

Organic Computing: Towards structured design of processes

*Interdisciplinary Symposium
to be held in Paderborn,
Nov 23-24, 2001*

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Program and collected position statements

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Program

Friday, 23 November

- 08:30 Shuttle pickup at Hotel Stadthaus
- 08:45 Shuttle pickup at Best Western Hotel
- 09:00 Registration
- 09:20 *Welcome* (C. von der Malsburg)

I Problems (*Chair: C. von der Malsburg*)

- 09:30 *Problems with IT systems* (J. Lanier)
- 09:50 Discussion
- 10:20 *Problems in the neurosciences* (R. Douglas)
- 10:40 Discussion
- 11:10 Coffee break
- 11:40 *Problems in genetic control* (H. Herzog)
- 12:00 Discussion
- 13:00 Lunch
- 14:00 Guided tour of the Heinz-Nixdorf Museum

II Bridges (*Chair: R. Douglas*)

- 15:00 *Genetic control: has life discovered structured programming?* (B. Meyer)
- 15:20 Discussion
- 15:50 *Computer and brain: Common aspects of functional organization* (H. Ritter)
- 16:10 Discussion
- 16:40 Coffee break
- 17:00 *Brain and genome: do they share organizational principles?* (W. von Seelen)
- 17:20 Discussion
- 18:00 Guided tour of the exhibition Computer.Gehirn at the Heinz-Nixdorf Museum
- 19:15 Reception and Dinner
- Shuttle transfer to hotels

Saturday, 24 November

09:00 Shuttle pickup at Hotel Stadthaus

09:15 Shuttle pickup at Best Western Hotel

III Towards a science of organization (*Chair: P.Schuster*)

9:30 *Self-organization: from structure formation to organized processes* (G. Schöner)

9:50 Discussion

10:20 *Modularity as a structural principle* (J. Eklundh)

10:40 Discussion

11:10 Coffee break

11:40 *Shifting attention from details to principles* (N.N.)

12:00 Discussion

13:00 Lunch

IV Conclusion (*Chair: H. Ritter*)

14:00 *Report about session I* (R. Würtz)

14:20 Discussion

14:40 *Report about session II* (N.N.)

15:00 Discussion

15:20 Coffee break

15:40 *Report about session III* (N.N.)

16:00 Discussion

16:20 *Where to go from here?* (N.N.)

16:40 Final discussion

17:00 End of symposium

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Chapter 1

Introduction

1.1 Organic Computing

Christoph von der Malsburg

Coming to grips with the organizational structure of large systems is a problem common to several fields of science. This interdisciplinary symposium targets the neurosciences, molecular biology, and computer science. Progress in all three fields is breathtaking, molecular biology and the neurosciences are producing factual data at prodigious rates with the help of ever more powerful experimental techniques, and computer technology is bringing more computing power on-line daily at an exponential rate. However, as a result all three fields are on the verge of being drowned in detail, missing the forest for the trees and falling far short of their potential. We feel that meaningful communication between the three fields and others is urgently required, and is indeed possible on a high conceptual level. In many respects the problems of those fields are complementary to each other, and many concepts, methods and ideas could be traded. In addition, there is a thirst for new ideas in all three areas, and new intellectual talent has to be attracted by career opportunities. We expect that a new intellectual field will eventually form around the science of organization, and this symposium intends to prepare the way. In this development, the field of physics will have to play an important role as a source of methods, concepts and talent. Physics has a great track record of bringing simplicity out in phenomena of seemingly great complexity by a simple change in perspective. We feel that organic structures are inherently simple if looked at the right way.

Interdisciplinary Cooperation

Computer Science was originally focused entirely on the algorithmic principle, according to which a dumb process in the machine is totally dependent on the planning, interpretation, diagnostics and understanding in the mind of a human in front of the machine. It became quickly evident in the fifties that beyond a few dozen instructions the process in the machine becomes unintelligible and unevolvable — the so-called spaghetti code phenomenon. In response, computer science embarked on a long and rather successful process of developing tall hierarchies of control structures of great functional power, operational stability and evolvability. Today, much of the organizational infrastructure originally in the exclusive possession of humans resides in the computer, and systems with millions of lines of code are common. Strangely, during this entire process, computer science never gave up its fixation on the algorithmic principle as its central paradigm, with the consequence that today tremendous human and economic resources are absorbed by the necessity to attend to detail hidden deep in systems, and in consequence computer systems are inflexible, unreliable and awkward to use. A more appropriate computing paradigm would be the living cell, or indeed all living structures, considering them as organic computers. Organisms are certainly not algorithmically controlled, and yet they are computers of a complexity, autonomy, reliability and flexibility far beyond any product of human technology. To

solve its eternal software crisis, computer science will have to study and inherit the organizational principles embodied in the organic computers of life. Conventional computer architectures will not have to change, at least not any time soon, and algorithms will remain important as basic mode of implementation and in terms of functional components, but systems are to be organically controlled on their higher levels.

Molecular biology by now is a large-scale industry churning out GigaBytes of information per day on molecules and their structure and interactions, and it is high time to mount a serious effort to develop the concepts required to comprehend the over-all organization of the living cell. Life has run into the spaghetti code problem billions of years ago and has undoubtedly solved it by building organized hierarchies to make the cell, and later the organism, evolvable and stable and flexible in their operation. At present, molecular biology sees computer science in a merely ancillary role of providing data base management (and this is indeed where the bulk of the effort must go within the next few years), but computer science can play a much more fundamental role, by making available its body of knowledge on how to organize complex functional hierarchies.

The Neurosciences in the broadest sense have a very long tradition of studying brain and mind, the most awesome of all organic computers, and there is a great wealth of concepts to describe and characterize its organization. However, much of this information is scattered over fields with very different tradition and language, and all the ideas that have been formulated over the centuries will only be safely in our possession once they have been embodied and tried in functional artificial systems. Computational neurobiology is the field in which this ought to happen, but also this field is in dire need of raising its sight from the details of particular sub-systems or elementary functional phenomena to gain the perspective of a more principled approach. In consequence, the field probably has as much to gain as it has to give in this interdisciplinary venture.

Physics has a great tradition of coming up with simplified descriptions of seemingly complex problems, descriptions that are conceptually simple enough to be amenable to quantitative and strict analysis while still being able to capture the essence of the phenomenon studied. Thermodynamics in both its statistical and phenomenological form constitutes a perfect example at hand. Young physicists are all over the exciting fields at issue here, and they come equipped with a very appropriate set of intellectual skills and perspectives. It is about time that physics as a field starts to actively embrace the problem of organization.

Towards a New Computing Paradigm

A delicate balance will have to be struck to ensure solid experimental grounding while at the same time avoiding to be overwhelmed by indigested facts. Besides the familiar concept of the algorithmically controlled deterministic machine a new computing paradigm must be defined following the model of the living cell and of the brain and their ability to organize complex, purposeful behavior. Rigid determinism must be relaxed, individual processes embedded in a continuum of variants held on track by general principles and goal projections, not by detailed insight and analysis by a distant programmer as in the algorithmic mode of control. Molecular, nano-scale and quantum computers, should they become a reality, will only be feasible on the basis of an organic computing paradigm, and the fruits of the genetic revolution can only be reaped if the cell is conceived of as a computer.

A system is not to be defined on the level of individual devices or processes but on that of the abstract structure of the process and the abstract structure of the implementation system. The system is to be defined in terms of an architecture: a set of structural and functional constraints which leave room for flexible adaptation in particular situations, but reduce the search space sufficiently so that the system can, autonomously and in reasonable time, find a solution to the problem at hand. Stirring a mixture of water, soap and oil in a vessel spontaneously forms membranes of soap separating oil and water, and the membranes curl into vesicles and “organelles,” forming an ideal architecture for cytoplasmic organization. The body plan of the quadruped is an architecture that allows evolution to easily adapt to very different life styles. Nerve and glia cells with their behavioral repertoire constitute an architecture that naturally defines a structured universe of connectivity patterns and

signal equilibria, a universe from which the parametric control of the genes can select the specific structure of specific nervous systems.

The object-oriented style of programming is an architecture that takes into account the necessity to bundle and protect tightly coupled functional components while loosely coupling independent processes, and it exploits the mechanism of structural inheritance of more specific processes from more general ones. Object-oriented programming has vastly boosted the efficiency of coding, reliability and flexibility of large programming systems. These systems are the only easily accessible examples of tall hierarchies of interacting processes. But that technology will have to go the extra step of turning system function and evolution into an autonomous adaptive process. The way is shown by life with its adaptive mechanisms of evolution, learning and self-organization. These have already served as models for very successful computing systems in the context of artificial neural networks, fuzzy logic, and genetic programming. What will have to be developed in the coming years is the application of these concepts to whole computing systems, not just small embedded sub-processes. Central concepts will have to be the principle of independent convergence as well as closed loops, according to which no decision is taken in a system unless agreement is reached on independent pathways and on the basis of independent evidence, and no conclusion can survive unless it is corroborated by back-flow from its own consequences. These concepts are central to the field of belief propagation, and computer vision is presently revolutionized by mechanisms of cue integration, a particular form of independent convergence. This style of computing is expensive in terms of process and data volume, but with dirt-cheap computer chips and exploding software development cost it is the right choice.

The new computing paradigm will require profound adaptations in terms of basic instincts, methodologies and, of course, education in the relevant fields. The discrete mathematics of the finite automata and symbol systems of Turing machines will have to give way to continuous mathematics. Design will have to be replaced by adaptation. Deterministic systems will have to give way to statistical descriptions of infinite sets of systems and processes ruled by probability distributions. Small sets of non-linear coupled differential equations will have to be seen as mere stepping stones to complex hierarchies of layered systems. Individual structure formation processes will have to be seen as elements of long chains in which the pattern formed in one step sets the boundary conditions for the next (for which cell division, ontogenesis, cellular differentiation and thought processes are prime examples). Eventually, this endeavor should lead to a structural theory of the universe of all organic computing structures and processes.

Chapter 2

Information technology

2.1 A few thoughts on organic computing

Wolfgang Banzhaf

In today's computers the information content of a stored bit sequence depends heavily on its position in memory. Specific data are located at specific positions. For execution of algorithms, the interpretation of data is done by an instruction flow which again refers to specific pre-defined memory locations. Changing the position of data randomly will perturb the content of memory and spoil the intended computation. Changing the position of instructions - and therefore its order - will disrupt the computational process altogether resulting in unpredictable outcomes.

Conventional computers are nothing more than macroscopic information processing machines. The term *machines* is used here in a broad sense, meaning all types of tools that are put together by humans to act and serve specific purposes. In the realm of machines of macroscopic size, parts are produced and put together in a predefined order and at specific locations for the machine to function properly. If one doesn't follow the order of construction and positions the parts inappropriately, such a machine will not function. Even if a machine put together properly and starts working, there are weaknesses. By using the machine it will be strained and, once enough time under usage has passed, it will break at some critical point.

Both the construction and functioning of machines at macroscopic levels are to be seen in contrast to what happens at the molecular scale. It is here where I see "organic computing" playing a role. On the molecular level, Brownian motion provides a constant influx of randomness into a system. Thus indeterminism is much more widespread than engineers would accept. Also, it is very difficult to position two parts of a molecular machine in appropriate places with the use of (molecular?) tools. As a consequence, attaching meaning to locations is virtually impossible. In addition, the coordination of sequential actions is difficult to achieve. Instead, things will usually happen in unpredictable sequence. Finally, the purpose of microscopic devices is often to achieve a collective effect due to the low power of single devices. Due to mechanisms of adaptation, straining of those collections will not wear them out, but will strengthen them.

As Nature has demonstrated, these features of molecular systems are by no means weaknesses. Just the opposite, they can be put to good use for achieving macroscopic effects.

- Brownian motion provides a source of energy for movements of molecules in search for appropriate partners.
- Indeterminism at the molecular level allows new things to happen.
- Specificity by location can be substituted through specificity by pattern. 3D shapes carry information content and are critical for possible reactions between molecules.

- If it is difficult to achieve defined sequences, asynchronous parallelism is the natural mode of action. Predictability might come as a consequence of collective action.
- Due to reaction kinetics, adaptivity is built into molecular systems. Provided the systems are open (which is mostly the case) and sufficiently buffered, consumption of molecules generates more of the same.

It is therefore proposed to consider these features as the core of organic computing. We believe that the information content of molecules or macromolecules can be used as driving force for computation. On an operational level, this can be summarized by the following table.

