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MODELING BIOLOGY:
Structures, Behavior, Evolution

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organized by Luciano da Fontoura Costa and Gerd B. Müller

Konrad Lorenz Institute
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The topic

In the biosciences, the rapidly growing amount of experimental results and the increasing complexity of the phenomena under investigation pose an unprecedented challenge for the interpretation and integration of the accumulated data. Abstraction and modeling are required. Due to the improvement of computational methods, the modeling of biological phenomena has reached a completely new stage. It is now possible to model spatial and temporal interactions of nearly all processes in hitherto unknown detail, and with increasing sophistication. The generation of models promotes the organization of data and knowledge, the formulation of hypotheses, the estimation of measures, and the analysis and classification of results. At the same time, bottom up models elucidate the properties of natural biological systems. Therefore, the concepts and methods used in modeling and simulation are a key for major advances in the biological sciences. The present workshop investigates the ways in which the new modeling strategies help and influence our understanding of biological processes.

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Chandrajit Bajaj Modeling and Quantitative Visualization of Virus Ultrastructure
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DEVELOPMENT

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George McGhee Exploring the Spectrum of Existent, Nonexistent, and Impossible Form
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Abstracts

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Computational Models of Dendritic Morphology: From Parsimonious to Biological Insight

The structural complexity and natural variability of individual neurons make it exceedingly difficult to achieve a complete characterization of dendritic morphology. In recent years we have proposed a novel solution to this open problem. We have implemented computational algorithms to simulate dendritic morphology based on distributions of parameters measured from the experimental data. Because the quantitative description of dendritic morphology of a neuronal class is necessarily statistical, any successful model of cellular neuroanatomy ought to be intrinsically stochastic. The resulting virtual (computer generated) neurons are statistically and visually compatible with the real cells of the corresponding morphological class. Thus, these synthetic neurons define (by construction) the amount of morphological information that is effectively captured by a given set of measurements. We have designed, implemented, and optimized a variety of algorithms for dendritic modeling, based both on local and global parameters, and on Markov and hidden-Markov approaches, applying them to morphological classes as diverse as pyramidal, granule, stellate, and Purkinje cells. Computational algorithms also yield mechanistic clues regarding developmental processes and the relationship between dendritic structure and electrophysiological activity. Our models suggest that dendrites of hippocampal principal cells may be repulsed by their own cell bodies during growth, and that two distinct mechanisms of branching may be active during the development of apical trees in CA1 (but not CA3) pyramidal cells.
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Modeling and Quantitative Visualization of Virus Ultrastructure

Knowledge of the three dimensional structure of viruses, provide not only the mechanistic descriptions for how such trojan horses act but also clues in developing therapeutic interventions. This talk and paper shall survey the computational modeling of the protective packing (capsids) of viruses, and their individual sub-units (capsomeres), at both atomic and psuedo-atomic resolutions. Details shall also be provided of efficient geometric and image processing techniques for the detection of the various inherent symmetries, and the boundaries of asymmetric subunits, within reconstructed 3D cryo electron microscopy virus maps, and demonstrate their applications in generating and quantitating compact smooth approximation models of the ultrastructure of virus packings. These multi-resolution computer models of viruses can additionally be visualized and explored at interactive rates on current desktop computers, using a combination of surface/volume/texture rendering algorithms, and graphics hardware acceleration.

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Biological Shape and Function: The Hummingbird Effect

Several physical, chemical, and biological properties of natural structures and objects are, to a great extent, defined or at least influenced by their respective geometrical properties. For instance, in sharp metallic points the lines of force of electrical fields tend to converge, a phenomenon that is exploited in lightning rod construction. Chemical binding and docking is also highly determined by the respective shapes of the molecules. At a more macroscopic level, the shapes of organismal structures play a decisive role for survival of species, e.g., allowing hummingbirds to nourish from specific flowers through their highly specialized beaks. These are but a few examples of the general shape/function paradigm, which provides one of the key perspectives for understading the complexities of biology. The current talk will discuss this paradigm and, given its generality for bridging structure and function, show how the novel concept of complex networks is poised to pave the way towards the re-integration of biology, and perhaps of science as a whole.

