# SECTION 11 THEORETICAL BIOLOGY

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*(until 1-1-2006, from then onwards: P. Haccou)*

## GENERAL INTRODUCTION

The section organises its activities around the grand unifying theory of biology: Darwinism. Organisms differ from the entities of physics and chemistry by the fact that they reproduce. That they do so only almost faithfully is the main cause of their present day diversity and complexity. Moreover, they are composed from parts in a hierarchical manner, leading to a combinatorial explosion of possibilities: the space of possible organisms is huge, and existing organisms occupy a nearly empty subset of this space. To understand its population, it is necessary to integrate studies of the principles by which organisms are built (development), their inner workings (function and so-called internal selection), the workings of the selective arena (population and community ecology), and the history of their descent (phylogeny). The section provides a single home for the IBL theoreticians active in these areas, thus creating a platform for the cross-fertilisation of disciplines, as well as of techniques, be they statistical, computational, or mathematical. Moreover, their independent affiliation allows the members of the section a great diversity of collaboration with the empirically oriented sections of the IBL, or outside the IBL if theoretical developments so demand. Historically, the section concentrated mainly on the phenotypic level, a strategy justified by the contorted and (in certain aspects) weak link between the genotypic and the phenotypic levels, and the apparent domination of the selective regime in determining many features of great biological interest, as corroborated by the predictive power of the theory. The theories of physiologically structured populations and of adaptive dynamics are internationally recognised successes. In more recent years the interface towards the genetic level is attracting more attention, with i.a. activities in the area of evo-devo and RNA function.

Research themes:

**1. Bio-Informatics and Self-Organising Systems**

**2. Innovations and Constraints in Evolution**

**3. Ecological Dynamics and ESS Theory**

**4. Adaptive Dynamics**

**5. Methodological Foundations of Phylogenetics**

## 1. Bio-Informatics and Self-Organising Systems (dr. A.P. Gultyaev)

This project aims to contribute to the field of Bio-informatics by data-mining and the simulation of complex systems, and to the theory of self-organising complex systems. In the theme there is a distinct accent on intracellular processes, in particular those relating to the secondary and tertiary structure of RNA in relation to its function and evolution.

Possible chaperone-like effects of small RNAs on the folding of large RNA molecules have been studied by computer simulations. The simulations have been performed for the folding of ribosomal RNAs (rRNAs) of a number of organisms in the presence of small nucleolar RNAs (snoRNAs) in eukaryotes or snoRNA-like small RNAs (sRNAs) in Archaea. These computer experiments have been performed using genetic algorithm with a modification that incorporates a transient chaperone-like binding of small RNAs to specific sites on rRNAs. The chaperone effect was estimated by comparison of the final structure predictions with those produced by simulations in the absence of sRNAs and with the phylogenetically proven rRNA structures. The preliminary results show that sRNA molecules possessing two complementary sites at rRNAs guide the folding of rRNA, in particular, assisting in the formation of long-range interactions. Such a chaperone effect is more pronounced at higher temperatures and seems to be more significant in thermophylic Archaea. However, a similar influence can be also seen for eukaryotic snoRNAs with two binding sites. Some evolutionary comparisons between topologically similar snoRNA/rRNA complexes in various species may elucidate the features of coevolution and adaptation of rRNAs and sRNAs in various environments. In thermophilic Archaea, sRNA chaperone activity seems to be an adaptation of ribosome assembly process for the increased folding uncertainty at elevated temperatures. Analysis of rRNA folding pathways allows one to propose a mechanism of such an effect, based on sRNA-induced constraints imposed on the folding of rRNA domains. (Sacha Gultyaev/Ruud Schoemaker).

The conserved RNA structures of translational enhancers in a group of plant viruses have been predicted. The functioning of these enhancers is validated in experiments. Interestingly, strong conformational requirements in the structures result in the possibility of synergistic cooperation of enhancers from different viruses in stimulating RNA translation. (Sacha Gultyaev, in collaboration with the groups of Prof. C. Pleij, LIC and of Dr. F. Meulewaeter, Bayer Crop Science NV, Gent, Belgium).