Conventional Concept	Organic Computing
data	substances or molecules
processing	chemical reaction
algorithm	collective effect of substances and their reaction laws

One of the key questions of this approach is how to achieve target functions. My perspective on achieving well defined functions with highly complex material is biased through experience in artificial evolutionary systems. Artificial evolution does not require a precise definition of processing steps

to achieve a certain goal, but rather a clear idea about what the goal would be. This goal is then "implemented" as a fitness function for the system at hand, and a multitude of entities (trials) which fulfill the criteria of the goal to various degrees is compared. Those implementations that fulfill the criteria better are preferred for amplification through variation and combination. Variation and combination are driven mostly by stochastic events. After some iterations through such a process one can observe the trials to develop toward the desired goal.

Provided the underlying computational substrate is sufficiently flexible, this approach should yield many different functions accessible.

2.2

Dan Hammerstrom

I tend to think of all design, whether biological or man-made as dealing with information flow, that is, who needs what and when. From this perspective, then one can talk about organic computation leveraging certain characteristics of information flow. Two important characteristics are encapsulation and distribution. Encapsulation is where most information is “hidden” such that only the most important information is made available outside of a subsystem. *Encapsulation* forms the basis for most hardware and software systems design methodologies.

Distribution is not a traditional design technique for man-made systems, but is evident in biological systems. A distributed system can be loosely defined as a system with overlapping, though not completely redundant, capabilities. That is, where subsystems share in the task at hand.

From an information theoretic perspective, distribution can be defined as the degree of participation of a single “unit” in the information representations used by the system. Holograms, for example, are completely distributed, each “unit,” participates in all representations, and sits at one end of the spectrum. Traditional computer science tends to be at the other end of this spectrum, where a unit (say a bit or a memory location) participates in one representation, or a particular function has exclusive control of an event. This is the essence of symbolic computing, which is all we really know how to do (even floating point arithmetic is merely the manipulation of symbols, according to a predetermined set of rules, that represent analog quantities). Organic systems on the other hand seem to be somewhere in the middle and in fact different subsystems probably sit at different points on the spectrum, since there are different requirements for computation representation and input/output.

Biological systems have requirements such as distributed manufacturing and reliable (fault tolerant) function. Fault tolerance favors distribution, that is, the elimination of single points of failure. Likewise, distribution contributes to faster response, since many units are computing a similar function in parallel. Most pattern recognition tasks seem to involve a kind of “some part of everything” to “some part of everything else” comparison, so the more widely information is distributed the easier it is to access.

However, there are also disadvantages to distribution, learning for example, and the subsequent required modifications to the representation, is more difficult to do since now such have to be coordinated. And although distribution and encapsulation are not mutually exclusive, they do tend to work against each other.

For many years Chip designers have relied on a relationship called *Rent’s Rule*. E.F. Rent of IBM published two internal memoranda in 1960 that contained the log plots of the “number of pins” versus “number of circuits” in a logic design. These data tend to form a straight line in a log-log plot and yield the relationship $N_p = N_g \cdot Kp^b$, where

- N_p is the number of external signal connections to a logic block
- N_g is the number of logic gates in the block
- b is Rent’s constant, and
- K_p is a proportionality constant

The values of K_p and b for the IBM computers were reported to be 2.5 and 0.6, respectively. Rent’s rule then is an indirect, heuristic measure of communication locality for computer systems.

Rent’s rule basically says that as a module gets larger (contains more gates), the number of external connections gets smaller (exponentially so) relative to the number of internal connections. The drop off is much more rapid than if connections were randomly placed. Although the constants have changed somewhat, Rent’s Rule still holds, in spite of the fact that the design styles from the old IBM days

have changed significantly. The relationship is still used by chip designers to estimate interconnectivity requirements, as well as the metal connectivity resources in chip fabrication. This is particularly true for FPGAs that are designed to handle a range of designs.

Is there something fundamental about how we design logic that makes Rent's Rule such a universal relationship? Is there a Rent's Rule equivalent in organic computation?

Nervous systems seem to be fairly localized, Braitenberg and Schütz (1998), *Cortex: Statistics and Geometry of Neuronal Connectivity*, describe "metric" (high density connections to physically local units, based on actual two-dimensional layout) and "ametric" (low density point to point connections to densely connected groups throughout the array). Is this a fundamental aspect of cortical algorithms? Just as in silicon, in organic systems connections are expensive, they take space and metabolism, increase the probability of error, and they require genetic material to describe how they are built.

Concerning the nervous system, Carver Mead expressed these considerations eloquently in his ground-breaking book on neural network VLSI (Mead 1989):

" Computation is always done in the context of neighboring information. For a neighborhood to be meaningful, nearby areas in the neural structure must represent information that is more closely related than that represented by areas further away.

Visual areas in the cortex that begin the processing sequence are mapped retinotopically. Higher-level areas represent more abstract information, but areas that are close together still represent similar information.

It is this map property that organizes the cortex such that most wires can be short and highly shared; it is perhaps the single most important architectural principle in the brain."

Perhaps in evolution's search for minimal connectivity, it stumbled upon an architecture of minimized connectivity that also added new computational capabilities. Perhaps localized connectivity, coupled with cortical dynamics, allowed parallel localized stabilization via Braitenberg's "metric" connections and abstraction linkages via the "ametric" connections.

So, does Rent's rule say something fundamental about the way humans design logic, or is there something more basic about information transfer in complex systems? Is there a comparable Rent's Rule pertaining to the amount of information being transferred? In other words is there an information theoretic dual, where the required information to be transferred at chip boundaries bears a similar relationship to the internal gate count.

In biological systems such information flow has probably been optimized by evolution to provide just the right degree of distribution and encapsulation. There is a strong information theoretic component here, but it goes beyond existing information theory. I do not believe that existing Physics techniques would contribute extensively to this, since I feel that the organizational techniques that living matter have evolved are unique to life and are not found much in the non-organic natural world. Unlike such non-organic matter, life has a need to hold itself together, to communication status and control information constantly among the various components. It is here that we may discover the secrets to organic organization and computing power.

This information theoretic perspective suggests a number of interesting experiments both at the genetic/protein level as well as within nervous systems.

2.3 Biomolecular Level for Organic Computing

John S. McCaskill

The main architectural distinguishing feature and one great advantage of biological information processing systems over conventional technology lies in their construction principle: genetic encoding, self-organization and natural selection. These impart natural information processing systems with modularity, robustness, self-repair and economy and allow them to operate in a distributed fashion with high use of local control and to be adaptive to varying information flows and adept at real world interactive data processing. Currently, the biomolecular level (in vitro) provides an optimal point of approach to the utilization of these properties of information systems for the following reasons:

- (i) biomolecular systems are closed in the sense that their construction mechanisms are understood and involve only biomolecular and simpler chemical components
- (ii) there are numerous proofs of computational universality for even simple idealizations of interacting biomolecular systems
- (iii) custom hardware, if it can be generated rapidly and conveniently solves the major problems of general purpose efficient parallel computing: biomolecular systems hold this promise
- (iv) biomolecular systems operate near the thermal limit of energy dissipation with extreme parallelism and three dimensional information storage
- (v) there is a good and rapidly improving physico-chemical understanding of the properties of biomolecular systems
- (vi) the tools for manipulating biomolecular information have undergone rapid progress to the point where many processes are already routine in vitro (e.g. PCR, sequencing, transcription, restriction ?)
- (vii) biomolecular systems can evolve in the laboratory, and are small and cheap enough that combinatorial and evolutionary construction of biomolecular computing devices are feasible
- (viii) experimental proofs of basic modes of computation already exist for biomolecular computing and work is continuing on integration and improving reliability on benchmark problems
- (ix) the flexibility of these systems is encouraging theoretical computer scientists to expand their vision of parallel information processing to new models and architectures
- (x) the systems have direct practical value in the short term as on-line computing interfaces in pharmaceutical search engines and molecular diagnostics
- (xi) the systems have an interface to the photolithographic processing procedures of the computer chip industry and current projects involving the integration of DNA Computing for example in microfluidic devices or on DNA-Chips or with electronic control are proving feasible

Biomolecular computing devices make a self-constructing and even boot-strapping computer viable in principle and are worthy of study for this reason in their own right. Germany is in a unique position to capitalize on this development, given appropriate support.

2.4 PUPS - A Computational Environment For Building Complex Dynamical Software Systems

Mark A. O'Neill

The underlying philosophy behind organic computation is simple. As Dawkins has stated in his book *The Blind Watchmaker* [Dawkins, 1986] complex computer programs are effectively biological entities. Essentially, we are asserting that beyond a certain level of complexity, the centralist view of computation espoused by Von Neumann and others tends to break down. This means that the approach to program design advocated by classical computer science is not tenable¹ when implementing large scale, parallel computations, which may interact with complex distributed datasets and which must be both flexible and efficient. In order to efficiently exploit network and parallel computational environments, a radical paradigm shift which adopts, adapts and even extends biological processes: organic computation is required.

Biological systems have effectively spent many millenia evolving solutions to the problems inherent in complex, fault tolerant distributed computations. Although some progress has been made within the organic computing arena by adapting biological and physical processes of cumulative evolution [Genetic Algorithms or GA's and simulated annealing] and (crudely) modeling of neuronal architectures [Artificial Neural Networks or ANN's] relatively little work has been reported on how one might implement computations as non-centralized homeostatic digital organisms capable of meaningful interaction with their [Cyberspace] environment². It is clear that this approach to computation would be a very effective method of implementing persistent and complex computations including:

- Bio- and neuro- informatic databases and modeling systems (e.g. models of neuronal wiring, ecological models, trainable systems for recognizing biological objects such as insects, plants or birds).
- Self organizing parallel database systems (for example massively parallel implementations of the Prolog AI System)³.
- Large scale distributed computations (e.g. weather and climate modelling codes, protein (secondary and tertiary structure determination codes), large scale ab-initio quantum mechanical codes).
- Intelligent [Internet] agent applications.

All these types of problem are either persistent (e.g. they have lifetimes of weeks, months or even years), or they need to manipulate data which are relationally tangled [see O'Neill and Hilgetag, 2001] or have inter-relationships which may be fuzzy or even contradictory [O'Neill and Hilgetag, 2001]. In addition, the size and complexity of the underlying problem means that codes which attempt to solve these problems must be inherently parallel (and scalable). Many problems in analytical biology, like the classification of organisms, the modelling of macromolecules, or the structural analysis of metabolic or neural networks, fall into one or more of the above classes, as does parallel database technology.

PUPS4 [Portable UNIX Programming System] is a software environment (written in *ANSI-C*) which has been developed to allow efficient computational representation and analysis of such data.

¹In fact not only is it very hard to implement complex computations, it is nigh on impossible to prove correctness in the mathematical sense!

²Here we are advocating the idea of a living process which is capable of continual monitoring of both its own internal state and that of its environment, and which can act appropriately on the information it receives in order to optimize the resources available to it (and its computational payload). The biological realm is a rich source of potential behaviors for such an entity.

The **PUPS** environment can be used as a general development tool for database and stochastic classification applications. As the complexity of analytical biology problems may lead to computation times of several days or weeks even on powerful computer hardware and require the manipulation of complex relational data, the **PUPS** environment gives support for persistent computations by providing mechanisms for dynamic interaction and homeostatic protection of computational processes and persistent object storage in order to facilitate [parallel] interaction with complex data. In addition to this basic functionality, the PUPS environment may be integrated with other Open Source software systems such as the **MOSIX** cluster computing environment [see <http://www.mosix.org>] (which permits **PUPS** processes to be dynamically load-balanced within a computing cluster) and the Tennessee checkpointing library (which permits **PUPS** processes to be stopped, stored and then restarted without loss of context) in order to enhance its capabilities. Further information about the **PUPS** environment is available at the **PUPS** website: <http://riposte.usc.edu/pups> At the present time, the most significant applications written using the **PUPS** environment are **DAISY**, a trainable pattern recognition system, **ITG** a stereo reconstruction tool, and the *Smboltzmann/Seriate* family of neuroinformatics tools. Further details of these applications may be found at <http://riposte.usc.edu/pups/projects>.

References

O'Neill M.A. And C.C. Hilgetag, PUPS and CANTOR - A computational environment for dynamical representation and analysis of complex neurobiological data, Proc. Roy. Soc. Lond. A, Special Theme Issue on Neurobiological Databasing, Ed. R. Kotter, 2001.

Dawkin R. The Blind Watchmaker, Penguin Books, Edn. 1, 1986.

2.5 Comments to workshop

Mark A. O'Neill

Q: *What is the discipline you represent?*

A: Biological computing especially the use of homeostasis within parallel and network computer environments.