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Modelling Social Behaviour in Robot-Human Interaction – The Human in the Loop

The chapter/talk will discuss the issue of modelling social behaviour from an Artificial Life perspective and with reference to experiments on robot-human interaction. Particular emphasis will be put on the notion of emergent social behaviour as opposed to explicitly implementing models of behaviour (or cognitive models of "social intelligence"). Illustrative examples will be drawn from two ongoing project that I have been involved in: 1) the Aurora project (www.aurora-project.com) which investigates the possible use of robots in therapy or education of children with autism, 2) the European project Cogniron (www.cogniron.org) which studies the development of a cognitive robot companion. Three scenarios will be discussed in more detail: a) dyadic interactions involving two agents (robot and human), b) triadic interactions comprising a second human as part of the "interaction-loop", c) interactions between groups of people and a human-sized robot. The scenarios studies in the Aurora project point towards the possible role of robots as mediators, i.e. agents that facilitate and mediate human-human interaction. Robotics research has traditionally focussed on realizing social behaviour (or models of "social intelligence") explicitly, e.g. in the hardware and software of the robot. In contrast, our work exemplifies a more interaction-centred approach whereby the robot serves as a salient object or tool that does not necessarily need to embody "social intelligence", or models of social behaviour, explicitly. The chapter/talk will argue for the importance of a bottom-up, interaction-centred approach towards modelling social behaviour in the area of robot-human research.

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Visualization and Modeling of Embryonic Gene Expression

A major challenge for developmental biology in the post-genome era is to corroborate an integrative view of the interactions between genes, epigenetic mechanisms, and morphogenetic processes in ontogeny and phylogeny. This task will require novel visualization technologies for a detailed spatio-temporal mapping of gene expression patterns to ontogenetic sequences, as well as a new set of

computational tools that allow for the integration of these data with other causal developmental factors into mathematical models. Such descriptive models may then be subjected to virtual experiments, testing their capacity to account for regular morphogenesis, teratology, and phylogenetic transformation. Here we present a visualization and modeling platform that is based on the GeneEMAC[1] technology in conjunction with a GIS related[2] database structure. This platform allows for the collection, storage, and analysis of large quantities of gene expression data in the context of an accurate four-dimensional virtual reconstruction of morphogenesis in ontogenetic sequences. We discuss several of the technical challenges of this approach and give an overview of its potential.

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[2] Salazar-Ciudad, I. and Jernvall, J. (2002). A gene network model accounting for development and evolution of mammalian teeth. PNAS. 99: 8116-20.

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Whys and Wherefores of Computer Modelling in Behavioural Biology

The use of bottom-up computer modelling to investigate biological theory is now widespread, but it is all too easy to forget to ask why, and how, this approach should be used. The question of why is perhaps most easily answered, as computational models allow some of the more difficult yet realistic aspects of biological systems, such as nonlinear interactions, spatial and stochastic effects, to be modelled more easily. This still begs the question of how to analyse and interpret such models, and what benefits they can provide to our understanding. Much has been said on this already for general biological theory, such as whether "simulation models" are indeed models, or systems which are instantiations of real biological processes and hence sources of empirical data for our theorising. For behavioural biology, one approach is to use simulation models to investigate the "design space" of specific biological systems, determining the processes that may lead to observed behaviours as well as examining unrealised alternatives and the constraints which may have limited evolution's exploration of this "design space". Social insects provide a particularly accessible system to apply this approach to, both in the domain of individual and collective behaviours.

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Exploring the Spectrum of Existent, Nonexistent, and Impossible Form

Theoretical morphospaces are multidimensional spaces produced by systematically varying the parameter of a mathematical model of form, and are specifically produced without any measurement data from real organic form. As such, theoretical morphospaces are not only independent of existent morphology, they can be used to create nonexistent morphology and also to identify regions of morphospace that contain geometrically impossible biological forms. Plotting the actual distribution of the existent morphologies found in a group of organisms within a theoretical morphospace can reveal empty, unutilized regions of morphospace that are the product of evolutionary constraint. For a given group of organisms, can we conceptually map the distribution and boundaries of geometric, developmental, functional, and temporal constraints within theoretical morphospace? If we accomplish this, we would be well on the way to understanding why certain morphologic solutions are repeatedly

evolved in life, convergent evolution, as function of the (I suspect) vastly larger areas of morphospace into which life cannot venture.

