

Survey

**'Robustness
in Immune System Models'**

for the
NiSIS Task Force
'Nature-inspired Robustness'

by
BioControl Jena GmbH

**Nature-inspired Robustness –
State-of-the-art in Evolutionary Design
of Robust Devices and Robust Algorithms**

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1 Introduction

Robustness is a relatively new research topic. It got into the focus of scientific research with the advent of systems biology considering biological systems and processes in a holistic perspective. In the age of molecular biology the investigation of properties of bio-molecules scarcely offered any chance to truly understand the essence of biological robustness, neither of biological systems nor of biological processes.

Although models of heritage bio-molecules, nucleic acids and proteins, have been developed that allowed in principle to understand cellular processes such as replication, transcription, and translation, proof reading, and DNA repair, these models belong to some kind of physicochemical biology rather than to the true life science, systems biology, with its branch of behavioural biology. In particular, Robustness of bio-molecules in molecular biology is sometimes confused with micro-mechanical rigidity.

The sheer complexity of heritage bio-molecules is already a hint to one of the prerequisites of robustness. Robustness requires a minimum of complexity. Robust biological entities consist of many (heterogeneous) interacting components. They have modular structure or hierarchical organization. One of the current research directions considers Robustness an emergent phenomenon in complex systems. Another important prerequisite of Robustness is variability of the entity and its components.

Robustness is sturdiness versus perturbations, internal (mutations) and external (stress) perturbations. Robust systems escape damage or even extinction in virtue of their variability and their capability of compensation and reparation, i.e. by virtue of their adaptability and evolvability.

Robustness is a rather multifaceted phenomenon. This Survey is to show many of its aspects. There is, however, no warranty whether or not this description is complete and exhaustive. Also, it is merely a matter of taste to say that there is not any definition of Robustness or that there are too many. There are serious attempts to grasp as many as possible of the aspects of Robustness in one generally valid definition. Besides, however, there are many very specific definitions that concern just a particular biological phenomenon.

Several principal problems still remain without answer and are subject to current robustness research. What are the organizational principles that characterize highly robust systems and what are the costs of their realization? How is the robustness of a system related to evolvability, adaptability and the systems' degree of fitness? [1].

Analysing biological strategies of Robustness may guide the design processes of non-biological systems especially in engineering applications [1]. Impact assessment is an important integrative part of a project on Nature-inspired Smart Information Systems. It is certainly wise to try incorporation of robustness features into devices or algorithms one or several at a time rather than all of them simultaneously, to see what happens, and to decide on next steps of design.

1.1 References Chapter 1

- [1] Hoffman, S. Introduction to Robustness of Biological Systems. [web page] Oct 2007. URL: http://www.physcon2007.agnld.uni-potsdam.de/MS_IS/MS25/MS_hoffmann.pdf [Accessed 3 Oct 2007]

2 Natural and Artificial Robustness

2.1 Robust Natural Systems

Robustness of Natural Systems (robust versus perturbation by the external and internal environment) is one of their most remarkable properties. Examples of robust natural systems are the immune system, homeostasis, blood circulation, heartbeat, respiration, metabolism. As a consequence, organisms incorporating these systems are also robust. What do these systems have in common as a tentative source of their common robustness? They all came into existence by evolution. Evolution, as a trial and error process by mutation and selection of species in a population, makes survive organisms with advantageous system mutants and makes those with disadvantageous ones die out. Sufficiently fast propagation of a species is a major selection advantage since it guarantees rapid access to nutrition and rapid occupation of living space. Another major selection advantage is robustness to be viable and remain alive long enough to propagate. Seen from this perspective, robustness is a prerequisite of survival and long term existence. Non-robust systems are failed attempts of natural evolution; they have died out and do not exist any more. From this perspective, evolution is the reason of robustness. Nevertheless, Nature might have invented several different mechanisms to maintain robustness.

2.2 Robust Artificial Systems

When trying to understand robustness of Natural Systems to transfer their mechanisms of robustness to Artificial Systems it is certainly a good idea to survey available definitions of the notion of Robustness. Unfortunately, different definitions of robustness, available so far, do not so much reflect different mechanisms but rather refer to the particular case of application in an artificial system. Even a single mechanism of robustness is difficult to understand and even more to imitate or implement in a Nature-inspired artificial system since robustness of natural systems is the result of an evolutionary design rather than the result of a rational design. Moreover, in these definitions, inspiration from Nature in robust artificial systems is not always obvious.

2.3 Definitions of Robustness

Let us have a look at definitions of robustness available in the Web.
Robustness is

- the property of being strong and healthy in constitution
- the characteristic of being strong enough to withstand intellectual challenge; 'the lack of robustness in the findings may be due to the small size of the sample' [2]
- In the context of computer software, robustness is the resilience of the system, especially when under stress or when confronted with invalid input. For example, an operating system is considered robust if it operates correctly when it is starved of memory or storage space, or when confronted with an application that has bugs or is behaving in an illegal fashion - such as trying to

access memory or storage belonging to other tasks in a multitasking system. [3]

- The degree to which a system or component can still function in the presence of partial failures or other adverse, invalid, or abnormal conditions. [4]
- Messages are considerably less affected by component failures than direct calls between components, because messages are stored in queues and remain there until processed appropriately. Messaging is similar to transaction processing, because message processing is guaranteed. [5]
- A measure of how sensitive a particular method is to violation of its assumptions. [6]
- Robustness defines the ability of the numerical method to provide a solution despite variabilities in the initial solution and control parameters. This incorporates issues of fault tolerance. Generally, robustness is achieved at the expense of accuracy. [7]
- The condition of a product or process design that remains relatively stable, with a minimum of variation, even though factors that influence operations or usage, such as environment and wear, are constantly changing. [8]
- Dependability of a system, product, or process to continue operating well even though conditions are constantly changing. [9]

As mentioned above, these definitions do scarcely give any clue on how robustness can be obtained in artificial systems (devices or computational algorithms) by Nature-inspired reasoning since they do not refer in any way to mechanisms of robustness in natural systems. Nevertheless, they have been quoted here since they at least provide an impression of how broad the meaning of the notion of Robustness is.