Q: *What are the pressing problems to be tackled in the medium term?*

A: In order to do the sort of things that I want to do, that is large scale self organizing databases, advanced generic modular pattern recognition, the biggest medium term problems are:

- Designing architecture which will support complexity: I am particularly interested in the concept of "soft hardware architectures" in which one can have self building networks of processors with emergent computational capabilities.
- Designing smart parallel compilers, possibly based on program slicing techniques – such tools are potentially capable of automatically transforming serial codes into a form which can be run on parallel/network hardware with significant efficiency.

Q: *What techniques are available to pursue solutions? Who is already applying these techniques?*

A: In terms of the sort of homeostatic computing environments I have been involved in developing, the principal users are bio- and neuro- informaticists: the environment was designed to support persistent neuroinformatic computations and has since been used to develop large scale bio-informatic

and database applications (see <http://riposte.usc.edu/pups/projects> for details (a description of the environments itself may be found at <http://riposte.usc.edu/pups>

Q: *Could different disciplines possibly benefit from using similar techniques?*

A: Yes – again talking from experience – the PUPS system has also been used to build applications in the GIS domain (and could also be used for large scale numerical codes, e.g weather modelling)

Q: *Where are possible synergies?*

A: Of course, very strong synergies with biological systems. At present we are only seeing the tip of the iceberg, in terms of what is possible for biologically inspired computer systems.

Q: *Are there promising general approaches requiring funding/backing?*

A: Yes.

2.6 A View on “Organic Computation”

Frank Pasemann

Frank Pasemann studied Mathematics and Physics, received his PhD in Theoretical Physics in 1977, his Habilitation in 1985. He is Professor for Theoretical Physics at the University of Clausthal-Zellerfeld since 1985. Worked on Mathematical Physics and Elementary Particle Theory. Changed his interests to neuroscience in 1990. Worked since then at the Research Center Jülich, the Max-Planck-Institute for Mathematics in the Sciences, Leipzig, and is currently scientific director of the TheorieLabor, University Jena. He will join the FhG Institute for Artificial Intelligent Systems (AiS), Sankt Augustin in 2002. His research interests include Nonlinear Dynamics, Complex Adaptive Systems, Evolution and Learning of Neural Networks, Behavior-Based Robotics.

2.6.1 General View

We expect that a new intellectual field of science like “organic computing” will try to understand the emergence of cognitive (what ever this means in detail) processes in biological and in artificial organisms. I think that multidisciplinary efforts have to be more precisely guided to the study of the relationship between structural organization of brains – their mechanisms for adaptation and learning – and the generated behavior of organisms in specific environments. Analytical investigations of biological systems – either bottom up, from the molecular level, the cell level, to neural circuits and whole brains, or top-down – let to an increasingly specialized and fragmented knowledge which still has not found to a satisfying understanding of this relationship.

We therefore propose a complementary synthetical approach to artificial neural systems to acquire additional data on the relation between brains and behavior. On the background of the neurosciences, this approach will be based on ideas and findings coming from fields like embodied cognition, artificial life, evolutionary robotics, dynamical systems theory, complexity theory, and others. As an example for this type of view on “organic computing” and as a brief description of my possible contributions to the discussion a sketch of one possible approach is given in the following.

2.6.2 A Modular Neurodynamics Approach

I. Cognition

Starting point is the assumption that the term “cognition” needs reference to a body and to an environment (embodiment, embeddedness). Such systems are understood as adapting, learning and acting in a sensory-motor loop. The physical properties of a specific body and a specific environment as well as the possible states of body and environment are understood as defining the *concrete boundary conditions* for the structural and functional self-organization of cognitive neural systems.

Remark: An essential point here seems to be a deeper theoretical understanding of adaptive complex systems. Complex systems are here *not* understood as pure (classical) physical systems. In reference to neural systems one has to distinguish between structural and dynamical complexity. Of course, an appropriate notion of complexity still has to be developed and corresponding mathematical (working) definitions have to be applied. This direction is followed, for example, by the “Neurodynamics Group” at the MPI for Mathematics in the Sciences, Leipzig.

II. Neurodynamics

A basic aspect of the approach is deduced from the neurobiological observation that brains have a highly recurrent connectivity structure. For a system with such massive excitatory and inhibitory feedback connections one has to expect a variety of complex dynamical phenomena. The richness

of dynamical behaviors provided by such systems can be found already for small recurrent neural networks with trivial neurons (i.e. additive, with sigmoidal transfer functions). They are described as families of *parameterized* dynamical systems (with parameters given by synaptic strength, bias terms, “slow” inputs, etc.).

Besides convergent behavior (like that of “classical” neural networks) one observes any kind of oscillatory behavior, quasi-periodicity and chaos. Many attractors - even of different types - can exist for one and the same set of parameters (multi-functionality), and one finds “generalized” hysteresis effects (short term memory), bifurcation phenomena (stability-instability of specific “mental” states), synchronization effects (selection of behavior relevant subspaces), clustering according to amplitudes, frequencies, and the like. This gives rise to the assumption that for higher-dimensional systems (larger brains) there is a whole unexplored ocean of dynamical phenomena, which is able to provide all the flexibility and abundance needed to generate something like cognitive behavior.

Remark: Dynamics of small networks in dependence of their (coupling) structure has been systematically analyzed over the last years – for instance in [1], [5], especially also synchronization properties [3].

III. Modularity

Besides the suggestion that biological brains have a modular organization (functional areas, hyper-columns of the cortex), modularity is also a good design strategy for artificial neural systems. Modules can be relatively “simple” networks, which can be incrementally added to a system. Thus, artificial cognitive systems should be realized as coupled recurrent neuromodules. Coupling structures can reduce as well as enhance dynamical behavior of composed systems. It may be useful to discern between structural, functional and temporal modularity. The last type refers to the fact that parts of coupled systems may have different functionality at different times.

Finally, modularity in coupled nonlinear systems will play the role of a productive metaphor: Neuromodules in an operating system can not be identified, neither structurally nor functionally!

A Working Hypothesis: Cognitive abilities of biological and artificial brains are based on complex dynamical properties of modular recurrent neural networks. They may appear as an emergence phenomena. Cognition is represented by global brain processes which are the result of interacting neurodynamical subsystems. Cognitive or “mental” states are represented by *basins* of corresponding (dynamical) attractors. Cognitive neurodynamics in an operating system is always a *transient dynamics*.

But: Theory tells us that *dynamical properties of (coupled) recurrent networks in general can not be known in advance*. Thus:

Cognitive neural systems can not be designed or constructed

in a classical manner. We therefore suggest to use

IV. Evolution and Learning

Evolutionary algorithms should be used primarily to develop the *recurrent structure* of neural networks producing behavior relevant dynamics. Pure parameter optimization - that’s what conventional genetic algorithm approaches are doing - is not enough. At the same time algorithms like *ENS³ evolution of neural systems by stochastic synthesis* [2] may at the same time also optimize parameters – although parameter optimization preferably should be done by convenient *learning rules*. Co-evolution of already developed, functionally segregated neuromodules should lead to effective coupling structures, creating composed systems with larger variability and complexity of behavior-relevant dynamics.

Behavior relevant learning rules for recurrent networks of general type do not exist yet. One possible way to derive them is to view neurons as “active” elements in complex systems.

V. Evolutionary Robotics

Behavior-based robotics allows to study neurodynamics related to behavior in well defined environments and/or to internal conditions. Interesting artificial systems may be realized as software agents (“screen creatures”) or physical robots (animates, biomorphs, etc.). Evolution of brains for behavior-based robotics (see for instance [4]) will allow to study *structured systems* of interacting neuromodules, and neural mechanisms for coordinating *multiple behaviors*. Being able to simultaneously observe the behavior of artificial systems acting successfully in given environments and to analyze specific aspects of their underlying neurodynamical properties, will possibly provide better models for cognitive processes and also a deeper understanding of biological brain functions.

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Q: *What is the discipline you represent?*

A: Physics, Computer Science and Electrical Engineering

Q: *What are the pressing problems to be tackled in the medium term?*

A: To build robust vision systems is a dream since long. And it will stay so, I am afraid, if the idealistic approach to information processing continues to be pursued. That approach consists in tackling the problem of building intelligent vision systems without sufficient experimental evidence on how nature's vision systems may function. Typically, one derives the theory of image recognition and understanding from general theories (information theory, signal processing theory, etc.) that have never been able to describe an intelligent system successfully!

What is necessary is the *experimental* investigation of how pulsed neural networks process signals and - more important - what constitutes information as well as information processing in these networks. By experiments I mean not only wetware, but also simulations of simple integrate-and-fire-neurons as well as synapses. By painfully observing the effects on the pulse pattern train of a network when presented with well-defined input signals will tell us a lot about what information processing is about. Clearly, experiments must be accompanied by modelling what is measured, and model hypothesis may inspire the right question to be asked by an experiment.

Q: *What techniques are available to pursue solutions?*

A: The first theory of information, I know of, was thermodynamics; here, entropy means information about how matter forms state patterns. Unfortunately, there is no simple translation of thermodynamics into pulse dynamics. But the basic approach may be copied: (1) start out from the equations of motions which are now the signal equations for neurons and synapses; (2) derive an expression for the total energy of the network parts of which are stored at the membranes, carried by the pulses transmitted or are input from external sources; (3) check for what is reproducibly measurable from the network, ie. for the transition from microdynamics to macrodynamics: mean value of the energy, distribution of firing patterns, entropy and derivable quantities like pulse rates; and so on...

Q: *Who is already applying these techniques?*

A: This way, we were able to define information and information processing. Information resident in a network is given by the entropy of the network which, in turn is represented by the distribution function of firing patterns occurring in the network during a sufficiently large time of observation. Information processing by a network receiving input from another network, then, is the mapping of entropy of the fostering network into entropy of the receiving network. In other words, information is carried by stochastic sequences of firing patterns, and information processing is the production of new stochastic sequences of firing patterns by a neural network being input a stochastic sequence of given firing patterns. A recent result of ours explains how synchrony of neurons appears when the same features are presented to the neurons. For instance, in the case of a spot detector, all neurons getting input from the spot (the pixels of which have equal illuminosity (10% noise)) respond with one and the same pulse rate. It is shown that a wave front of firing events continuously runs over the spot with a frequency given by the pulse rate. Hence, the distribution function of firing patterns is sharp, but not like a delta peak: synchrony is an effect at the macro scale, it doesn't happen at the micro-scale of the signal equations. Other features than a spot call for other connections by synapses than just next-neighbour connection as was the case for spot detection.

My group seems to be performing these techniques for the first time, to the best of my knowledge.

Q: *Where are possible synergies?*

A: Experiments with real neurons and synapses will give more insight into the adaptation behaviour of synapses. Hebb's rule is best summoned by locality, causality and simplicity. The results for synchrony mentioned above were received with a rule saying weights should grow if at the time of pulse reception more than half of the threshold is reached, otherwise fall. Interaction of synapses would highly influence pulse dynamics, and a fortiori, information processing. So - do other synaptic rules exist than the one supporting synchrony? (more synergies in an update)

Q: *Are there promising general approaches requiring funding/backing?*

A: Yes. I believe our experimental-theoretical work on information processing by pulse neural networks is a fundamental approach that justifies and needs general funding.

Chapter 3

Neural computation, soft computing, robotics

3.1

Wolfram Erlhagen

My scientific interests range across cognitive science, theoretical neuroscience and autonomous robotics. My research deals with the problem of the interpretation of neurophysiological and behavioural data using methods from non-linear dynamics and mathematical optimisation. More specifically, I have worked in the domain of motor behaviour and the domain of visual perception with the aim to establish a theoretical framework which allows to bridge both levels of description in brain research. A second major interest is the transfer of theoretical concepts developed to explain experimental data into the domain of autonomous robotics.