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**Evolutionary Information-Theoretic Foundations of Sensory Ecology:
Channels of Organism-Specific Meaningful Information**

Information theory developed by C. Shannon and his followers in the mathematical theory of communication surprisingly but successfully abstracted away from the questions of (1) the origin and maintenance of information channels, and (2) the meaning of information. However, in understanding the evolutionary sensory ecology of the many information channels used by particular organisms, one is confronted with exactly these issues. What is the origin of particular channels in an embodied organism? How do they benefit the organism? Why this type of sensor and not another? Sensors are costly to build, maintain, operate, and carry. The costs and benefits of access to particular information have an impact on survival and reproductive success in a particular ecological context. We introduce a framework in which channels of meaningful information (sensors, actuators, internal channels within and between organisms and/or between an organism and its environment) can each be treated using an extended Shannon information theory. Rigorous information metrics relate source-target informational channels to organism-specific notions of relevance and utility. The study of such organism-specific measures of relevant information is aimed at the development of a predicative theory applicable to the evolution of sensory channels in both biological and artificial systems. We also briefly consider the issues of the temporal horizon and interaction in this framework. Computer simulation, robotic, and biological models illustrating the approach yield insight into the selection of sensory channels in relation to their relevance to an organism's reproductive success.

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Optimization and Plant Evolution

Computer models are used to mimic the early evolution of ancient vascular plants (tracheophytes). These models have three components: (1) an N-dimensional domain of all mathematically conceivable ancient morphologies (a morphospace); (2) an numerical assessment of the ability (fitness) of each morphology to intercept light, maintain mechanical stability, conserve water, and produce and disperse spores); and (3) an algorithm that searches the morphospace for successively more fit variants (an adaptive walk). Beginning with the most ancient plant form, evolution is simulated by locating neighboring morphologies that progressively perform one or more tasks more efficiently. The resulting simulated 'adaptive walks' indicate that early tracheophyte evolution involved optimizing the performance of many tasks simultaneously rather than maximizing the performance of one or only a few tasks individually and that the requirement for optimization accelerated the tempo of morphological evolution in the Silurian and Devonian.

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Exploring the Protein Funnel Energy Landscape for Folding and Function

Globally the energy landscape of a folding protein resembles a partially rough funnel. Using minimalist model simulations together with analytical theory, we learn about good (minimally frustrated) folding sequences and non-folding (frustrated) sequences. In addition to the need to minimize energetic frustration, the fold topology also plays a major role in the folding mechanism. Some folding motifs are easier to design than others, suggesting the possibility that evolution not only selected sequences with sufficiently small energetic frustration but also more easily designable native structures. We have demonstrated for several proteins (such as CI2 and SH3) that they are sufficiently well designed (i.e., reduced energetic frustration) that much of the heterogeneity observed in their transition state ensemble (TSE) is determined by topology. Topological effects go beyond the TSE. The overall structure of the on-route and off-route (traps) intermediates for the folding of more complex proteins is also strongly influenced by topology.

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Multicellular Modeling of Cell Adhesion and Chemotaxis

The cellular slime mold Dictyostelium discoideum is a widely used model system for studying a variety of basic processes in development, including cell-cell signaling, signal transduction, pattern formation and cell motility. Here I will discuss cell movements and signaling in Dictyostelium and introduce a biologically realistic three dimensional mathematical model that facilitates the simulation and visualization of these processes. The building blocks of the model are individual, deformable, ellipsoidal cells; each cell having certain given properties, not necessarily the same for all cells. Since the model is based on known processes, the parameters can be estimated or measured experimentally. I will show simulations of the cell streaming during aggregation and the collective motion of an aggregate of cells driven by a small group of pacemakers. The results are compared with experimental data and examples are shown that highlight the interplay of chemotaxis and adhesion on cell sorting and movements in Dictyostelium. The model predicts that the motion of two-dimensional slugs results from the same behavior that is exhibited by individual cells; it is not necessary to invoke different mechanisms or behaviors. I will also demonstrate how differences in adhesion between pre-stalk and pre-spore cells, affect the sorting and separation of those cell types that occur during the slug stage, and I will suggest and explain why chemotaxis alone might not be sufficient to achieve complete sorting. Finally I will discuss how different models of the signaling system and differences in the cAMP wave propagation influence the results.