Clearly, extensive reasoning on mechanisms that render a system robust is needed. Some elements of these mechanisms that might be suspected to play a role in ascertaining and maintaining robustness are Fault Tolerance, Redundancy, Feedback Loops, particular Network properties, such as scalability, Regeneration, Self-healing and Self-repairing properties. Of course, thorough studies of robust natural systems are indispensable to get enough insight in their behaviour in order to do rational design of Nature-inspired robust artificial systems or of Nature-inspired robust algorithms, in the spirit of NiSIS. An appropriate method of investigation seems to be comparative analytical modelling of tentative Kinetic schemes of a natural system known to be robust. Another Method might be extensive comparative Data Mining of Data Sets produced from measurement of robust systems under different conditions. Most important are underpinning mathematical theories such as Constructive Systems, Theory of Chemical Organisations (Peter Dittrich, Jena), Linguistic Chemistry (Walter Fontana, Santa Fe), Process Algebra, Equifinality in non-linear open systems (Ludwig von Bertalanffy), Dynamic Simulation, Stability and bifurcation analyses, Metabolic Control Analysis (MCA), Metabolic Pathway Analysis of elementary modes (Stefan Schuster, Jena), Metabolic Flux Analysis, Optimization, Evolutionary Game Theory and others.

Much more general is the definition of robustness given by Wikipedia [10]. Robustness is the quality of being able to withstand stresses, pressures, or changes in procedure or circumstance. A system, organism or design may be said to be 'robust' if it is capable of coping well with variations (sometimes unpredictable variations) in its operating environment with minimal damage, alteration or loss of functionality.

2.4 The Term Robustness in the NiSIS Roadmap

Let us check the instances of the term Robustness in the NiSIS Roadmap.

Data Technologies

Nature-inspired algorithms (Genetic Algorithms, Particle Swarm Optimization, Foraging, Ant colony) are the state-of-the-art solution techniques for some problems in emerging computing environments such as autonomic computing, ubiquitous computing, P2P systems, the Grid and the Semantic Web, where the interaction of large numbers of decentralised, parallel, asynchronous, and distributed components (software or hardware) is demanded.

Essential for tackling the scalability problem is the introduction of modularity into the system. This requires defining the global goal, designing the activity of the local small entities, defining the interactions among the entities, and achieving the emergence of **robust** global behaviour. The global goal is not the sum of the local goals, but beyond that. Inspiration from biology, such as the concept of stigmergy (i.e., indirect communication via modifications of the environment, message passing), is particularly useful in the design of information systems that can adapt to unexpected environmental changes without pre-programmed system behaviour.

In Chapter 4 of NiSIS Roadmap: Grand Challenges, the term **Robustness** is mentioned in the context of Bio-mimetic Intelligence:

The conceptual Grand Challenge for building smart information systems is the mimicking of many of the desirable qualities, features and capabilities of the natural systems showing intelligent behaviour, both in their distinct functionalities and in their aggregated actions.

We can identify the collection of these characteristics under the common umbrella of **Bio-mimetic Intelligence** (Bmi) or, in other words, the ability of an information system to *mimic* nature-inspired adaptive and intelligent behaviour to better pursue its goals, to improve the **robustness**, efficiency and usefulness of its functionalities and enhance its interfacing capabilities to the external world.

Grand Challenge 1: Computational Nervous System

The *rationale* behind the design of a Computational Nervous System (CNS) is the development of '*sensing*' *capabilities* in information systems. These capabilities, when addressing an information system, are related both to the acquisition of information from the external world (e.g. artificial vision, speech understanding, etc.) and the understanding of its internal functioning and performance (e.g. autonomic computing).

The *ultimate goal* is to provide an information system with a CNS able to acquire data and information in a **robust** way and, at the same time, able to manage uncertainty and as in biological systems, self-adapt and self-repair.

The *expected benefits* can be: the increased ability to acquire information; the additional safety provided by self-assessing mechanisms and, therefore, the better quality of the acquired information; the **robustness** aspect to systems failure or performance degradation; a better, fitter and efficient representation of the external world and the system's inner status.

Technological and scientific improvements are required in the field of sensors, sensor networks, nonlinear control systems (e.g. **robustness**, stability, adaptivity, etc.), evolutionary computation, computational intelligence and machine learning, signal processing, etc.

Grand Challenge 3: Distributed Cooperative Intelligence

The *rationale* behind the design of Distributed Cooperative Intelligence (DCI) is the necessity of dealing with the increasing complexity of information systems through non-centralized mechanisms, as in biological systems.

The *ultimate goal* is to develop information systems able to survive and improve their fitness through time by the distributed optimization and adaptation of all its components.

The *expected benefits* can be: improved **robustness** to failure, computation errors and run time, improved computational efficiency, improved **robustness** to network communication faults, improved control of distributed systems, plants or organizations.