Over the last decades facts about different aspects of the vast area of neuroscience accumulate at an increasing pace, but the insights gained about the actual principles underlying the operations of the brain as the “most awesome of all organic computers” have accumulated much more slowly. One reason for this is the specialization of individual neuroscientists, each studying the brain at a particular level of description, tied to the techniques and methods available. I completely agree with the general statement in the letter of invitation that only a combined effort of behavioural sciences, neurobiology, physical, mathematical and computer sciences may develop and apply the advanced tools and approaches that are essential for major advances in the understanding of the structure and function of the nervous system. Without any doubt, simulation studies and formal mathematical analysis have constituted a complementary methodology to integrate experimental observations in order to formulate testable models of aspects of neural function. However, it seems to me that I am more sceptical about whether we are already “equipped with a very appropriate set of (theoretical) skills and perspectives” for the understanding of more complex problems. I will try to illustrate my scepticism using the example of an application of mathematical information theory in theoretical neuroscience. In recent years, an attempt has been made to reconstruct from single neuron activity or neuronal population activity external physical variables such as position, size and colour of an object on a screen. An important question, which has been addressed is the accuracy of the reconstruction as a function of the number and type of the individual cells. The focus on physical information processing neglect the experimental findings in behavioural studies that a physical stimulation on the retina is neither sufficient nor necessary to create a percept. A second problematic issue is the definition of a hierarchical processing architecture based on experimental data (as suggested in the description of the symposium). Often this problem raises not because of incomplete data sets but because the experimental findings reveal a tight, bi-directional coupling between individual processing stages. In summary, there is still a need for substantial improvements on the conceptual level before we can

expect to design a new generation of organic computers based on our theoretical understanding of brain functions. A third comment concerns more the technical skills necessary for the new computing paradigm. As an example, non-linear dynamical systems have been proven to provide a limited set of structural and functional constraints for the architecture of computing systems. The concepts of bifurcation and stability allow, in principle, for flexible adaptation. However, a complex hierarchy of layered systems with adaptive connections call in question the structural stability of the whole system. A often very sophisticated mathematical analysis is necessary to deal with this problem. All together, despite the enormous growth in the number of facts and regularities observed in experimental and theoretical neurosciences, the current state of the field does not allow an efficient dissemination of these observations and especially their integration in coherent theoretical frameworks.

The design of complete “living” artefacts endowed with the ability for behaviour evolution and life-long automatic adaptation may be a research program which finally will also help to understand the complexity of the nervous system. Creating a two-way interaction, hypothesis on brain function can be tested using robot technology, and robot technology can profit from the gained insights. The work with a complete artefact will thus help to gain the perspective of a more principled approach for a new computing paradigm.

3.2

Martin A. Giese

3.2.1 Self-description

I have studied electrical engineering and psychology at the Ruhr-Universität Bochum. I received my diploma and PhD degree from the Institute for Neuroinformatics in Bochum working on nonlinear dynamics models for visuo-motor coordination and the perceptual organization of low-level motion perception. Since my postdoctorate at M.I.T. my main field of research is high-level vision. After building up a research Lab for HONDA R&D America's in Cambridge (USA) I changed to Tübingen where I am now leading a research group for "Action Representation and Learning" that is based jointly at the Department for Cognitive Neurology and the Max-Planck Institute for Biological Cybernetics.

3.2.2 Main Interests

My research focuses on computational methods for the learning-based representation of complex movements and actions. Using methods from theoretical neuroscience, machine learning, dynamical systems theory, and computer vision we investigate, on one hand, the representation of complex movements and actions in the brain. This includes primarily theoretical modeling, but also psychophysical experiments. On the other hand, we are developing technical methods for the learning-based representation of complex movements that can be applied in the context of computer animation, robotics, and for the analysis of data from neurological patients.

3.2.3 Statement about "Organic Computing"

The visual cortex can be seen as an impressive example of organic computing. At the same time it is one of the most intensely studied parts of the brain. In my view, the high performance of information processing in the visual cortex is based on the combination of two general principles: (1) Efficient encoding of high-dimensional information and complex pattern spaces, and (2) flexibility by controlled dynamic adaptation of the system structure.

At least for high-level vision the first principle is a necessary requirement. The underlying data, like complex visual objects or actions, are elements from high-dimensional pattern spaces with complex structure. Direct modeling of such patterns with heuristic methods is computationally very expensive or even impracticable. The same is true for standard systematic approaches, like approximations of patterns with complete sets of basis functions ("Fourier transform"). In consequence, learning techniques have become an essential tool for the representation of complex patterns in computer vision, and recently also in computer graphics.

Learning is tightly linked to the problem of generalization. Learning methods requiring hundred thousands of training examples are not appropriate for the solution of many practical problems, nor do they provide a plausible model for learning in the brain. In machine learning the problem of controlling the generalization error with a limited number of training examples has become one major topic. A fundamental insight is that efficient generalization requires a joint control of the representation accuracy and the complexity (capacity) of the models that are used for encoding. Regularization theory and Structural Risk Minimization provide an elegant mathematical framework that allows a treatment of this problem in the context of simple statistical problems, like classification and regression. However, only a small number of problems in vision can be mapped onto these simple statistical problems.

The most striking difference between present machine learning systems, even if they are based on hierarchical structures (trees), and the brain is the high flexibility and adaptivity of the cortical

system. The idea of a control of representation accuracy and model complexity seems, however, to be fundamental for the visual cortex as well as for organic computing. Beyond being crucial for efficient learning, it might allow to circumvent the so-called “binding problem”. This problem arises when objects (like visual stimuli) with a large number of relevant feature dimensions are neurally encoded without control of representation accuracy. In this case the amount of required computational resources explodes with the number of encoded dimensions (curse of dimensionality). A frequent solution of this problem is to encode only small groups of features jointly in separate feature maps, implying the non-trivial problem that later on the information in multiple feature maps must be integrated into a coherent percept.

The second important principle in the visual cortex seems is dynamic adaptivity. Adaptivity is required to integrate different sources of information, e.g. visual cues, with varying degrees of reliability, and also for the integration of prior knowledge of the system with the stimulus information. To realize adaptivity two major approaches have been developed in computational vision and in neuroscience. In computer vision probabilistic approaches, e.g. using a Bayesian framework, are dominating. Such approaches can be easily linked to statistical descriptions of data, and allow to benefit from a variety of standard methods that have been developed in the context of signal processing. The definition of statistical priors makes it possible to integrate stimulus information with system intrinsic knowledge. In addition, information can be dynamically processed using stochastic descriptions of dynamical systems such as Kalman filters, CONDENSATION, and Hidden Markov Models.

A disadvantage of probabilistic approaches is that a control of the dynamics and convergence behavior of complex systems that integrate many different modules is difficult. At least some intuitive approaches for the solution of these problems exist for a second approach, dynamic neural networks. This framework is dominant in neuroscience for modeling of adaptive processes in the brain. The distributed representation of information in neural networks is in several aspects similar to a probabilistic encoding of information. In addition, dynamic neural representations allow for simple cases an analysis of dynamic and self-organization phenomena. The drawback of dynamic neural systems as general framework for organic computing” is that the system structure is often based on choices of the modeler, or on constraints resulting from neurophysiology which are not available for more general problems. A combination of Bayesian statistical approaches with methods from nonlinear neural network dynamics might be interesting as a starting point for the study of adaptivity in learning- based representations of information.

In terms of synergies, statistical problems that can be treated in the context of statistical learning theory seem to be useful for an automatic analysis of large data sets in molecular biology aiming at the detection of highly predictive feature combinations. Insights from computer vision and dynamic neural networks may be useful for treating adaptivity in other systems that require distributed representation of information with self-organization and flexible integration of multiple information sources. The study of the visual system, and in particular of attention, is likely going to contribute to an understanding of the computational meaning of hierarchical structures. I also expect new insights from this field how adaptivity can be realized in complex systems. A combination of learning theory with mechanisms for the realization of adaptivity appears to be a fundamental problem that might have important general implications.

3.2.4 Possible Contribution

The representation of complex movement patterns (biological motion) provides an example for a computational problem that is solved in very different ways by the brain and by algorithms in computer science. In the biological system encoding of high-dimensional data and adaptivity in hierarchical structures are crucial for the solution of this problem. In addition to a discussion from a computational perspective, I could provide some psychophysical demonstrations that illustrate the performance and adaptivity of the visual system for the solution of this recognition problem, both of which are out of reach for the existing technical solutions.

3.3

Thomas Martinetz

3.3.1 Affiliation

The Institute for Neuro- and Bioinformatics (INB) of the University of Lübeck is interested in the principles of information processing in biological systems and their transfer into artificial systems. Besides the information processing in the nervous system or within a cell this also includes the information processing in ensembles of biological individuals which leads to what is known as swarm intelligence. All these systems employ the structure and the dynamics of networks for computation and adaptation. Currently, the research focus of the INB is in Neural Networks for Machine Learning, regulatory networks in the cell controlling gene expression and swarm intelligence, e.g. for RoboCup.

3.3.2 Some “uncensored” thoughts on Organic Computing

Today's von Neumann Computers can be seen as dynamic systems. The state of the system is determined by the state of the memory, and the dynamics is determined by the processing unit which manipulates the memory depending on its content. The dynamics is fixed and cannot be changed. Most of the time the system stays in a fixpoint. When we start a computation, we put the system in a certain initial state, from where the state starts a trajectory through the state space determined by the system dynamics. The initial state is determined by what we want to compute, which includes the data and the algorithm. Certain points on the trajectory then yield the results of the computation. Usually this is the fixpoint which is reached at the end. The underlying dynamics is relatively simple and we know it completely (of course, we designed it). In particular, the change of the state only depends on a few coordinates within the high-dimensional state space, and with each time step the state changes only in a few dimensions. This is the characteristic of the serial von Neumann computer.

Organic systems are dynamic systems, too. Can we exploit their dynamics for computation? Organic structures emerged during evolution simply because they developed sufficient stability. Stability is their “purpose”, not computation. But to achieve stability, these structures employ adaptation, a behavior which we associate with computational capabilities.

If we look at a simple cell, different genes are expressed, i.e., different proteins are produced, depending on the environmental challenge the cell has to cope with. The situation is very similar if we look at the nervous system. Different neural activities are triggered to react on the situation which might destroy the organism. If we think in terms of dynamical systems, in all these cases through adequate sensors certain aspects of the environment are part of the system state. Within a cell, the state can be described by the concentration of each protein. A certain environmental situation might then lead to an increase or decrease of certain proteins. This sets the system into a certain state from which the system dynamics proceeds its trajectory through the state space. Only if this trajectory stays in a certain realm of the state space, we regard the respective organic structure a being still existent.

These regulatory networks in the cell and neural networks in the nervous system are structurally very close. The expression level of a gene corresponds the activation level of a neuron, and the transcription factors (which itself are products of gene expression) with binding sites on the promoter of a gene correspond to the input of a neuron. To exploit these organic systems for computation in the sense we use today's computers, one would have to understand the dynamics of such a systems completely enough to be able to set an initial state corresponding to the computation one wants to perform. The result would again be given by the final state.

There are several major challenges to be solved. First of all, the system dynamics has to be understood. This is extremely difficult, since all these organic systems consist of many single elements

which interact with each other in a nonlinear way. In contrast to von Neumann computers, the change of the system state depends on the projection on a much larger subspace, and with a time step the state changes in many more dimensions. In other words, in contrast to von Neumann computers parallel computation takes place. This complex network dynamics is the difficulty, but at the same time the reason for the high potential of organic systems.

Secondly, one has to be able to keep this dynamics under control. It is a well known fact that systems with this structure exhibit chaotic behavior. Only slight deviations in the state space might then lead to completely different trajectories, i.e., results of the computation. Nature has found means to keep these systems under control. Therefore, solutions for this problem seem to exist.

Thirdly, techniques are necessary which allow to determine the state of the respective organic system. For example, DNA-chip technology now allows to measure the expression of certain genes in a tissue, although still very imprecisely. Microarray technology now allows to determine simultaneously the activity of many neurons in neural tissue. With being able to determine the state, we also have to be able to set the system into a desired state, i.e., the state which corresponds to the computation one wants to perform.

Although all these challenges are major problems on their own, the fourth one I regard as the main one: How can we obtain a compiler for such systems. Even if we can determine and set the state of our organic system, even if we completely know and are able to control its dynamics, we still have to find a means which translates a desired computation into the corresponding state trajectory of dynamic system. If we had a general solution, we could employ any dynamic system for computation. This does not mean, however, that with any dynamic system any computation can be performed. Similar to special purpose computers, most dynamic systems would be restricted to special computational tasks.

Even the two organic systems mentioned before, the cell and the nervous system, exhibit huge differences in their complexity. The dimensionality of the state space of a cell is in the order of the number of genes (proteins) it can express, i.e., of 10.000 - 100.000. To describe completely the state space of a neural network, not only the activity of each neuron, but also the state of each synapse has to be considered. This leads to a state space dimensionality of rather 10.000 - 100.000 billion. The dynamics, of course, is an additional complexity factor.

Who knows, perhaps it would be easier to exploit organic systems of "higher order", like ant colonies or human social organizations. Instead of using skin tissue for computation, perhaps one will employ the complicated network dependencies between small, medium and global enterprises for solving computational tasks.

3.4

Klaus-Robert Müller and Jens Kohlmorgen

Q: *What is the discipline you represent?*

A: Neural computation, data analysis, signal processing, pattern recognition.