Various structural and functional aspects of RNA pseudoknots are analyzed in the review published in Encyclopedia of Life Sciences, John Wiley & Sons (collaboration with C.W.A. Pleij, Leiden and E. Westhof, Strasbourg, France).

Existence of conserved structures in one of the segments of influenza virus genome is predicted. These structures are conserved in both influenza A and B viruses and seem to have a regulatory function. The suggested folds are confirmed by phylogenetic analysis, biochemical and biophysical experiments (collaboration with R.C.L. Olsthoorn, Leiden and H.A. Heus, Nijmegen).

## 2. Innovations and Constraints in Evolution (dr. F. Galis, Prof. dr. J.A.J. Metz)

This project focuses on innovations and mechanisms that facilitate evolutionary changes at the organismal level, in particular the constraining effects of internal selection, i.e., selection caused by characteristics of the developmental system. The main focus is on the conservation of the early organogenesis stage and on the conservation of adult traits that are determined during that stage, with the goal of understanding the interplay between genetic architecture, developmental mechanisms and stabilising selection.

A first subproject on Evo-Devo largely concentrates on the role of internal selection as a conserving evolutionary force. A collaborative experimental program is going on with the Pathology department of the VUMC (Free University Medical Center). A central question in understanding biological diversity is how developmental pathways constrain evolution: the fundamental constancy of gene networks and developmental mechanisms underlying body plans is poorly understood. Such understanding is essential i.a. to determine how data obtained from model organisms generalize. Because many adult traits are determined during early organogenesis, early developmental events have a persisting influence. In this project we focus on how such projected effects constrain the power of natural selection in shaping adaptive evolution. Our working hypothesis is that strong integration between the patterning of the embryonic axes is the root cause of the conservation of body plans. Due to this integration, positive mutational changes of some character cause that many negative pleiotropic effects (abnormalities) elsewhere that they are nearly excluded (so-called internal selection). We have studied as an example of extreme conservation the number of cervical vertebrae in mammals, which is virtually always seven. This number has not changed despite millions of years of evolution with drastic changes in external selection pressures. The number of vertebrae of adjacent thoracic and other vertebrae is far more variable among mammals. The cause of this evolutionary constraint is unknown. We have investigated in humans whether internal selection constrains changes of the number of cervical vertebrae. To this end, we have determined the incidence of variations on the number of cervical, thoracic and lumbar vertebrae in radiographs of human foetuses and infants that died and analysed several existing datasets on the incidence in infants and adults. We found that individuals with a change in the number of cervical vertebrae have an extremely high chance to die before reproduction. Furthermore, we found that cervical ribs are associated with the presence of multiple and major congenital anomalies. Changes in the number of thoracic vertebrae appear to experience considerably weaker internal selection. This is in agreement with the weaker evolutionary constraint on these variations. In a meta-analysis of the literature we have identified specific couplings between the A-P patterning of the mesoderm determining the number of cervical vertebrae and the A-P patterning of other germ layers and/or patterning along other embryonic axes. Such couplings include patterning of the lateral plate mesoderm, the neural tissues, the left/right axis and midline. The multiple, correlated defects that we found in human foetuses can be understood as resulting from such couplings. We intend to further test the predicted couplings by statistically analysing for the incidence of specific combinations of abnormalities in our dataset. This work is done in collaboration with Dr. Liliane Wijnaendts (pathologist), VUMC, Dr. Hans Feuth (internal diseases) and Dr. F.M. Helmerhorst (gynaecologist), LUMC)