2.5 References Chapter 2

- [2] [web page] URL: <http://wordnet.princeton.edu/perl/webwn?s=robustness>
- [3] [web page] URL: <http://en.wikipedia.org/wiki/Robustness>
- [4] [web page] URL: <http://www.stsc.hill.af.mil/crosstalk/1994/07/xt94d07l.asp>
- [5] [web page] URL: <http://msdn.microsoft.com/library/en-us/vbcon/html/vbconIntroductionToMessagingInVisualStudio.asp>
- [6] [web page] URL: <http://www.bcu.ubc.ca/~otto/EvolDisc/Glossary.html>
- [7] [web page] URL: <http://www.grc.nasa.gov/WWW/wind/valid/tutorial/glossary.html>
- [8] [web page] URL: http://www.onesixsigma.com/tools_resources/glossary/glossary_r.php
- [9] [web page] URL: <http://schools.cbe.ab.ca/logistics/r.html>
- [10] [web page] URL: <http://en.wikipedia.org/wiki/Robust>

3 Objects of Robustness

3.1 Robust Systems

3.1.1 Robust Systems Theory and Applications

'Adaptive and Learning Systems for Signal Processing, Communications and Control Series' is a book that might be recommended to get started. The purpose of this book is to introduce the reader to the theory of control systems, with particular emphasis on the applicability of the results.

This book is a complete, up-to-date textbook on an increasingly important subject.

Robust Systems Theory and Applications covers both the techniques used in linear robust control analysis/synthesis and in robust (control-oriented) identification. The main analysis and design methods are complemented by elaborated examples and a group of worked-out applications that stress specific practical issues: nonlinearities, robustness against changes in operating conditions, uncertain infinite dimensional plants, and actuator and sensor limitations. Designed expressly as a textbook for master's and first-year PhD students, this volume:

- Introduces basic robustness concepts in the context of SISO systems described by Laplace transforms, establishing connections with well-known classical control techniques
- Presents the internal stabilization problem from two different points of view: algebraic and state-space
- Introduces the four basic problems in robust control and the Loop shaping design method. Presents the optimal H_2 control problem from a different viewpoint, including an analysis of the robustness properties of H_2 controllers and a treatment of the generalized H_2 problem
- Presents the H_2 control problem using both the state-space approach developed in the late 1980s and a Linear Matrix Inequality approach (developed in the mid 1990s) that encompasses more general problems
- Discusses more general types of uncertainties (parametric and mixed type) and μ -synthesis as a design tool
- Presents an overview of optimal H_1 control theory and covers the fundamentals of its star-norm approximation
- Presents the basic tools of model order reduction
- Provides a tutorial on robust identification
- Offers numerous end-of-chapter problems and worked-out examples of robust control

3.1.2 Building Robust Systems, an essay

Another source of instruction is the essay 'Building Robust Systems' [12]. It concentrates on how to make robust and evolvable systems.

Abstract: It is hard to build robust systems: systems that have acceptable behaviour over a larger class of situations that was anticipated by their designers. The most robust systems are evolvable: they can be easily adapted to new

situations with only minor modification. How can we design systems that are flexible in this way?

Observations of biological systems tell us a great deal about how to make robust and evolvable systems. Techniques originally developed in support of symbolic Artificial Intelligence can be viewed as ways of enhancing robustness and evolvability in programs and other engineered systems. By contrast, common practice of computer science actively discourages the construction of robust systems.

This essay is very well written, comprehensive and instructive. It is of high interest, particularly to bio-informaticians. It is a good supplement to the Roadmap of NiSIS. Reading is warmly recommended.

Several aspects of robustness of natural living systems are discussed one after another, as described by paragraph headlines such as:

- Redundancy and degeneracy (several copies of the same functionality, several equivalent functionalities)
- Exploratory Behaviour (the desired outcome is produced by a generate-and-test mechanism, just like in evolution in general)

Compartments and localization (cell differentiation depends on cell environment, selection of particular behaviours from cellular genome, modularity)

- Self-reconfiguring and self-repairing, self-monitoring
- Defense, repair, and regeneration (restriction enzymes in bacteria, immune system in mammals, liver tissue, diversity reduces vulnerability)
- Composition to build compound functions (self-configuring in the genome, in the brain)

All of these features seem costly, consuming vast resources, and to be simply non-economic at first glance, when considering implementation in artificial systems. Yet these are ingredients in evolvable systems. To make truly robust systems we must be willing to pay for what appears to be a rather elaborate infrastructure. The value, in enhanced adaptability, may be even more extreme. Indeed, the cost of our brittle infrastructure probably greatly exceeds the cost of a robust design, both in the cost of disasters and in the lost opportunity costs due to the time of redesign and rebuilding.

Further topics considered in this essay are

- The problem with correctness of functions in unforeseen situations
- Infrastructure to Support Generalizability
- Extensible generic operations (adaptation in meaning of operators to data types of operands, as in some advanced programming languages)
- Generate and test (dependency-directed backtracking)
- Constraints generalize procedures
- Degeneracy in engineering (mechanism from the AI problem-solving world for degenerate designs: goal-directed invocation)

Infrastructure to Support Robustness and Evolvability

- Combinators
- Continuations
- Backtracking and concurrency
- Arbitrary association

- Dynamically configured interfaces

Conclusion: Our increasing dependence on computational and communications infrastructure, and the development of ever more sophisticated attacks on that infrastructure, make it imperative that we turn our attention to robustness.

As part of the continuing work to build artificially intelligent symbolic systems we have, incidentally, developed technological tools that can be used to support principles of robust design. For example, rather than thinking of backtracking as a method of organizing search we can employ it to increase the general applicability of components in a complex system that builds itself to meet certain constraints.

