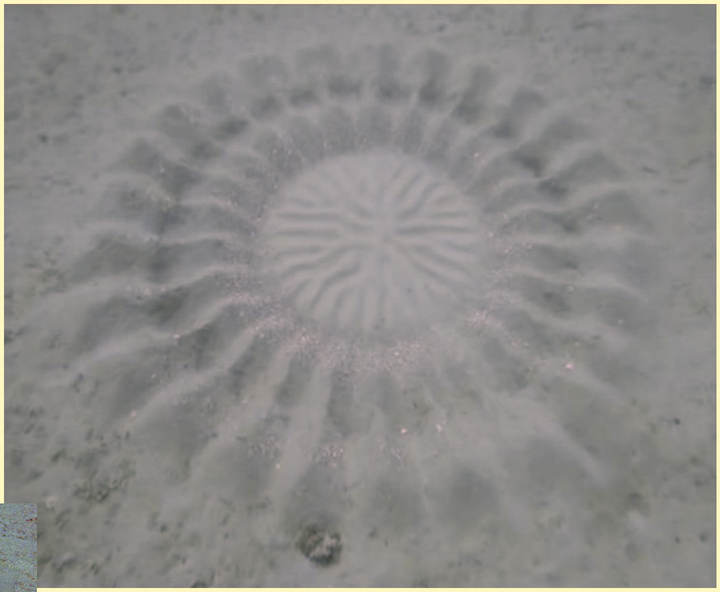
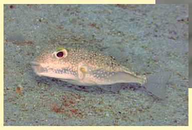
| 1977–1985 | Researcher at TNO (Central Laboratory, later Technology for Society) in Delft |
| 1985–2015 | Professor Theoretical Biology, VU University Amsterdam |
| 1985–1995 | Advisor at TNO Delft |
| 2005 | Professeur invité, Marseille University |
| 2009 | Doctor Honoris Causa, Marseille University |
| 2009– | Member of the Dutch Academy of Science |
| 2011 | Professeur invité, Lille University |





*Torquigener*