Q: *What are the pressing problems to be tackled in the medium term?*

A:

- organizing and understanding (by learning)
 - very large amounts of high-dimensional data (genome, text, web, video, brain signals etc.)
 - very small sets of high-dimensional data (e.g. microarray measurements)
- how to structure “unstructured” data
- how to visualize and explain high-dimensional large/small data set
- designing better user interfaces (e.g. by using more (neuro-)physiologically designed devices)

Q: *What techniques are available to pursue solutions?*

A: Machine learning, probabilistic modeling, state-of-the-art signal processing, organizational principles from neuroscience. Though, robustness, explanatory power and reliability of the techniques are not yet optimal and clearly need further improvement.

Q: *Who is already applying these techniques?*

A: As this is “trendy”, many groups are working in this field.

Q: *Could different disciplines possibly benefit from using similar techniques? Where are possible synergies?*

A: Real world applications in general provide a sanity check to mathematical theories or algorithms. Moreover understanding organization principles from the brain or the cell will give a boost to solving larger and more difficult application problems.

Q: *Are there promising general approaches requiring funding/backing?*

A: As the pressing problems are still not solved, there is a great need for interdisciplinary research that will provide the necessary cross-fertilization to move beyond existing borders.

3.5

Erkki Oja

Q: *What is the discipline you represent?*

A: Neural computation, data analysis, signal processing, pattern recognition.

Q: *What are the pressing problems to be tackled in the medium term?*

A: In short and medium term, fast and reliable computer systems to manage and analyze the vast data masses (text, images, measurements, digital sound and video, etc.) available in databases and the Web. How to extract information and knowledge, to be used by humans, from this kind of scattered data storages? Another problem are the advanced user interfaces using natural language, speech, and visualizations.

Q: *What techniques are available to pursue solutions?*

A: It seems that some kind of machine learning, as well as probabilistic modeling, are necessary or at least highly useful to tackle such problems. This machine learning is unsupervised and aims at finding a suitable compressed representation of the data. When models are learned from the actual data, they are able to explain the data, and meaningful inferences and decisions can be based on the compressed models.

Q: *Who is already applying these techniques?*

A: This is the recent trend in neurocomputing with many research groups all over the world.

Q: *Could different disciplines possibly benefit from using similar techniques? Where are possible synergies?*

A: The techniques of neurocomputing and soft computing are rather generic and can be used in a variety of different real-world problems. This is also closely connected to computational neuroscience in the sense that artificial systems provide a "reality check" for some ideas about the real brain. If we can really find out the learning algorithms that the brain is using, this will have an enormous impact on both neuroscience and on the artificial neural systems.

Q: *Are there promising general approaches requiring funding/backing?*

A: The "golden age" of neurocomputing funding seems to be over, partly because many of the promises were not achieved. But those hard problems did not go away. Compared to the the 1980's, we have now improved methods and vastly increased computational power. Also, there is a significant amount of new knowledge about the real brain given by the new instrumentation and imaging techniques. The situation has really changed in 20 years, and something new will come out of this.

3.6

Ingo Rechenberg

3.6.1 Some previous results in bionics research

The task of Bionics is the analysis of biological processes and structures and their synthesis for innovative engineering design. The idea of bionics is based on the fact of evolution and coevolution in nature.

It has proved successful building on biological evolution. Fishes and birds have developed till now unknown fluid flow refinements, such as riblets to reduce skin friction, spread pen feathers to decrease the wing tip vortex and reflux bags to prevent flow separation. The current research in Berlin shows that the microstructure of the scales of the sand fish, living in the Sahara, reduces the solid friction around 20% when compared with polished steel. Finally, The practical application of Evolutionary Computation in optimization and the design of biological inspired Neural Networks proved the effectiveness of organic computing methods.

3.6.2 Future research of the Institute in Berlin

1. **Primitive imitation of parts of the brain by means of *massive* Neural Networks.** After the present level of knowledge only a Nested Evolution Strategy (a current development of the evolution strategists in Berlin) may be able to create a neural Network containing millions of artificial neurons.
2. **Research on Distributed Autonomous Mobile Systems (DAMS).** Living beings seldom operate solitary. They form groups whose network structure offers them an evolutionary advantage. Examples are slime fungi, bird, fish, insect swarms and ant colonies. It is a challenge for the research in the field of Organic Computing to create robot swarms, which move and act in a bunch Besides the task of robot soccer, a hard benchmark problem may be the creation of a real swarm of MAVs (Micro Air Vehicles) moving in an orderly formation. Researchers in the USA and Europe discuss this problem today. The Institute in Berlin has started a project in this field called "Hesmo Robotics" ($\epsilon\sigma\mu\rho$ = swarm of bees):

1. to keep by means of a multi-sensor system a real swarm of driven balloon-robots together
2. to program a real balloon swarm to act in a cooperative manner

It is possible to present some preliminary results at the Symposium.

3.7.1 Affiliation

The Future Technology Research Division of Honda R&D Europe at Offenbach, Germany, is interested in the identification of principles from biological information processing and their application to the design and optimisation of technical systems. Currently, the focus is on the development of a hierarchical neural control structure for an adaptive humanoid vision system that incorporates biological learning, robustness and stability. At the same time, we explore the principles of evolution and research the combination of neural processing, phylogeny and ontogeny. Furthermore, evolutionary technology is used for the optimisation of complex engineering problems in design and process control.

3.7.2 Some informal thoughts on organic computing

Biological systems in particular those involved in processing information are far from being understood in the physical sense (i.e., described by a few governing principles and observables), in the technical sense (i.e., we can drive the system towards a state or attractor where it does something which we want it to do) and certainly in an constructive sense (i.e., we cannot build one). Thus, new ideas and approaches are needed and organic computing tries to accomplish this by collecting expertise from different disciplines and by awakening physics from its decades of sleep with regard to the life sciences. Parenthetically, it is interesting to note that traditional computer science is trying hard to incorporate fundamental principles of organic computing (as noted in the introduction provided by the organisers) like self-healing, stability and self-organisation as a governing principle into today's technology, see e.g. the eLiza project by IBM. Although the approach is half-heartedly, it demonstrates the urgent need of today's information technology to realize the principles which biological systems demonstrate seemingly effortlessly.

Organic computing from my point of view should concentrate on three different principles or directions.

The inseparability of hardware and software As pointed out in the introductory text, traditional computer science has taken a fundamentally different path for the construction of information processing systems than biology. Nevertheless, as the complexity¹ of the computing devices grows, the need for properties of biological systems, like e.g. stability and robustness increases (as indicated above). One such major difference is the distinction between hardware (the universal computer) and software (the algorithm on the tape which is read by the computer). This type of generality is very different from the generality of biological information processing systems. Looking at the neural system, the brain hardware (in the sense of tissues and cells, which we can touch and feel) should not be seen as a particular type of hardware, which is most feasible to run "brain software" on, but instead it is the *manifestation* of the organisation of the neural computation process itself. Ironically, this property is often ignored in the design of neural hardware. No algorithm is executed on the huge set of interconnected neurons, the network is the algorithm. Biological structures are very specialised for the type of computing they perform. Generality does not manifest itself in the final organisation of the structure but in the process of design, it is inherent in the learning and computing process. Thus, instead of building

¹What is complex? Firstly, everything is complex up to that moment when we understood how it works. Secondly, for a more useful working definition, we will apply the mesoscopic point of view, i.e., a complex system is one that consists of "many" strongly interacting sub-systems. Here "many" means too many for differential equations (i.e., more than two?) and not enough for a useful statistical description like in thermodynamics.

one general computer, biology builds specialised information processing systems which are continuously interconnected on paths which are realised via development, learning and structural plasticity. This way, efficiency and robustness are a result of the design not a constraint.

So far we have either aimed at extracting algorithmic principles of biological systems and execute them on our computing machines (like in conventional neural networks research) or we have used algorithmic principles of computer science like Boolean logic and imposed it on new hardware structures like quantum or DNA computers. Both ways, we separate the inseparable and in turn we probably lose a large part of the exciting properties of biological information processing. Research into organic computing can provide a way out of this dilemma.

Development and growth Biological information processing systems differ fundamentally from technical systems in another respect. The construction phase and the operation phase largely overlap. If we take structural learning as an integral part of organic computing into account, the construction period even fully embraces the operation time of the system. In technical systems both are separated and the operation time is even stopped in between for servicing. Development and growth reflect to a certain degree the evolutionary process and it is as much a constraint that biology had to cope with as it is a way to combine such contradicting properties like flexibility and robustness or variability and stability. Gradual development of system complexity leads to architectural principles which cannot be understood by solely analysing the working system itself. The integration of new modules and functionalities into existing structures might even lead to a prolonged period of learning and in turn to a higher degree of variability under changing conditions. Already, the analysis of these principles for simulated “software” systems can lead to interesting insight, e.g. Sendhoff et al. [1]. Even more is to be expected from research into organic development and growth. Although activities are still sparse compared to “non-organic” computational intelligence, programs on such topics as self-assembling and growing materials could be augmented by the information processing aspect. The combination of organic growth and biological information processing is likely to give unique insight into the organisational principles which cannot be achieved by any of the existing disciplines alone.

The fitness principle of biological information processing systems The tautology of the “survival of the fittest” has haunted evolutionary biology for a long time and although with respect to molecular evolutionary biology (see M. Eigen [2]) several successful attempts have been made to resolve it, it still remains to be a problem at many different levels of organisation. Organic computing systems are a result of an evolutionary process and without taking the designing process into account we are unlikely to understand the product. Organic computers compute and ultimately this must either be an accident of evolution or a driving force. Let us assume the latter is the case, is it possible to find a macroscopic observable with a microscopic justification (of course the notion of entropy springs to mind) which is the driving force of the process? Or the other way round: What describes the evolution of organic computers? If we find such an observable we could use it for all three levels of description, the physical, the technical and the constructional level.

Surely others will add their directions and principles and people will argue (probably with good cause) against the ones described above. However, above all we should not run into one potential trap: We have not yet gained satisfactory understanding of any of the related fields ranging from cognitive neuroscience to molecular biology, thus we are taking on a more complex problem before solving the simpler ones. Synergies between disciplines are often quoted but success stories are rare. In my view organic computing, has much potential but the endeavour will be enormous.

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3.8 Approaches and problems in the study and design of modular systems

Jochen Triesch

3.8.1 Introduction

In the study of complex systems such as the living cell, the human body, or the brain, modularity is a ubiquitous theme. Practically all complex biological systems exhibit some degree of modular organization and it can be argued that only these are the blue prints that were able to evolve efficiently. Research in recent years in a number of fields such as neural computation, theoretical biology, and artificial life has repeatedly pointed to emergent phenomena in complex systems that are hard to predict from studying the individual subsystems in isolation (social insects or the brain are good examples) and that these phenomena play an important role in the success of natural systems.

In computing (and engineering in general) large systems are also invariably organized in a modular fashion and this is indeed the only way the design complexities of large technical or software systems can be mastered. The design methodology for such systems is typically that of “divide and conquer” where the problem to be solved by the system is divided into sub-problems to be solved by individual subsystems, which may be divided into sub-subsystems solving sub-subproblems and so forth. The success of this approach has been tremendous. It lies at the heart of the technical advances of our modern civilization. What I would like to argue here is that despite its tremendous success the divide and conquer approach to building modular systems has serious problems and that we can learn from biology how to overcome them. Also, it can be argued that the dominance of the “divide and conquer” methodology in the sciences may hinder progress in the study of complex biological systems by creating the illusion that complex systems can be understood by studying their subsystems in isolation, just as an engineer would be able to design a subsystem with only very little knowledge about other subsystems involved, and then trying to put the pieces back together.

In the following I will elaborate on two important points where today’s computing systems are differently organized from their biological counterparts and trace back the resulting problems to a “blind” application of the divide and conquer methodology.

3.8.2 Flexibility

Today’s computing systems are stuck in inflexibility. They typically do exactly what they were designed to do at the outset (and often not even this) but nothing else. Even if a program contains components that could be re-combined to solve a different task, the interfaces and control structures are fixed and do not allow this. My electronic mail tool, for example, has no problem sorting all the messages in my “INB ox” according to their date, the name of the sender, etc., but it does not allow to sort, say, the lines of an individual message, although the necessary algorithmic structures are certainly present.