Another subproject is on the intra-specific relationship between size and longevity in dogs in collaboration with Tom van Dooren and Inke van der Sluijs of the Animal Ecology section and with Marc Nussbaumer of the Natural History Museum in Berne. We found that the widespread notion that lifespan decreases with size intraspecifically, which is mainly based on dog data, does not hold true for dogs. This notion is based on a misinterpretation of the data. This conclusion is not only important to dogs, since the negative intraspecific relationship in dogs is usually assumed to be representative for the situation in mammals and, in particular, humans, i.e., large humans die younger than small ones. Although large dogs indeed die surprisingly young, this is only true when different breeds are compared, but not within breeds. We have shown that within breeds the relationship is not negative and even slightly (but significantly) positive in the larger of our two datasets. Furthermore, we have shown, using results from the literature, that the very early deaths in dogs from large breeds (St. Bernard, Newfoundland, Irish Wolfhound, Great Dane etc.) are to an important extent the result of diseases associated with the extremely high growth rates that have been co-selected with size. The earlier found negative intraspecific relationship is considered as puzzling as it contrasts with the positive relationship found across species. It is also in disagreement with the predictions of the free radical theory of aging. Laying bare the intrinsic relationship between size and longevity by accounting for the confounding effects of differences between breeds, removes both problems to a considerable extent. We expect the dog pattern to be exemplary for aging patterns of animals bred in captivity, such as laboratory rats.

### 3. Ecological Dynamics and ESS Theory (dr. P. Haccou, Prof. dr. J.A.J.Metz~~, dr. C.G.F. de Kovel~~ drs. C. Rüffler)

This project considers the population dynamics of single species as well as processes involving the interaction between several species on ecological time scales. In one direction novel mathematical tools are developed for the translation from complex individual level causes to population dynamical consequences. In the opposite direction the ESS route allows the prediction, based on their population dynamical consequences, of properties of individuals. In addition statistical methods are developed for analysing ecological data as well as data on individuals, in a manner useful for evolutionary theorising.

The first suite of projects deal with population dynamics per se:
One subproject concerns population dynamics in randomly fluctuating environments. The theoretical predictions on invasion success in fluctuating environments were compared with empirical results from laboratory experiments.  In addition we developed conservation guidelines to protect populations from going extinct when there is environmental uncertainty. We examined effects of the presence and reliability of cues about the current population size on such strategies, and optimal monitoring effort to improve cue reliability for multiple year situations. We are now extending the models to situations with multi-species interactions. As a first example we consider a case where an invasive alien species poses a threat to an endemic protected species (collaboration with Hiroyuki Yokomizo and Yoh Iwasa, Kyushu).

We study dynamics of small populations, including demographic stochasticity.

In 2005 we published a book on modeling biological systems with branching processes (coll. with Peter Jagers, Gothenburg, and Vladimir Vatutin, Moscow). We examined the probability of introgression of insecticide resistence genes in white fly populations with such models (coll. with Inez Demon and Frank van den Bosch, Rothamsted). Furthermore, we derived methods for studying properties such as the expected time until successful invasion of multitype processes (coll. with Sao Serra, Gothenburg).

The idea of environmental feedback loop, basic to the technical developments in the theory of structured populations, also underlies the idea of feedback dimension: the number of essential variables occurring in this loop. Starting from a sufficiently abstract and therefore general characterisation of this idea we have derived a general extension of Levin's idea that there can be no more species than resources, applicable to fluctuating environments, as well as a more quantitative variant, relating the options for coexistence in dependence on additional niche variables to the “bandwidth” of the feedback loop (collaboration with Géza Meszéna, Budapest).

The other projects all concern the ESS end of the spectrum:~~.~~
We have shown that in a structured population with multiple birth states it is possible to use the characteristic polynomial of the next generation operator evaluated at 1 as a fitness proxy for ESS calculations, even when the goal is to prove global uninvadability, provided the demographic parameters are continuous in the traits and the set of feasible trait values is connected.

W~~Further, w~~e have analysed the general unfolding of the evolutionary outcomes of simple standard bilinear evolutionary games under the occurrence of natural nonlinearities.