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Modeling Developmental Asymmetries

An impressive body of knowledge has been generated in the past decade regarding the establishment of Left/Right asymmetry. There are three kinds of insights that have appeared in the literature in this relatively young field: first, theoretical insights, concerning possible theories about the initial mechanisms responsible for L/R asymmetry (e.g., chirality of a theoretically postulated protein; Brown & Wolpert, 1990); second, epigenetic mechanisms such as cilia movement in the nodal cells of mice embryo (Nonaka et al., 1998), and ion flux through cellular Gap junctions in early Xenopus gastrulation (Levin & Mercola, 1998); and third, gene expression data and some correlations about the spatiotemporal actions of these genes (Capdevila et al., 2000). Despite this, we still know very little

about how side-specific signaling pathways are regulated, and even less about the mechanisms that these pathways use to coordinate the generation of the normal body plan. We present here three modeling strategies to tackle early specification of left/right asymmetries. At the molecular level, the early expression of Notch is necessary in order to differentially elicit the expression of Nodal in the left side of the perinodal region in chick and zebrafish. Modeling critical steps of the gene network associated with the Notch pathway characterizes and predicts the behavior of perinodal cells under different conditions (Raya et al., 2004). The dynamics of ciliary movement in the node of the early mouse embryo provides a level of oscillatory phenomena (a mechanical one) that is paramount for the early specification of the L/R axis. Several strategies can be used to model this behavior, such as the use of rowers, rotlets, or stoskelets (Buceta et al, in press). Finally, the looping of the heart tube is one of the first manifestations of organ asymmetry in vertebrates. Modeling cell adhesiveness provides an entry point to understand this phenomenon (Rasskin-Gutman and Izpisúa-Belmonte, 2004).

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Modeling Complex Bio-Behavioral Systems

To adequately model complex bio-behavioral systems, modeling strategies must be adaptable to the changing demands of modeling complex systems as well as new discoveries and errors that occur during the modeling process. I begin by describing 9 dimensions that characterize models and the modeling process (i.e., model medium, realism, detail, generality, match, precision, tractability, integration, and level). I argue that no single type of model (e.g., mathematical, computational, or robotic) or modeling strategy can simultaneously optimize all of these dimensions. However, progress can be made by adopting a multi-modeling approach in which different types of models and modeling strategies focus on different dimensions of the modeling process. I discuss examples of multi-modeling approaches, including a project I am working on that uses individual-based models, system dynamic models, robotic models, neural-networks, genetic algorithms, and boot-strap Monte Carlo simulations to address sensorimotor development in infant mammals.

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Competition and Cooperation in Neural Development

Neurons are the principal information processing elements of the nervous system. With their highly branched axons and dendrites they form a dense network of synaptic connections. Neurons show enormous diversity and variation in shapes, both within and between different cell types. Neuronal development is a highly dynamic process in which many mechanisms are involved. Despite its complexity the developmental process results in neuronal networks that are able to support functional dynamics at all levels of brain function. Understanding the principles of such a robust developmental process is a major challenge in neuroscience. Among the mechanisms involved in neuronal development we may distinguish basic biophysical mechanisms, organizational mechanisms emerging from the molecular machinery in neurons, interactions of neurons with each other and with their local environments, and reciprocal interactions of neurons with their own states of electrical activation. Correspondingly, different modelling approaches can be distinguished in exploring the implications of hypothesized rules or mechanisms on the development of neuronal shapes and network connectivity. Several of such approaches will be outlined.