SECTION 11 THEORETICAL BIOLOGY

Section Leader ~~J.A.J. Metz~~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.

In 2006, structure-function relationships and evolution of RNA molecules in various biological systems have been further analyzed. In particular:

Using comparative sequence analysis and RNA structure predictions, the evolution of conserved structures encoded in segment 8 of influenza virus genome is further analyzed. It is shown that the region around the 3'splice site of the nonstructural (NS) protein mRNA can be folded into alternative structures. Furthermore, a unique mutation in modern dominant lineage of H5N1 avian influenza strains dramatically affects the equlibrium between these alternatives. Thus a conformational shift in currently circulating avian flu viruses is suggested. Our data demonstrate that besides changes at the protein level, changes in RNA secondary structure should be seriously considered when attempting to explain influenza virus evolution. Existence of predicted structures is also confirmed by *in vitro* experiments (collaboration with dr. R.C.L. Olsthoorn, Leiden Institute of Chemistry and dr. H.A. Heus, Radboud University Nijmegen - manuscript is published in *Bioinformatics* in 2007).

Using conserved RNA structures encoded in one of plant genes (enod40), involved in symbiotic interactions with bacteria or fungi, a number of new enod40 homologues in various plant families has been found by similarity searches in the nucleotide sequence databases. RNA secondary structure predictions and comparative analysis of enod40 RNAs allowed us to determine the most conserved structural features, present in all known enod40 genes. Remarkably, it has been discovered that the topology and evolution of one of the conserved enod40 RNA structural domains are similar to to those of expansion segments found in structural RNAs such as rRNAs, RNase P and SRP RNAs. Surprisingly, the enod40 RNA structural elements are much stronger conserved than the encoded peptides. These findings suggest that some general functions of enod40 gene could be determined by the RNA structure, whereas short enod40 peptides may be responsible for more diverse functions found only in certain plant families (collaboration with dr. Andreas Roussis, Agricultural University of Athens, Greece - manuscript is published in *Nucleic Acids Research* in 2007).

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 (i.e., the number of cervical vertebrae in mammals and the number of digits in tetrapods), 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).
In 2006 we have continued our collaboration with the Pathology department of the VUmc (Free University Medical Center), in particular with Dr. Liliane Wijnaendts. We have continued our study on the incidence of an abnormal number of cervical vertebrae in fetuses and infants that died in hospital. Variations of the number of cervical vertebrae indicate a disturbance of the early organogenesis stage. Our study shows that such disturbances lead to multiple, mainly negative, effects and that cervical ribs are reliable indicators of medical risks. Our study further shows that the multiple effects are the result of the extremely strong interactivity of morphogenetic and patterning processes during the early patterning of the embryonic axes. The results have led to a publication in Evolution in 2006.

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 have now also started a collaboration with Dr. E. Teske, veterinary oncologist at the University of Utrecht. In this collaboration we study variations in the number of digits and cervical vertebrae in dogs. Such variations, in particular variations in the number of digits, are much more common in dogs than in humans. Dogs, therefore provide us with a better study system to find out more about associations between these variations and associated medical risks, in particular cancer. Preliminary results show that the extension of our study to dogs is promising.

Finally, we have carried out a theoretical study on the evolution of novelties. Our earlier results showed that strong stabilizing selection is very important in preventing novelties to persist in populations. We now conclude that relaxed selection is important in breaking such constraints and that relaxed selection, together with directional selection is important for the establishment of evolutionary novelties.

3. Ecological Dynamics and ESS Theory (dr. P. Haccou, Prof. dr. J.A.J.Metz)

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.

We developed conservation guidelines to protect populations from going extinct when there is environmental uncertainty for situations with multi-species interactions. As a first example we considered a case where an invasive alien species poses a threat to an endemic protected species, and calculated optimal allocation of conservation effort to extermination of the alien species and protection of the endemic species (collaboration with Hiroyuki Yokomizo and Yoh Iwasa, Kyushu, paper published in JTB, 2007).

We further examined the probability of introgression of insecticide resistence genes in white fly populations with branching process models, in collaboration with Inez Demon and Frank van den Bosch, Rothamsted, paper published in TPB, 2007). We derived methods for studying the expected time until successful invasion of multitype processes, and examined the hazard rate, i.e. the chance per time unit of an invasion that will eventually lead to successful establishment (coll. with Sao Serra, Gothenburg, paper published in TPB, 2007). These methods will be extended to study introgression of modified genes through hybridization between cultivars and their wild relatives (coll. with the section plant ecology and the Centre of environmental sciences, Leiden University).

4. Adaptive Dynamics (Prof. dr. J.A.J. Metz, dr. P. Haccou)

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.

For a chapter in the Encyclopedia of Ecology an historical and methodological study was made of how the fitness concept of evolutionary ecology differs from that of population genetics, the former being geared towards dealing with long term evolution through the repeated invasion of mutants for potentially complicated ecological scenarios, the latter with short term changes in relative frequencies of types for heavily simplified ecological scenarios.

The ecological conditions allowing for the definition of a general invasion fitness concept were analyzed in detail, the most essential one being that reproduction should be clonal as is the case for e.g. alleles. Based on these analyses a framework was built within which a general definition of invasion fitnmess can be formalized, and varous novel recipes were derived for calculating (proxies for) invasion fitness in a large variety of instances. The invasion fitness concept extends to any aggregates treatable as meta-individuals. Individual- and meta-individual-level invasion fitnesses coincide when the latter is larger than per capita within aggregate growth. Calculating invasion fitness through a meta-individual route often works beyond calculations based on inclusive fitness arguments, but provides less insight. In particular, Mendelian diploids are aggregates of clonally reproducing genes; conditions were derived for when predictions for virtual cloning diploids coincide with those from gene-based calculations.

Thanks to the happy confluence of some general consistency results of Stefan Geritz and the perturbation results from the PhD work of Michel Durinx it has become possible to reopen the long stagnant mathematical investigation of the events after initial diversification at branching points in higher dimensional trait spaces. In particular, finally the initial stages of a proof are starting to materialize that the incipient branches all align in two clusters symmetrically around the singular point along the dominant axis of the invader Hessian of the invasion fitness at the singular point. Another matter is that this does not necessarily mean that there may not be diversification orthogonal to this axis within the those clusters. However, the present conjecture is that of the various types within such a cluster all but one eventually go extinct.

In the context of an analysis of the tug of war between alleles and modifiers about the fate of the phenotypic expression of genetic dimorphisms in populations with differentiated sex roles (i.e. almost all natural populations), a study has been has been initiated of the genericity of various types of developmental and genetic constraints that may arise through the interplay of the genetic architecture and the developmental map. Although only the simplest cases have been fully resolved yet, a good deal of mathematical machinery has been developed in order to eventually cope with the general case.

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

Prof. Dr. J.A.J. (Hans) Metz	Professor UL (0-appointment)

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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.

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DISSERTATIONS

Claus Rueffler, 27 april 2006. Thesis : Traits traded off. Promotor: Prof. dr. J.A.J. Metz