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Using a suite of related models that occur in more phenomenological and more mechanistically based variants, we have shown how natural trade-off assumptions made for the various cases lead to radically different biological conclusions. This may serve as a warning against the use of less-than-well-argued trade-off assumptions.

We have developed a classification approach for a class of simple life-history models. The considered model class is characterized by the assumptions that individuals can occur in two states, discrete time population dynamics, density-dependent population growth and two evolving traits that are coupled by a trade-off. Individual models differ in the choice of traits that are considered to evolve and in the way population regulation is incorporated. We classify models according to curvature properties of the fitness landscape and to their potential to support an optimization criterion. The first classification allows us to infer whether trait combinations that are characterized by a zero fitness gradient correspond to minima or maxima of the fitness landscape and how this property depends on the curvature of the trade-off. The second classification distinguishes scenarios where evolutionary change is frequency independent from scenarios that involve frequency dependence and therefore potentially allow for the coexistence of different types. Given certain symmetry assumptions we can extend the classification in the latter case by splitting selection into a density-dependent and into a frequency-dependent component. The classification is derived from a fitness measure that is sign equivalent to invasion fitness but algebraically simpler. We applied our approach to several simple life-history models and demonstrated how our classification allows for an analytical analysis.

~~Another~~ A final subproject concerns the merger of population genetics with the theory of physiologically structured populations. Almost the whole of population genetics is based on the Hardy-Weinberg assumption. Yet, this assumption only holds when there is no difference whatsoever in the life history parameters of the sexes, a situation almost never realised in nature. Using the fitness proxy referred to above, we have derived general global uninvadability criteria for simple genetic polymorphisms without making the Hardy-Weinberg assumption. Luckily, ideal free ESSes (where all male fitnesses are equalised and so are the female fitnesses) can be calculated in the classical way, as for them the general uninvadability criteria reduce to those for the Hardy-Weinberg case. So here the classical results are all right, even though the textbook derivations are wrong.

### 4. Adaptive Dynamics (Prof. dr. J.A.J. Metz, dr. P. Haccou, dr. C.G.F. de Kovel, drs. M. Durinx, drs. C. Rüffler)

This project considers evolutionary time-scales and the species level as well as between-species interaction. The aim here is the construction of an overarching theory of phenotypic evolution, as a direct dynamical extension of the evolutionary statics of ESS theory. This theory also deals with co-evolution and with the treelike structure of character evolution through adaptive speciation.

We made considerable progress in the further development of appropriate mathematical techniques:
In collaboration with Peter Jagers, Serik Sagitov (Gothenburg) and Vladimir Vatutin (Moscow) we have started investigating stochastic properties of evoltionary paths, such as expected time until population branching.

We have extended the adaptive dynamics tools to a system with diploid sexual genetics. In particular, we envisaged a system with two ecologically different types of gametes: macrogametes and microgametes, and assumed that the effective production of those different gamete types would depend on the organism's phenotype in different ways, so that there would be sex-specific selection as a rule, rather than as an exception. Starting from an internally stable bi-allelic polymorphism, we investigated the further evolution of the three phenotypes, either through mutations that were completely linked to the alleles at the focal locus (cis-mutations) or through mutations on some recombinational distance r from that focal locus, so-called trans-mutations or modifiers. For this system, we developed canonical equations and uninvadability criteria. Since we wanted to describe the situation with cis-mutations on the phenotypic level – which does not come naturally , we had to develop new methodology. It turned out that where without sex-specific selection the genetic architecture is of little consequence for the phenotypic evolution, with sex-specific selection a whole array of new phenomena appeared. Combining cis and trans-mutations, as seems natural, brought further unexpected results. When evolution proceeds through cis –mutations, the mutational covariance matrix remains part of the equations for equilibrium, while the mutational covariance matrix changes itself with each substitution.