3.1.3 Robust Systems Laboratory

The self-representation of the Robust Systems Laboratory reads like this [13]:

A UNIFYING THEME, ROBUSTNESS AND UNCERTAINTY MANAGEMENT:

ROBUSTNESS against disturbances and model uncertainty is at the heart of control practice. Indeed, in the (completely unrealistic) case where both all external disturbances and a model of the system to be controlled are exactly known, there is no need for feedback: optimal performance can be achieved with an open loop controller. Interest in robust control arose in the late 70's where it was shown that many popular control methods led to fragile closed loop systems, and the field has been very active since. Indeed, very recent research has shown that the concept of robustness through feedback is not limited just to control, appearing in fields as dissimilar as physics, network management and biology. At the Robust Systems Lab we are developing both theory and tractable algorithms to address various aspects of the problem ranging from the transformation of experimental signals from the physical plant to a set of models (robust identification), to the synthesis of a controller for that set of models (robust control).

COMPUTER VISION SYSTEMS bring together imaging devices, computers, and sophisticated algorithms to solve problems in areas such as industrial inspection, autonomous navigation, human-computer interfaces, medicine, image retrieval from databases, realistic computer graphics rendering, document analysis, and remote sensing.

The goal of computer vision is to make useful decisions about real physical objects and scenes based on sensed images. Achieving this goal requires obtaining and using descriptions (models) of the sensors and the world. At the Robust Systems Laboratory we study how to build these models and how to use them while being robust against disturbances such as noise, clutter, and model uncertainty.

Computer vision is an exciting but disorganized field that builds on very diverse disciplines such as image processing, statistics, pattern recognition, control theory and system identification, physics, geometry, computer graphics, and learning theory.

The goal of the ROBUST SYSTEMS LABORATORY is to develop both theoretical tools and specific algorithms leading to robust systems, capable of achieving near optimal performance under a wide range of conditions.

3.1.4 Robust System Design with Uncertain Information

A short Article on 'Robust System Design with Uncertain Information' written from an experimental and technological perspective can be found at [14].

3.2 Robust Processes

Web entries on Robust Processes in their majority concern business processes, administrative, educational, and learning processes, less frequently they concern technological processes e.g. in the technological domain of chemistry.

3.2.1 Design of Simple and Robust Process Plants

To the latter topic refers the book 'Design of Simple and Robust Process Plants' [15]. This book covers the design of simple and robust processing plants, and is intended to inform managers and engineers in the process industry, involved in process design, control design and operation, but is also interesting for students.

The book is unique since it is the first comprehensive work addressing both the total process design and operational approach.

Technological developments during the last decade made the design of really competitive processes possible. Mechanical developments have resulted in reliable and robust equipment. Process developments have created opportunities to minimize the amount of equipment; furthermore, different logistic approaches, integration of process functionality and intensification of the unit operations are possible. Computer and control technology allows remote-control operation and first pass prime production.

Readers familiar with the ideas of NiSIS might recognize in this robust process design some features of inspiration from Nature.

3.2.2 Robustness of business processes

To the former topic (of robust processes) refers the Web entry of the Enterprise Computing Institute that considers the robustness of business processes [16].

What exactly is meant by a process being truly robust and what characteristics are inherent in such a process? This article presents as many as 24 of the most important traits, together with their definitions, that your process should have in order to attain this robustness.

Although interesting, this article is only mentioned but not presented, not at last since it follows a non-evolutionary definition of robustness that considers robust to be a synonym of rigid.

3.3 Robust Networks

The question about networks that immediately comes to mind reads like this. What about the Web? The Web is a particular Network. Its services may be characterized to be both administrative and educational.

Do the present efforts at a renewal of the Web aim at enhancing its robustness? Certainly they aim at enhancing security and protection, at early recognition of and defence against threat and danger, at avoiding crashes, and also at optimising Web services and administration, and at improvement of data stream control. Are these objectives elements of robustness enhancement or even Nature-inspired robustness enhancement?

3.3.1 Design Principles for a Robust Network Infrastructure

The article 'Design Principles for a Robust Network Infrastructure' will help answer these questions [17].

In this article of three pages the present and the future situation of the Internet are compared. At present, seemingly trivial failures are able to disrupt the Internet largely without bound. This is because a fundamental assumption underlying the design of many Internet protocols is that systems are *fail-stop* – they completely and detectably stop working when they fail. Over the past few years, operator errors in the form of router configuration mistakes have led to several spectacular disruptions to Internet connectivity.

For the future; the authors argue that a key research challenge is to design network protocols and distributed systems that are as robust against arbitrary failures as today's Internet is against fail-stop failures. Only by meeting this challenge can we make the Internet significantly more reliable.

Yet unlike the case for simple failures, there is an almost complete lack of principles and techniques to help design protocols that can withstand arbitrary failures.

Providing robustness against arbitrary failures will require new research. Established bodies of work such as cryptographic security and fault tolerance via consensus are certainly useful tools to help achieve robustness. But they are not a solution in their own right for the arbitrary failures that remain in practice.

Because of the success of Internet designers in addressing fail-stop errors and the widespread use of authentication for critical services, the remainder – authorized hosts making syntactically correct but factually wrong statements – are a major source of unreliability in the Internet today.