Biological systems, in contrast, exhibit a great amount of flexibility. The brain learns to flexibly coordinate its competencies on the spot to solve problems that it has never encountered before. We routinely handle tasks (like driving a car) that evolution cannot “have known about”, when our human ancestors appeared on the evolutionary landscape – the time of our brain’s “design”. To this end, the brain’s modules can each participate in many different tasks (one subsystem, many tasks) with the control and communication between modules self-organizing on the spot. This is in sharp contrast to a system designed in the divide and conquer style, where a module is tailored to a particular pre-specified sub-task (one subsystem, one task), and its interfaces are designed with nothing else in mind. We need to understand the basis for this “organizational flexibility” in brain like systems and learn to model it and apply it in artificial computational systems. We need to learn how to build systems

less with the intent of pre-planning every allowed task and implementing its solution but more with the intent of giving the subsystems a capacity to flexibly self-organize so that they may learn to solve tasks that we did not even think of initially.

3.8.3 Robustness

Today's computing systems are very unreliable. One reason for this is that when designing a system in a divide and conquer fashion, one is led to specify exactly one solution to each sub-problem. When for some reason, this solution does not work in a particular situation, the consequences are often fatal – the system “critically depends” on the proper functioning of the subsystem. The brain, in contrast, has an amazing ability to look for many ways to solve a problem in parallel, flexibly using whatever module seems to contribute to the solution. A good example for this is human visual perception, where many “cues” like stereo vision, shape from shading, structure from motion, etc. are used to infer the three dimensional layout of the world, and the brain flexibly integrates whatever is available and agreeable, automatically suppressing cues that fail and thus not critically depending on any single cue. Accordingly, our computing systems should be designed such that they do not immediately break down if a sub-system fails. This idea is fundamental to the field of neural networks and the benefits of distributed representations (graceful degradation upon failure of single neurons) have been well studied. However, we need to extend this idea to the domain of how dynamic networks of modules can generate complex behavior in a robust fashion.

Of particular importance will be the study of modular systems whose subsystems operate concurrently. While the dominance of the single processor computer has kept the design of parallel systems from becoming a main stream topic in computer science, this situation may change soon. But how can we design parallel systems that are robust to the unexpected failure or sluggishness of individual subsystems? The brain seems to have mastered these problems. I believe that the key lies in a style of computing that may be described as “anytime in/anytime out”. First, computations in individual modules must be structured in such a way that new inputs from other modules are integrated seamlessly into the ongoing computations. Second, individual subsystems must be ready to output “the current best guess” (given the information received and processed so far) at any time. A computing architecture like this should exhibit robustness to the occurrences of deadlocks.

3.8.4 Summary

I have argued that two problems of today's computing systems, the lack of flexibility and robustness, are rooted in a “blind” application of the divide and conquer methodology to design modular systems. Biological systems have overcome these problems and we need to better understand and model these remarkable feats in biological systems. On the computing side, while it would be foolish to throw the divide and conquer methodology over board all together, it needs to be augmented by ideas taken from biological computational systems. To this end, I have discussed three design principles: 1) a self-organized collaboration of flexibly coupled modules with a flat control hierarchy instead of rigid interfaces in a strictly hierarchical architecture, 2) the avoidance of “critical” dependencies among subsystems, and 3) an “anytime in/anytime out” computation scheme for concurrently operating subsystems.

3.9 Some Ideas about Organic Computing

Laurenz Wiskott

Well, I have been thinking about a possible position statement for the symposium on organic computing for quite some time now, but I still feel that I cannot provide any particularly qualified text. So be warned that this is a rather naive statement, in the sense that I have no experience in hardware issues of organic computing and that I did not take the time to educate myself by reading related papers. I have some experience in neuroinformatic, but I don't feel like speculating on that, since, as far as I understand, the focus of the symposium is on combining and communicating between these fields rather than pushing forward any single discipline. I also feel that ethical issues should be raised, although I have not much experience on that either. So here are some unqualified speculations and fragments on hardware-software and ethical issues of organic computing in the (partly rather far) future. Maybe they will induce some qualified thoughts on the reader's side.

3.9.1 Hardware-Software Issues

It appears to me that with fundamentally different and much smaller computing and communication hardware, such as molecules and nanotubes, it will not be feasible or economical anymore to reliably produce a detailed layout of these elements on a chip (or whatever it might be called). Thus it will be important to develop software that can run on unreliable hardware. Some steps in this direction have already been made based on the classical silicon chips.

If one thinks along these lines a bit further, one might find that it would be even more efficient if one gave up the idea of producing a chip with a detailed layout altogether. The goal then would be to produce something that has as many computational elements as possible in a statistically reasonable configuration. By this I mean that the different types of computational molecules and nanotubes are placed such that as many molecules as possible are connected in a way that allows communication between them and yields as many computational degrees of freedom as possible. I guess this would most likely be a three-dimensional structure, let's call it a lump in contrast to a chip. That way one might be able to produce enormous computational power at very low costs, and it would not matter at all, if only 10% of it or less could actually be used for computation.

The problem, however, would then be to program this 'computational lump' (colump). This, of course, requires an interface. So let's imagine a thousand (or many more) 'wires' that are connected to the periphery of the colump. These are the technical means of communication with the colump (I see, this is not particularly innovative). What would be mechanisms by which the computational properties of the colump could be modified, i.e. how could it be technically programmed?

- (i) One way might be to physically change the colump, e.g. by applying strong currents to burn away parts of the colump (quite brutal).
- (ii) It might be possible to grow additional computational elements on the surface or within the chip. This growth could be guided by geometrical constraints or, for example, by activity levels within the colump.
- (iii) By applying global voltages or light of specific spectra to the colump, one might be able to influence the computational properties of all elements on the chip (quite unspecific). This could be used for resetting or controlling the overall activity or plasticity.
- (iv) Another way would be to program individual elements to do one or another computation (quite unrealistic, since individual elements are hardly addressable).
- (v) Finally, the state of individual elements could change based on their computational experience, much like local learning rules in neural networks (feasible and specific, but not well controllable).

The hardware as imagined here would not permit classical programming in any way. A colume would be too complex to tell it in detail what to do. Also, there would be no way of downloading a program, since the computational elements would not be well addressable and each colume would be different in any case. Notice that there is no clear distinction between soft- and hardware anymore. So, how could the colume be taught to do something useful, with the technical mechanisms outlined above? I see three possibilities that will have to work together: configuring, self-organization, and teaching.

Configuring: The mechanisms (i) to (iv) above would all be different ways of configuring the colume to increase its performance and adapt it to specific needs. (i) to (iii) are all quite unspecific. (iv) is specific but probably applicable only in rare cases. (i) and (ii) would result in permanent configuration changes while (iii) and (iv) could be used for reconfigurations on a fast time scale. In general, I think, configuring the colume could only set the frame within which more refined techniques can be applied.

Self-organization: The states of the computing elements themselves are probably the best signals to modify the computational properties of the elements. This is very much in the spirit of neural network learning rules. By self-organization I mean a process by which the colume changes its computational properties without any specifically structured input.

Some rather unspecific input will be needed to provide energy (?) or to guide the colume through different phases of the self-organization process.

- (i) One principle of self-organization could be to reduce redundancy between computing elements by a learning rule that makes state patterns of connected elements statistically independent. This could serve to increase the number of computational degrees of freedom in the colume.
- (ii) Another principle could be just the opposite. It might be favorable to have local redundancy to make computation more reliable or to improve the effective connectivity. By the latter I mean the following: if a single element is only connected to a few other elements, a group of tightly coupled elements would be connected to many other groups of elements, which would be advantageous. A learning rule could increase local correlations and reduce global statistical dependencies simultaneously.
- (iii) Self-organization could also be used to improve communication within the colume by establishing long range connectivity and connectivity to the communication 'wires'. For example, a learning rule could favor propagation of states through the colume and by that establish signaling pathways.

Teaching: Configuring and self-organization can only prestructure the colume, so that it has advantageous properties for the main teaching phase. Teaching would be technically similar to self-organization with the difference that structured input is used so that the colume can adapt to particular data and environments. This could be controlled by some global techniques of configuring as described above.

What types of computation could be realized in this way? Some possible computations are known from neuroinformatics, first of all associative memories, e.g. Hopfield nets. These memories not only provide storage capacity but also some computational power in that they complete stored patterns from incomplete cues. This can also be used for temporal patterns such as speech. One could imagine a little device, with which you can store some acoustic information and then recall the information with incomplete cues such as just the first few words of a sentence or story. This might be useful as an address book, where you just say the name of a person and the device completes the address and phone number. These types of networks could also perform some more complicated computation, such

as finding similar patterns, grouping patterns etc., so that the device structures the stored patterns in some reasonable way.

Due to the homogeneity of the columns, it would probably be difficult to implement very complex computations which require very different types of computation working together. It would then be necessary to combine columns of different characteristics like in our brain, where different quite homogeneous areas are connected and working together.

In summary, the art of 'programming' would be to select the right columns, connect them in the right way, configure them, run a suitable self-organization scheme, and then train the system.

These types of columns would probably not be suitable for applications that can be well formalized or where reproducibility is important, like in science. Imagine you do some simulations with a column and nobody can reproduce your results.

Problems also arise from the fact that programs cannot be uploaded from or downloaded onto these columns. There might be no way of making a backup, for instance, or it would be very difficult to delete some information without destroying other information (one might implement forgetting though). Your computer would really become a personal device, which cannot be replaced easily, because it had years of teaching and adaptation to your needs. It might be possible, though, to connect your old computer with your new computer for a couple of months and have the old computer teach your new computer all it needs to know to serve you best.

So much to the software(/hardware) issues of organic computing as I see them. If we will be able to actually build and 'program' such computers, there will also arise a number of ethical questions, which I discuss in the following.

3.9.2 Ethical issues

I would like to list some ethical questions here and give intuitive and quick answers without any further justification. It may well be that on a second thought I would come to a different conclusion, but I think it is useful to have some answers here, so that everybody can disagree with them.

Q: *If we are able to build organic computers of high complexity, will we still be able to understand them in detail?*

A: No!

Q: *If we don't understand in detail how a complex organic computer (COC) works, can we assess, how reliably it will work? If yes, how?*

A: Only in a statistical sense by means of test runs.

Q: *If we can not say with certainty, that a COC works reliably, are we all owed to use it to control sensitive processes, like flying a jumbo jet?*

A: Yes, if a COC works on average more reliably than a human or a conventional computer.

Q: *Can we control a COC with a conventional program to make it more reliable?*

A: Yes! The least we can do is monitor it.

Q: *Who takes the responsibility if a COC fails and the jumbo jet crashes?*

A: I guess, the question of responsibility would not be much different from the situation of failing programs today, except if one assigns consciousness to the COC, in which case the COC itself might be made responsible; see below.

Q: *Could a COC have a comparable level of intelligence as we have?*

A: Yes! Furthermore, if it can have a comparable level of intelligence it is only a matter of scaling up the COC that it will be more intelligent than we are. However, intelligence is not a scalar quantity, the

levels of intelligence will differ greatly with the domain, mathematical intelligence, verbal intelligence, motoric intelligence, emotional intelligence etc. In some domains COCs will surpass us in others not.

Q: *Is consciousness something that emerges naturally with intelligence or could it be quite independent of it?*

A: I guess consciousness is not necessarily connected with intelligence but there will be a very strong correlation, so strong that it will be hard to prevent an intelligent COC from having consciousness.

Q: *Can there be consciousness without self-consciousness?*

A: I guess it would be possible if the COC could not sense its own actions. But then, I guess, the COC could not really learn to be intelligent. Thus, intelligence and self-consciousness are probably very closely coupled.

Q: *Could we decide from outside whether a COC has self-consciousness or not?*

A: We will never be able to tell with certainty. That even holds for other humans. But I guess, for communication, the COC will have human language. And then, from a certain level of intelligence onwards, we can't help but have the strong feeling that the COC has self-consciousness.

Q: *Is there a point at which we have to build in something like emotions into a COC in order to keep it motivated?*

A: Emotions might be helpful, but they might also be dangerous to have in a computer or undesirable for ethical reasons; see below. What are emotions in a computer anyhow?

Q: *If a COC has self-consciousness, do we have a responsibility for it? Can we simply turn it off, or would that be considered unethical? Can it be owned by somebody?*

A: Well, I think there are two reasonable points of view:

- a) If it has self-consciousness, it would be killing if we turned it off and it would be slavery if we owned it.
- b) It is not the self-consciousness or intelligence that matters but the ability to suffer. The question is, would a COC suffer if it knew that it will be turned off or if it were owned by somebody. This might be a strong reason for not building in something like emotions in a COC.

Q: *Could a COC take responsibility?*

A: Yes! But only if it had self-consciousness and, I guess, only if it had emotions. It must be able to feel guilty or bad about something.

Q: *Can it be guaranteed that COCs stay loyal to humans?*

A: No!