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We also made progress at the interface between theory and data:
Disruptive selection occurs when extreme phenotypes have a fitness advantage over more intermediate phenotypes. The phenomenon is particularly interesting when selection keeps a population in a disruptive regime. This can lead to increased phenotypic variation while disruptive selection itself is diminished or eliminated. We reviewed processes that increase phenotypic variation in response to disruptive selection and discuss some of the possible outcomes, such as sympatric species pairs, sexual dimorphisms, phenotypic plasticity and altered community assemblages. We also identify factors influencing the likelihoods of these different outcomes.

~~We~~ In addition we improved methods available for detecting selection in empirical datasets in two subprojects:
The first subproject dealt with a method in which allele frequency differences between two isolated populations of the same species are used to infer past selection. Allele frequencies in subpopulations of a species after a split has been made will start to drift apart in a predictable way, similar for all loci in the genome. Genes that are under selection in one of the subpopulations will tend to change allele frequencies much faster, pulling along surrounding parts of the genome, so-called hitchhiking. This subproject used simulations to assess the distance over which such hitchhiking would be detectable, depending on other parameters such as population size, strength of selection etc. Using the results one can assess the usefulness of this method for a given situation, and the number of markers probably needed.

The second subproject dealt with QTL-type data. A common method to detect loci responsible for phenotypic differences between two populations of the same species (or other levels of organization) is to associate genetic markers with phenotypes in an artificial cross between the two groups considered. This usually results in one to twenty so-called quantitative trait loci (QTLs). To infer whether the phenotypic differences between the groups are attributable to selection, a sign-test on the direction of the QTL-effects has been proposed. The distribution of size and direction of QTL-effects has been shown, however, to be strongly influenced by pleiotropy. In the literature, up till now, only the effects of directional selection towards a fixed target on the distribution of QTL-effects have been studies. In this subproject, we extended the work to different forms of selection to see whether different forms of selection would result in different distributions of QTL effects. Though some differences are present they would not be distinguishable in practice. All investigated forms of selection would be equally difficult or easy to detect, depending on how extensive pleiotropy is in practice. This work is not yet completed.

~~In collaboration with Peter Jagers, Serik Sagitov (Gothenburg) and Vladimir Vatutin (Moscow) we have started investigating stochastic properties of evoltionary paths, such as expected time until population branching.~~

## 5 Methodological Foundations of Phylogenetics (dr. M. Zandee, dr. P. Haccou)

This project aims to contribute to the development of conceptual and methodological issues in, as well as data analytical and computational techniques for, Phylogenetic Systematics. The project provides a home for the methodological and data analytical counterpart to projects 1, 2, and 4.

In collaboration with Russian researchers we are working on the project "Information system 'Simulation and Analysis of Complex Histories of Evolution' (SACHE)", funded by a grant from NWO. The aim of this project is to develop methods for studying processes of speciation and extinction on the basis of DNA sequences, that allow for effects of environmental changes as well as species interactions. The methods will be implemented in a software package that can generate numerical simulations of DNA sequences for several evolutionary models. The results can for instance be analysed with the usual molecular-phylogenetic approaches. On the one hand, this will help to design criteria to distinguish between alternative scenarios for explaining current bio-diversity. Thus it can be used to examine the impact of different environmental factors. On the other hand this approach will be useful for testing different models of population processes (here there is a connection with projects 3 and 4).

## PERSONNEL

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| Dr. R (Rino) Zandee | Assistant Professor UL |
| Dr. C.G.F. (Carolien) de Kovel | PD ALW (until 15/2/2006) |
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GRANTS

- NWO: Simulation and Analysis of Complex Histories of Evolution (SACHE). Exchange program with the Limnological Institute, Siberian Branch of the Russian Academy of Sciences, Irkutsk, funded by the Russian Foundation for Basic Research, on speciation in Lake Baikal. 1/4/2004-1/4/2007. Total amount: ¤115,000.