A natural class of robust networks The Authors' thesis is that it is possible to design protocols that are robust against these unforeseen, arbitrary failures, and that this will require design principles that differ from those in use today. Identifying these principles will require the synthesis of knowledge from across the domains of networking and systems, software engineering, formal methods, cryptography, algorithms, and human factors. The resulting principles must be easy to understand, efficient, and scalable, or they will never be used. Those principles are based on case studies of implementation bugs and Internet router configuration mistakes. Principles to provide robustness in the face of simple failures have been formed over the past three decades. The goal is to develop principles for robustness against arbitrary failures that are just as effective.

3.3.2 A natural class of robust networks

A theoretical investigation of network robustness, demonstrating that the dynamical robustness of complex networks is a direct consequence of their scale-free (i.e. scalable) topology, was done by Aldana and Cluzel [18]. Abstract: As biological studies shift from molecular description to system analysis we need to identify the design principles of large intracellular networks. In particular, without knowing the molecular details, we want to determine how cells reliably perform essential intracellular tasks. Recent analyses of signaling pathways and regulatory transcription networks have revealed a common network architecture, termed scale-free topology. Although the structural properties of such networks have been thoroughly studied, their dynamical properties remain largely unexplored. We present a prototype for the study of dynamical systems to predict the functional robustness of intracellular networks against variations of their internal parameters. We demonstrate that the dynamical robustness of these complex networks is a

direct consequence of their scale-free topology. By contrast, networks with homogeneous random topologies require fine-tuning of their internal parameters to sustain stable dynamical activity. Considering the ubiquity of scale-free networks in nature, we hypothesize that this topology is not only the result of aggregation processes such as preferential attachment; it may also be the result of evolutionary selective processes.

3.3.3 A scalable, robust network for parallel computing

The article 'A scalable, robust network for parallel computing' deals with robust design of networks but, more importantly, with robust design of computational algorithms in distributed systems and, therefore, is described in more detail under the headline 'Methods for Modelling Robustness' [19].

3.3.4 Robust Networks: From Graphs to Systems Biology

The book Robust Networks is quoted since it concerns one of the hot topics of NiSIS although it is not conclusive from the short description of the book what is meant by robust networks, since robustness is not mentioned explicitly [20].

Robust Networks discusses general principles behind network models and the essential concepts in mathematical modeling of molecular regulatory networks in biology. This book integrates biological mechanisms using a bottom-up approach in which genes and molecules are organized in complex networks. It relates abstract concepts in combinatorics and graph theory to questions in biology and addresses computational methods for deriving network models from data. It also addresses the testing of inferred networks by perturbation analysis on real biological systems using genomic techniques. With examples from research, this book is ideal for graduate students and researchers in computational biology.

3.4 Robust Control

3.4.1 Nature-inspired robust control

Rüdiger Brause identifies two mayor sources of system robustness: negative feedback and redundancy in system components (refer to the Article in the Appendix). As well known, negative feedback plays a role in many genetic, epigenetic, metabolic, biochemical reactions of living organism where an end product can regulate the rate of its own biosynthesis as a general control phenomenon. Implementation of negative feedback, therefore, is a kind of Nature-inspired robust control.

He considers a simple state space model consisting of a sensor as input x , an amplifier with amplification factor A , and an effector as output y .

If the parameter A varies, also the output $y = Ax$ varies. This system is not robust versus perturbation or noise on A .

Negative feedback of the fraction $k < 1$ of the output y , however, coupled back and superimposed to the input x gets the system robust.

$$y = A(x - ky) = Ax - kAy \quad \text{or} \quad y = A/(1+kA) x = A'x \quad \text{with} \quad A' = (1/A + k)^{-1}$$

It is shown that in the new system the new Amplification factor A' is approximately equal to the constant value $1/k$ as long as the Amplification factor A remains much greater than $1/k$ (i.e. $1/A$ much less than k), in spite of perturbation or noise. The stronger the feedback k ($1/1000$, $1/100$, $1/10$, ...) the more robustness. Negative feedback can render a system robust if perturbation is small

enough. Else, however, it is only redundancy that can help to keep the system robust, i.e. several robust systems (with feedback) in parallel with the same input and the same output, such that they can substitute each other if one of them is subject to perturbation.

This comparative model calculation represents a particular case of Robust Control. A Google search yields a lot of hits for Robust Control as key word.

3.4.2 Robust and Optimal Control

The Web recommends fundamental books on Robust Control, e.g. Robust and Optimal Control is class-tested at major institutions around the world and regarded as an 'Instant Classic' by reviewers, this work offers the most complete coverage of robust and H_∞ control available [21]. The clarity of the overall methodology: how one sets a problem up, introduces uncertainty models, weights, performance norms, etc. set this book apart from others in the field. Offers detailed treatment of topics not found elsewhere including – Riccati equations, m theory, H_∞ loop shaping, controller reduction, how to formulate problems in a LFT form. Key results are given immediately for quick access in the beginning of the book. Overall the book serves as a tremendous self-contained reference by having collected and developed all the important proofs and key results available. Problems sets are available on the Internet.

Features:

- Offers comprehensive coverage of both robust and *H_∞ control, allowing flexibility in both the selection and organization of topics.*
- Takes a self-contained approach, including detailed proof and development of each topic.
- Serves as either textbook or reference manual, designing coverage in such a way that readers do not need to cover previous chapters to access key results.
- Provides highlights of the key results at the beginning of the book.
- Constructs a strong instructional framework composed of...

Guidelines for selecting topics.

- Chapter Highlights.
- Numerous diagrams and figures.
- Worked examples showing step-by-step development.
- Lists of key terms and symbols.
- Chapter summaries.
- End-of-chapter notes.