Q: *What if they don't?*

Chapter 4

Molecular biology

4.1 Intracellular Organization as a Function of Cytoskeleton Dynamics

Günther Gerisch

4.1.1 Cell organization based on non-covalent polymer formation

Cell shape and motility is determined by the cytoskeleton. Two systems of the cytoskeleton, the actin and the microtubule system, rapidly change their organization in living cells. For instance, establishment and disassembly of actin structures can occur within less than 10 seconds. Each of these systems is characterized by monomer-polymer equilibria, which are controlled by a series of proteins and other regulatory factors. These regulatory elements alter in different ways the kinetics of polymerization and depolymerization. Normally, half of the actin in a cell is polymerized into filaments (F-actin). Proteins that regulate the actin equilibrium include:

1. Proteins that sequester monomeric actin (G-actin), e.g. profilin. (2)
2. Proteins that block elongation at the fast growing (“barbed”) end of actin filaments, or prevent depolymerization from the slow growing (“pointed”) end. (3)
3. F-actin severing proteins, which fragment actin filaments by intercalation along their length, e.g. gelsolin. (4)
4. Proteins that promote depolymerization from the slow growing (“pointed”) end of actin filaments, e.g. cofilin.

Typically, the microtubule system is built from a central organelle, the microtubule organizing center (MTOC), which duplicates during cell division, giving rise to the two poles of the spindle. Actin polymerization can occur at multiple, rapidly changing foci, often at the plasma membrane or at the cytoplasmic phase of internal vesicles. The site-specific organization of protein complexes from diffusible building blocks enables the actin system to participate in different cell functions such as cell motility, uptake of particles (phagocytosis), and mitotic cell division (cytokinesis).

4.1.2 Elements for computing cell motility

Regulatory processes in the cytoskeleton are in the following outlined using the actin system as an example. The formation and disassembly of actin supramolecular structures is regulated within a cell in a spatiotemporal pattern, and occurs either spontaneously or in response to external signal inputs.

Shape, visco-elastic properties, and membrane attachment of the actin network are determined by F-actin crosslinking, bundling, branching, and membrane-anchoring proteins. Crosslinkers connect actin filaments at different preferred angles. Filamin crosslinks actin filaments at 90° , a-actinin in a flexible way at variable angles. Bundling proteins connect actin filaments at 0° or 180° . The Arp2/3 complex, consisting of seven subunits, induces branches at 70° . Together, these proteins determine the geometry of actin assemblies. At the leading edge of a motile cell, actin filaments are cross-linked into a network at wide angles of 70° to 90° . Bundling proteins are responsible for arranging actin into a core of parallel filaments that form the axis of filopods or of the stereocilia, which act as acousto-mechanical signal transducers in the sensory cells of the inner ear. In a living cell, the shape of actin complexes is controlled by signal transduction pathways in which small GTPases such as rho, rac, and CDC42 act as molecular switches in channeling actin assembly towards stress fiber, filopod, or lamellipod formation.

Dynamics of the actin system or the microtubule apparatus largely depend on motor proteins. Motor proteins that move along actin filaments, the myosins, represent a large family of proteins in which a common motor head is linked to a variety of tails. These tails harbor domains that specify protein-protein or protein-lipid interactions and receive regulatory signals. The vast majority of myosins walk towards the fast growing end of actin filaments.

The regulation of all these activities has to be taken into account if the dynamic organization of a motile eukaryotic cell is modelled. In vitro, patterns have been analyzed that are generated by microtubules and actin-filaments in conjunction with motor proteins and other proteins that determine the shape of filament networks.

4.1.3 Autonomous generation of actin patterns in a moving cell and their modulation by signal inputs

Directional movement of a cell with no inherent polarity, for instance a fibroblast, depends on the generation of transient polarity into a way that the cell alternates between unpolarized and polarized states. The polarized state is characterized by a protruding leading edge at one pole and a retracting tail at the opposite pole. Each passage through an unpolarized state is accompanied by a change in direction. A polarized state can be stabilized by external signals, in particular by a concentration gradient of chemoattractant. Chemotactic signals are typically transmitted to the actin system through trans-membrane receptors that are coupled on the cytoplasmic phase of the membrane to heterotrimeric G-proteins. The intracellular processing of chemotactic signals and conversion of the signal input into a directed movement is currently under experimental and theoretical analysis in several research groups.

Directed cell movement requires coordination between different parts of an amoeboid cell. Firstly, protrusion of the leading edge is connected to retraction at the tail. Secondly, gain of adhesion to a substrate at the front region of a cell is correlated with loss of adhesion at the posterior region. There are temporal as well as spatial correlations between these events in a single cell. In the Dictyostelium cells studied in our group, front activities precede tail activities by about 5-10 seconds, suggesting that initiation of cytoskeletal organization at the front is followed by travelling of intracellular signals to the tail. Spatial correlation links front protrusion to tail retraction in an axial direction. In mutants lacking certain F-actin crosslinking proteins this geometric relationship is lost, in accord with the view that integrity of the actin network is one condition for intracellular coordination in a motile cell to work.

Cytokinesis as a complicated, cytoskeleton-driven process is a challenge for modelling Mitotic cell division provides an example of spatio-temporal control of cytoskeletal activities based on the interaction of microtubules with the actin system. The microtubule system is responsible for separating the chromosomes along the spindle and for transmitting signals that program the actin cortex of the cells. In the polar regions of a dividing cell, ruffling activities are induced, which in contact with a substrate pull the incipient daughter cells apart of each other. The midzone of a dividing cell is programmed to assume a concave shape, forming a cleavage furrow that incises the cell body until the

daughter cells are separated.

The bipolar differentiation of a dividing cell is accompanied (and caused) by the sorting out of actin-binding proteins to different regions of the cell cortex. The mechanism of this sorting-out is subject of current work. Examples for sorted proteins are the Arp2/3 complex and coronin, which accumulate in the ruffles of the cell poles, and cortexillin and myosin II, which are translocated to the cleavage furrow. The importance of most of these proteins for cytokinesis has been established by genetic knock-out experiments, indicating that proteins at different positions within a dividing cell need to act together in order to perform proper cytokinesis.

One mechanism by which polar regions and cleavage furrow are linked to each other is a directed flow of filamentous actin. Actin flows are consistently involved in various cell functions. In cytokinesis, flow is directed from the two poles to the midzone of a dividing cell, thus transporting actin polymerized at the cell poles to the cleavage furrow, where the actin filaments are disassembled. This flow may carry actin-associated proteins within the plasma membrane or along their inner surface in a centripetal direction.

Short-comings in modelling cell motility and cytokinesis from currently available data One desideratum in quantitatively modelling protein-protein and protein-lipid interactions in cytoskeletal networks is the scantiness of kinetic data. Only for few molecular interactions equilibrium constants are known. For even less interactions the rate constants of association and dissociation have been determined, although these are crucial for evaluating the dynamics of any system.

Another difficulty is due to the large number and diversity of regulatory proteins involved. Some of these proteins are "redundant" or overlapping in function, so that they may be omitted in an initial approach. Even then, the question remains which proteins compete with each other for binding to actin, and which ones interfere with the movement of myosin motors. Current experimental analysis of the actin polymerization/depolymerization kinetics in vitro limits itself to the effects of two or three proteins simultaneously interacting with actin.

4.2

Karen Lipkow

I am presently writing up my PhD thesis at the University of Oxford on molecular mechanisms of eucaryotic transposition, a field of DNA-recombination. Previously, I was investigating cell-fate specification during fly eye development at the Rockefeller University, New York. I am a molecular biologist, and so far my experience has been almost entirely experimental. For my first post-doctoral position, however, I am going to move into biomathematical modeling of signal transduction networks in bacterial chemotaxis. This will be in collaboration between experimental and theoretical groups in Oxford and Cambridge.

It has long been my foremost interest to understand and elucidate the underlying principles and mechanisms of evolution and development of living organisms. In this respect, I am especially intrigued by the concept of evolving networks, how they function and how they facilitate evolution.

I have always greatly enjoyed mathematics, physics and computing, and now that the available computing power is good enough to address more and more complicated questions in a reasonable time and theoretical biology is gaining momentum, I am very much looking forward to entering this highly interdisciplinary field.

From the viewpoint of a molecular biologist and from my present research experience of DNA recombination, I would like bring the concept of genome plasticity to notice. In genomes, and putatively in computing systems, the evolvability is greatly enhanced by chromosomal rearrangements and horizontal gene transfer between organisms of different species or even kingdoms.

In my present understanding, most modeling of cellular and molecular phenomena is deterministic, and Turing mechanisms are still widely used. In a few cases, stochastic methods have been used successfully, e.g. in chemotaxis and cytoskeletal dynamics, giving rise to more realistic results.

Additionally, an important feature of biological networks, recently observed independently by several groups, is that they are very robust to changes in parameter values and noise if the topology of the network connections is correct. The origin and characteristics of robust networks are still unclear and pose a fundamental question to both biology and organic computing.

4.3

Björn Öbrink

4.3.1 Discipline

Cell Biology, particularly regulation of signaling pathways.

4.3.2 Pressing problems

Cell biology is in a phase of transition from pure reductionistic processes to systems analyses, which requires a merge between experimental investigations and theoretical work based on mathematical models. Of particular interest is analysis of cell signaling and biochemical signaling pathways, which govern cellular behavior and fate decisions. Such analyses require novel thinking as well as development of new modeling approaches that can deal with both stochastic and deterministic processes coupled to diffusion and other types of mass transport within and between compartments of varying geometries within the cells. Due to the enormous complexity of the signaling pathways, large computational resources are required. One of the pressing problems is that in order to be meaningful, realistic parameter values must be utilized in these computational models. Such parameters include rate constants of the molecular interactions that are involved, local concentrations of the participating molecules, intracellular transport coefficients for the participating molecules, and coordinates of cellular geometry. To some degree these parameter values can be determined experimentally, and when this is done it would be desirable to directly couple these determinations to the computational algorithms. However, because of the complexity and huge combinatorial variability of these molecular interactions it seems unlikely that it will ever be possible to experimentally determine more than a fraction of the needed parameter values. The major problem with such determinations is not technical, but that such a large number of parameters need to be determined, which make it unlikely that it will ever be possible to perform this by brute force. To some degrees reasonable guesses of parameter values may be made, based upon modeling of molecular structures and interactions. However, we must also try to find other means of elucidating the general principles for the organization and function of cellular, biochemical networks. This requires high throughput computational algorithms that systematically can test a large number of parameter variations that can be used for predictions of key features in cellular behavior, which can then be compared with experimental observations. The real challenge is to find ways to approach such explorations of general principles for cellular behavior.

4.3.3 Available techniques

Several simulators for computational analyses of deterministic models exist, and there is some recent development of software for computing stochastic models of molecular interactions in cell signaling, that have yielded promising results.

4.3.4 Appliers

A handful of groups are analyzing cell signaling by deterministic and/or stochastic modeling.

4.3.5 Benefit for different disciplines

Possibly.

4.3.6 Possible synergies

I have no answer to this question.

4.3.7 Promising general approaches that require funding

Yes. Funding is needed to develop methods to couple computational modeling of signaling pathways both with experimental determinations of parameters for molecular interactions and with modeling of molecular structures.

Chapter 5

Bioinformatics

5.1

Miguel Andrade

Q: *What is the discipline you represent?*

A: Bioinformatics. The application of computational methods to molecular biology.

Q: *What are the pressing problems to be tackled in the medium term?*

A: Information crisis in two respects:

- (i) Too much information. Genome projects, protein expression analysis, mass spectrometry, structural genomics, are all applications of existing molecular biology techniques that are producing now massive amounts of data. New techniques are needed for handling this data (into databases) and to extract hypotheses from the data.
- (ii) False information. Experimental (and computationally derived) data in molecular biology is error prone. Many bioinformatics methods rely on the veracity of the information stored in databases. If there is erroneous information and it is used for deriving new knowledge, this error propagates. It is important to tag the information with a reliability value, and to adapt current bioinformatics methods so that they can filter the information that they use.

Q: *What techniques are available to pursue solutions?*

A:

- Database development and linking.
- Biological ontology development.
- Database coherence check.
- Analysis of scientific texts for information extraction.

Q: *Who is already applying these techniques?*

A: The swissprot groups in EBI (Cambridge, Rolf Apweiler) and SBI (Geneve, Amos Bairoch). The gene ontology consortium (e.g., Michael Ashburner, EBI). NLM-NCBI teams working on medline, and association of keywords to medline papers. Our group (EMBL-Heidelberg, Carolina Perez-Iratxeta, myself). Helmut Schmid (of the Institute fur Maschinelle Sprachverarbeitung, Stuttgart University -

by the way, could you invite him as a linguist interested in biology? Helmut Schmid (jschmid@ims.uni-stuttgart.de).