3.4.3 Essentials Of Robust Control

Essentials Of Robust Control [22] is based upon the popular Robust and Optimal Control [21]. This book offers a streamlined approach to robust control that reflects the most recent topics and developments in the field. Features Cover State of the Art topics, including Gap Metric, V-gap metric, Model validation, Real mu.

- Offers the essentials of both Robust and H_∞ control suitable for a graduate course or self study
- Adopts a self-contained approach, including detailed proof and development of each topic.

- Incorporates MATLAB tools accompanied by step-by-step illustrations throughout the book to execute computations.
- Supports discussions with numerous diagrams and figures.
- Guides readers through a wealth of worked examples depicting step by step development.
- Provides highlights of key results at the beginning of the book.
- Constructs a strong pedagogical framework in each chapter, including...
- Guidelines for selecting topics.
- Chapter Highlights.
- Lists of key terms and symbols.
- End of Chapter notes.
- Exercises.

3.4.4 MATLAB Robust Control Toolbox 3.2

MATLAB provides tools for Robust Control [23]. Design robust controllers for plants with uncertain parameters and unmodeled dynamics.

The Robust Control Toolbox provides tools for systematically factoring model uncertainty into your design to ensure consistent controller performance on the real plant. These tools let you quickly identify worst-case scenarios and automatically generate controllers with reduced sensitivity to parameter variations and modeling errors.

3.4.5 Model Uncertainty and Robust Control

The article 'Model Uncertainty and Robust Control' is a fundamental representation of theoretical control engineering [24].

Introduction

A key reason for using feedback is to reduce the effects of uncertainty which may appear in different forms as disturbances or as other imperfections in the models used to design the feedback law. Model uncertainty and robustness have been a central theme in the development of the field of automatic control. This paper gives an elementary presentation of the key results.

3.4.6 Robust Control Theory

Robust Control Theory is another interesting and instructive article on Robust Control [25].

Abstract:

Conventional control theory has allowed man to control and automate his environment for centuries. Modern control techniques have allowed engineers to optimize the control systems they build for cost and performance. However, optimal control algorithms are not always tolerant to changes in the control system or the environment. Robust control theory is a method to measure the performance changes of a control system with changing system parameters. Application of this technique is important to building dependable embedded systems. The goal is to allow exploration of the design space for alternatives that are insensitive to changes in the system and can maintain their stability and performance. One desirable outcome is for systems that exhibit graceful degradation in the presence of changes or partial system faults.

3.4.7 Automatic Control Laboratory

The Automatic Control Laboratory of the École Polytechnique Fédérale de Lausanne offers a course on Robust Control.

Objectives: Control of dynamic systems, so that certain properties remain unchanged under perturbations, is considered. In many cases, the controlled system can be presented as a family of dynamic models with parameters or frequency responses lying within admissible sets. Robust control deals with the problem of stability and performance validation for a family of models. The objective of this course is to give an insight into analysis and design of robust control systems. Although the content of course is focused on the H_∞ framework, the other approaches to robust control will also be covered in a tutorial way.

3.4.8 Foundations of Systems Biology

Textbooks and Monographs are particularly helpful for understanding robustness and robust control in terms of systems biology. The book Foundations of Systems Biology discusses robustness in Article 11 of Chapter IV (Cellular Simulation Computer Simulation of the Cell: Human Erythrocyte Model and its Application) and in Article 12 of Chapter V (System Level Analysis) [26].

Constructing Mathematical Models of Biological Signal Transduction Pathways: An Analysis of Robustness

Article 11 describes the Simulation Tool E-CELL and its application to simulation of entire cells of human erythrocytes for understanding metabolic pathways and metabolic osmosis. This article also discusses stability and robustness in the cellular simulation and the role of feed-back mechanism and redundancy.

Article 12 explains for two instances of application, bacterial chemotaxis and visual phototransduction in the retina, the robustness of biological signal transduction versus variation of system components and the environments, by integral feed-back control. Referred to also is homeostasis. Known models are reinterpreted to check whether or not they contain integral feed-back control. Three controller types are compared.

The Section on Robustness of biological systems shows that the mechanisms that render bio-systems insensitive to exogene and endogene perturbation are poorly understood yet.

The following Section deals with the portability of engineering methods and knowledge to bio-systems. Both technical and biological systems arise from some stepwise evolutionary process and are suboptimal for the purpose given. Also the relation between complexity and stability is similar for both types of systems.

Kitano dares the hypothesis that robustness and stability in both types of complex systems is achieved by

- System control
- Redundancy
- Modular design
- Structural Stability (of regulatory and metabolic paths)

In the introductory Article of his book, Kitano emphasizes the importance of parameter identification for model simulation. Parameter estimation from experimental data on biological systems is critical. Conventional Regression Analysis needs a model prior to simulation. In addition, bio-systems, as products of evolution, may have for some or even many of their parameters more than one

single true value which all pertain to practically identical system behaviour, in order to survive under changing conditions. From this perspective, undetermined model parameters are yet another aspect of robustness.

Data Mining is an alternative of regression analysis by not aiming at numerical parameter identification. Nevertheless, Data Mining leads to a semi-quantitative system model in terms of rules describing essential relationships among system quantities. Although bio-systems are robust versus exogene or endogene perturbation, measurements on them may suffer from considerable scattering due to their complexity and the complexity of measurement methods, due to hidden parameters, and due to the stochastic nature of molecular components. Data Mining, however, thanks to renunciation of numerical detail by clustering and thanks to inquiry in rules of relationship, only among value regions instead of exact values, is best appropriate to recognize nevertheless regularities and tendencies that can be condensed to result in a rule-based expert system.

3.4.9 A course on Robust Control

The course 'MATH 430 Modern Control theory F 36-12-0 48' [27] covers core topics in discrete and continuous time modern control theory: nonlinear differential equations, linearization, the algebraic theory of linear control systems which includes controllability, observability and minimal realizations; stability including Lyapunov stability and the design of robust stabilizers using control-Lyapunov functions; optimal control; state estimation via Luenberger and Kalman-Bucy filters. Laboratory experiments illustrate the lecture material, students are required to identify a high order under-actuated linear system and perform model verification experiments, and design and implement robust feedback controllers for a flexible structure, study robustness issues in controller design, and design dynamic controllers which employ state reconstruction from partial observations of the state.

3.5 Robustness versus Stability

Stability is defined as long-term maintenance of stationary states in the space of substance concentrations, or species populations of a dynamical system with given model parameters. In contrast, robustness is maintenance of functionality or performance of the dynamical system at particular positions in the parameter space of the dynamical system. An extended notion of robustness comprises not just parameter modification but also model modification to obtain long term maintenance of system behaviour in spite of parameter fluctuation due to noise or parameter shift due to perturbation.

3.6 Robustness Mechanisms in Natural Systems

3.6.1 Robustness Mechanisms in Biology.

The contribution by Rüdiger Brause at the NiSIS 2006 – 2nd Annual Symposium adopts a slightly different relationship between robustness and stability and also between robustness and adaptability, and it assigns robustness to the phenotype as robustness of biological entities against changes in the underlying environmental and genetic mechanisms[28].

Abstract: Robustness is an important concept within the biological world. We might define it by the *small variance of a state* of the subject, e.g. health, fitness or phenotype, *against changes in the underlying working conditions* compared to the variance of other possible states against the same changes.

Robustness differs from other concepts like stability and adaptivity (returning to a desired state), persistence, recovery and flexibility by its intrinsic structural components. Robustness may include topics like stability (small state perturbations lead to only small state changes) or structural stability (small structural parameter changes lead to a new system with the same qualitative behaviour), but include more aspects like organisation and architecture of a system, the offset between function, possible functional changes and architecture, and topics like the controversy between adaptivity and identity, i.e. plasticity vs. stability.

In our context we are mostly interested in mechanisms of robustness in the molecular biological world. We are interested in *phenotypic robustness*, i.e. the robustness of biological entities against changes in the underlying environmental and genetic mechanisms. There are two main robustness principles known in literature: canalization and neutrality.

He describes in molecular detail the genetic reasons for these observations. To his mind, the mechanisms are based on *Redundancy* of genes, *Deleterious variance suppression (anti-redundancy)* of genes.

Comment:

A far as inspiration from nature is concerned it is a bit questionable whether these genetic mechanisms might be mimicked in a Robust Artificial Systems. One might suspect nano-technology to be a means to imitate genetic processes in the spirit of **Bio-mimetic Intelligence** (Bml) which, in other words, is the ability of an information system to *mimic* nature-inspired adaptive and intelligent behaviour to better pursue its goals, to improve the robustness, efficiency and usefulness of its functionalities and enhance its interfacing capabilities to the external world. Whether this would be possible, however, seems to be an open question.

3.6.2 Nature Inspired Monitoring and Control – Survey on Information Flow in Biosystems

Another source of knowledge on Robustness in Natural Systems in molecular terms is NiSIS Task Force 'Nature Inspired Monitoring and Control' discussing basis mechanisms that confer robustness to biological and engineered systems [29].

With respect to Nature-inspired Modelling, Simulation, Optimisation and Control (NiMOC), the idea to assign Robustness to the phenotype is fruitful.

Inspiration from Nature means to understand the analogy or metaphor between evolutionary preparation and evolutionary design. The device for evolutionary preparation is replaced with the designer's laboratory. The mutations are replaced with the model variants (genotype, structure), while selection of species function is replaced with selection of simulation behaviour (phenotype, function). (quoted from Roadmap NiSIS, Chapter NiMOC)

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4 Methods for Modelling Robustness

4.1 Network-based Parallel Computation

The article 'A scalable, robust network for parallel computing' by Cappello and Mourloukos deals with robust design of computational algorithms [30]. Interestingly, again, just like with large intracellular networks, also with server networks, the dynamical robustness of complex self-organizing, scalable networks of n servers is a direct consequence of their scale-free topology.

Abstract: CX, a network-based computational exchange, is presented. The system's design integrates variations of ideas from other researchers, such as work stealing, non-blocking tasks, eager scheduling, and space-based coordination. The object-oriented API is simple, compact, and cleanly separates application logic from the logic that supports interprocess communication and fault tolerance. Computations, of course, run to completion in the presence of computational hosts that join and leave the ongoing computation. Such hosts, or producers, use task caching and prefetching to overlap computation with interprocessor communication. To break a potential task server bottleneck, a network of task servers is presented. Even though task servers are envisioned as reliable, the self-organizing, scalable network of n servers, described as a *sibling-connected fat tree*, tolerates a sequence of $n - 1$ server failures. Tasks are distributed throughout the server network via a simple 'diffusion' process.

CX is intended as a test bed for research on automated silent auctions, reputation services, authentication services, and bonding services. CX also provides a test bed for algorithm research into network-based parallel computation.

4.2 Underpinning Mathematical Theories: Process Algebra

The book 'Design of Simple and Robust Process Plants'; mentioned under the Heading 'Robust Processes', suggests some relation between Robustness and Competitive Processes. Likewise, the above article, 'A scalable, robust network for parallel computing', mentions interprocess communication and interprocessor communication. Indeed, it is plausible that competitive and communicating processes are a means to achieve robustness since, if equivalent, they may substitute for each other in order to choose the one that copes best with changed situations or else may decide to do an appropriate shared action.