Q: *Could different disciplines possibly benefit from using similar techniques?*

A: Yes. Any scientific discipline dealing with many objects with properties and relations between them (as in biology) could benefit from the development of techniques related to understanding better how to organize information and how to extract it from scientific text.

Q: *Where are possible synergies?*

A: Probably between linguistics and biology.

Q: *Are there promising general approaches requiring funding/backing?*

A: The generation of systems based on text analysis of the scientific literature needs funding for database acquisition (medline, scientific papers in full text, and the very expensive science citation index), storage and computational capacity. Also note that the contribution from linguists is crucial but they are underfunded in comparison to molecular biologists (that have a more direct connection to the pharma industry interests).

5.2 The need for a database for model types of biochemical systems

Ursula Kummer

With the increasing availability of biochemical data, the simulation of rather complex biochemical systems becomes feasible. Many techniques are employed for this purpose (e.g. ODEs, Monte Carlo simulations, P-Calculus etc.) However, up to now, the available experimental data are almost always not sufficient to provide all parameters which would be necessary to simulate a biochemical system in great detail.

However, even with arbitrary parameters biochemical reaction systems are restricted in their behavior by their topology. A simple example is an open system which contains a chain of coupled reactions in which all the reactions display simple Michaelis-Menten-kinetics. Such a system is not able to display e.g. oscillatory behavior with any set of parameters. Likewise, increasing the concentration of the first substrate will never lead to a decrease of the concentration of the last product, no matter what values the individual parameters have. Thus, the knowledge about a systems topology provides at least some insight in its possible behavior.

There are a number of tools which try to extract maximal information from a system's topology. So-called stoichiometric network analysis (SNA) and its modified form the elementary mode analysis determine all possible subsystems which are able to display steady state behavior. In addition, stability analysis can provide some insights into the possible nonlinear behavior. However, computing all possible behaviors with all possible parameter sets is impossible for most system, since the complexity of such a task is exponentially growing with the size of the system.

Therefore, on one hand, these techniques are often computational very expensive, even for small systems. On the other hand, they are not offering the possibility to use existing knowledge about a particular system for the analysis of another system which might describe a completely different experimental system, yet still has the same topology.

During the symposium, I would like to initiate discussions on the possibility for a database which contains model types for biochemical systems. This database should make use of the fact that biochemical systems (of a limited size) often display the same or a similar topology and that there are restrictions on the actual numbers of biochemical parameters. In some cases, it might be even feasible to really approximate all possible behaviors for a given system and even if this is computationally expensive it might be worthwhile, since it would aid the analysis of multiple real systems. At the moment, several database systems are planned which store explicit biochemical models, but none of those will contain model types and the possibility to compare and automatically analyze a new biochemical model with these.

The setup of such a database would demand the participation of mathematicians, bioinformaticians, theoretical biologists and experimentalist and therefore, the symposium offers an unique possibility to discuss it.

Chapter 6

Modeling and theoretical biology

6.1 Developmental Biology: about the strange relation between the experimentally and theoretically working community.

Hans Meinhardt

The following comments describe my personal view about the relation between theory and experiment in developmental biology, the field I am working on¹.

In most branches of natural science, theories are a common tool to achieve an understanding of complex processes. Development of an organism is achieved by a signaling between the cells and by a corresponding response of the cells. In the latter process, the activation of genes plays a dominant role that leads to the use of the information stored in the genes.

What can the theory provide? Development will not really be understood without a tight interaction between theory and experiment. In development, non-linear feedback loops play an essential role. These are difficult to understand. Several such systems coupled together are even harder to understand. Our intuition is inappropriate to predict the behavior of such systems. They have properties very different than their parts alone. The interaction of two substances can generate a pattern, while a single substance is, of course unable to do so. The same interaction can lead to patterns in space but also to patterns in time - the actual behavior depends on parameters such as spread or half-life. Thus, even if essential parts have been isolated, without a theory, the system is not necessarily understood. Models provide the unavoidable step from the observation to the paradigm regardless whether the modeling starts from the observed regulatory behavior or from distributions of molecules. Only when models are formulated in a mathematical way one can be sure that the hypotheses are free of internal contradictions and that they indeed account for the experimental observations. In this way, a hypothesis can be checked, modified and checked again. This leads to a continuing evolution of a model. Discrepancies between new observations and a hitherto successful model are very valuable since they uncover elements not yet understood. New experimental results are often only surprising if a theory predicted a different result. In order that an experiment can change a paradigm, a paradigm must exist.

If theories are needed, why it is so difficult to achieve a fruitful dialogue? The complexity of interactions which have recently been uncovered in development has led to the feeling that development is so complicated and contains so much evolutionary arbitrariness that straightforward theories are not helpful. Long time ago, there was a saying that theories based on interactions of two substances are too simple, those that based on three are too complex. Now we are confronted with hundreds of substances.

Often theories are regarded only as an intermediate step, as a tentative speculation, until the sparkling molecules have been found. Theoretical predictions that have been made before the corre-

¹for our actual models see <http://www.eb.tuebingen.mpg.de/abt.4/meinhardt/theory.html>

sponding molecule(s) were isolated are frequently regarded as something in competition, diminishing the achievement of the experimental finding. This causes an animosity, resulting in an active suppression of the preceding theoretical concepts. I know this from my own work. Although I correctly predicted the logic of the molecular interactions for several basic steps, the acceptance by the experimentalist is low.

The presently exploding amount of sequencing data lead in many places to the feeling that bioinformatics is a field of the future, with a corresponding giant funding. The analysis of sequencing data is certainly important. However, I have strong doubts whether this approach will provide much insight of how development works. To give an example, I don't expect that one can deduce from sequence comparisons how regeneration is accomplished or how size regulation of an organ is achieved.

In physics, many experiments would not have been done without a theoretical prediction. This is usually not so in developmental biology. One can clone genes, can isolate substances and perturb a system by introducing mutations — all without any theory. Therefore, to make reasonable experiments, the experimentalists need not the theoreticians (but observing that a particular gene is expressed at a particular location is not already an explanation of how this is accomplished.) This led to the habit that predictions made from the theoretical side are usually ignored even if the experiments confirmed the theory. Reference to the first observation of a particular gene expression pattern is made, as the rule, with great care. A concept developed on a theoretical basis is handled more as a speculation that can be, but need not to be mentioned. Thus, concepts in biology have a very different appreciation when compared to physics.

There is a bias within the experimentalist to regard development as a simple chain of induction: (i.e., one structure induces the next in the neighborhood, and so on) and to ignore facts in which a theory would be essential. In the two best-investigated systems, *Drosophila* and *Xenopus*, early pattern formation is accomplished either by maternally deposited determinants or by external asymmetries introduced by sperm entry. This has led to the relieving feeling that theories of pattern formation are not necessary (the mothers are doing this for us they impose the initiating pattern). In this respect it is very informative how happy the community reacted on the recent finding that also in the mouse an early determination takes place with the sperm entry. The well-known fact that any cell at least up to the eight cell state embryo can give rise to the whole organism and that, therefore, this early event can provide only some weak bias but not the pattern - this fact is mentally repressed.

Theoreticians have contributed to scepticism against theories. Frequently new models list only what can be accounted for but ignore phenomena which are difficult to integrate. The preconditions required that the model works at all are sometimes not sufficiently discussed. Opaque mathematical treatments of particular aspects sometimes hide more than that elucidate; treatments that cannot be followed by the experimentalists anyway. Often, new theories draw little attention of what preceding theories have achieved and where the differences are. This has had the consequence that the experimentally working community does not listen to the theoreticians since they do not listen to each other.

Since biologists rarely get an education in differential equations and computer simulations, most models are not developed by biologists but by physicists or mathematicians, i.e., by scientists familiar with these tools. However, to make models that are compatible with the rich source of data, nowadays one has to learn the many facts that have been collected by the biologists in the course of time. Therefore, the danger is high that the physicist/mathematician starts with wrong presumptions due to an incomplete knowledge of the facts. The experimentalists are happy since they became a fresh reason to ignore the theories.

Nevertheless, I am still convinced that theory will provide a substantial help for an understanding of development as a dynamic system. For several reasons I am optimistic that the mutual interaction will improve on long range. The reason may be summarized as follows: (i) the complexity is increasing so dramatically by the plethora of new observations, that even the specialists are familiar only with a narrow fragment of the field. With a theory it is much easier to memorize the details, since the details make sense. (ii) In earlier time, the biologist where educated to study the difference. Now,

since the basic mechanisms seem so well conserved, the need for unifying concepts is increasing. The next generation of students will grow up with this experience. (iii) As long as relatively few genes were known that are involved in development, every new gene was a substantial progress. With the inflation of genes, for young people the reward for finding the gene $N+1$ shrinks. Therefore, I expect, that the interest in concepts will gain thrust – hopefully.

What is missing is a ‘canonical’ basis of knowledge, a set of fundamentals the community agree upon such that the wheels, that has not to be discovered again and again. Of course, such fundamentals will not be static but change in the course of time like Newton’s theory of gravitation became modified by Einstein. No student can make an examination in physics without knowing of what Newton and Einstein has achieved. But which student has read and understood Turing, etc.? If theory would be once a standard part in the normal education, this would be a big step to make the interaction more fertile.

My dream would be that theoretically working subgroups would be established in good experimental institutes. According to my experience a close connection to experimentalist is very helpful, not for making theories for their latest findings but to maintain an up-to-date and inspiring knowledge of the observations. I would prefer such an organization in comparison of a pure theoretical institute since the cross-fertilization with other theoretical branches is presumably restricted. To give an example, the cross-fertilization between theoreticians dealing with development and those dealing with protein folding is certainly much more reduced than between theoreticians and experimentalists working in the same branch.

6.2

René Thomas

Much of our activity for many years has dealt with two of the preoccupations ably described in the invitation to this symposium as:

- not “missing the forest for the tree” and
- “bringing simplicity out in phenomena of seemingly great complexity by a simple change in perspective”.

We have tried to integrate data in the field of regulatory processes, starting from experimental Biology (bacteriophage genetics), and eventually extending the scope to the more general field of nonlinear dynamics.

6.2.1 Key words: essential qualitative features, feedback circuits, Jacobian matrix

Although we presently use mostly descriptions in terms of differential equations, we strongly feel that the emphasis should be put on finding the essential qualitative features of the dynamics of systems, then only turn to a fully quantitative description, if required.

It was realized that feedback circuits are not only present in nonlinear systems, but actually govern their dynamics: positive circuits are a necessary condition for multistationarity, negative circuits are required for stable attractors. As a matter of fact, all the circuits of a system appear in the analytic expression of its Jacobian matrix (incidentally, in nonlinear systems, a given circuit can be positive or negative depending on the location in phase space). This permits to identify all the feedback circuits and to grasp a wealth of information regarding the number and quality of the steady states.

6.2.2 Key words: logical analysis, asynchronous description, parameter space

In many cases, it is advantageous to begin with a so-called “logical description”, i. e., a description in which variables and functions can take only a limited number of values (in simple cases, 0 or 1 only). It is vital to use an asynchronous description, with continuous time. One essential aspect of the logical description is that here parameter space is cut into a finite number of boxes, each of which corresponds to a characteristic qualitative behavior. All boxes can be analyzed, but it is more operational to first identify the most interesting ones - usually those which lend to more complex behavior. One reaches then a view whose qualitative fit with the differential description is remarkable (at least for step functions and sigmoids, which are the most frequent regulatory interactions in Biology and other complex fields)

6.2.3 Key words: reverse logics

One way to study complex systems consists of starting from a model, itself built from a feedback between experimental data and rational considerations, and analyzing its dynamical possibilities.

Alternatively, one can dream of starting from facts alone and identify the set of models consistent with them (reverse logics). Clearly, even in a well-defined type of formalism, there will be several, and often many consistent models. Depending on the case, one can find the simplest ones and use them as starting points. Or, one can list the absolute logical requirements underlying the set of data, compare them with a preexisting but not entirely satisfactory model, and identify the discrepancies.

For two recent reviews, see

Thomas, R. and Kaufman, M., Multistationarity, the basis of cell differentiation and memory. I. Structural conditions of multistationarity and other nontrivial behavior, *Chaos*, 11 (2001) 170-179.

Thomas, R. and Kaufman, M., Multistationarity, the basis of cell differentiation and memory. II. Logical analysis of regulatory networks in terms of feedback circuits, *Chaos*, 11 (2001) 180-194.

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