Process Algebra is precisely the means to formalize competition, cooperation, and communication of processes. It is a means to describe redundancy not in system components but in system processes, not in static, configurative modules but in dynamic, functional modules. Therefore, Process Algebra is also a means to formalize robustness which is a dynamic rather than a static phenomenon.

4.2.1 Handbook of Process Algebra [31]

Synopsis: Process Algebra is a formal description technique for complex computer systems, especially those involving communicating, concurrently executing components. It is a subject that concurrently touches many topic areas of computer science and discrete math, including system design notations, logic, concurrency theory, specification and verification, operational semantics, algorithms, complexity theory, and, of course, algebra. This Handbook documents the fate of process algebra since its inception in the late 1970's to the present. It is

intended to serve as a reference source for researchers, students, and system designers and engineers interested in either the theory of process algebra or in learning what process algebra brings to the table as a formal system description and verification technique. The Handbook is divided into six parts spanning a total of 19 self-contained Chapters. The organization is as follows. Part 1, consisting of four chapters, covers a broad swath of the basic theory of process algebra. Part 2 contains two chapters devoted to the sub-specialization of process algebra known as finite-state processes, while the three chapters of Part 3 look at infinite-state processes, value-passing processes and mobile processes in particular. Part 4, also three chapters in length, explores several extensions to process algebra including real-time, probability and priority. The four chapters of Part 5 examine non-interleaving process algebras, while Part 6's three chapters address process-algebra tools and applications.

4.2.2 Process Algebra with Timing [32]

Synopsis: Timing issues are of growing importance for the conceptualization and design of computer-based systems. Timing may simply be essential for the correct behaviour of a system, e. g. of a controller. Even if timing is not essential for the correct behaviour of a system, there may be good reasons to introduce it in such a way that suitable timing becomes relevant for the correct behaviour of a complex system. This book is unique in presenting four algebraic theories about processes, each dealing with timing from a different point of view, in a coherent and systematic way. The timing of actions is either relative or absolute and the underlying time scale is either discrete or continuous. All presented theories are extensions of the algebra of communicating processes. The book is essential reading for researchers and advanced students interested in timing issues in the context of the design and analysis of concurrent and communicating processes.

4.2.3 Process calculus [33]

In computer science, the process calculi (or process algebras) are a diverse family of related approaches to formally modelling concurrent systems. Process calculi provide a tool for the high-level description of interactions, communications, and synchronizations between a collection of independent agents or processes. They also provide algebraic laws that allow process descriptions to be manipulated and analyzed, and permit formal reasoning about equivalences between processes (e.g., using bisimulation). Leading examples of process calculi include CSP, CCS, and ACP. More recent additions to the family include the π -calculus, the ambient calculus, PEPA and the fusion calculus.

Process Algebra, although originally developed for formalizing computational processes in computer-based systems, begins to play a major role for biomolecular interactions, Self-organization, Systems Biology, inter-cellular and signal transduction communication systems, membrane transport, and conformational change.

Some examples of application of Process Algebra to problems in this domain will be presented.

4.2.4 Machine learning bio-molecular interactions

Machine learning bio-molecular interactions from an original temporal logic based language uses the π -calculus process algebra for modeling biochemical interactions [34].

4.2.5 Reversible process algebras and self-organisation

The article 'Reversible process algebras and self-organisation' [35] focusses on

- Using process algebra as a model to describe bio molecular. interactions
- Modeling with π -calculus
- Modular way of implementing distributed systems

4.2.6 Process Algebras for Systems Biology

Process algebras have several attractive features which could be useful for modelling and understanding biological systems [36]:

- Process algebraic formulations make interactions/constraints explicit – not the case with classical ordinary differential equation models.
- Structure can also be apparent.
- Equivalence relations allow formal comparison of high-level descriptions.
- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software. These include qualitative and quantitative analysis, and model checking.

These features are of particular importance for the approach adopted in NiSIS on Modelling, Simulation, Optimization, and Control [37].

4.2.7 Modeling Signal Transduction Using Process Algebra

Recent years have shown a rapid accumulation of molecular information about inter-cellular and signal transduction communication systems, which play a pivotal role in evolution, development and disease. However, this information is diverse, disparate and fraught with detail, rendering analysis difficult. We propose a novel formal unifying view of signal transduction as a pure communication system. We establish this correspondence, and employ the pi-calculus, a process algebra originally designed for describing networks of inter-connected concurrent computational processes, to model signal transduction systems. The model is mathematically well defined and biologically visible. It represents both the dynamic behavior of the system over time, and the structural molecular implementation that underlies this behavior. We demonstrate the power of the pi-calculus to represent complex molecular networks by constructing a model for the receptor tyrosine kinase (RTK)-MAP kinase cascade pathway. The low level molecular details (e.g. residues, domains) fit clearly and visibly within the representation and serve as the basis for the entire scope of global network behavior (e.g. feedback, cross talk). This uniform, integrated, scalable theoretical framework based on the pi-calculus, can be employed to study signal transduction at molecular, evolutionary and cybernetic levels: 1. Simulation and formal mathematical verification allow to predict the effect if changes in low-level components (molecules and below) on global outcome. This can serve for functional as well as evolutionary studies. 2. Formal methods for the comparison of processes represented in process algebras (e.g. bisimulation) serve as a basis for a novel measure of homology of pathways, the dynamics of signaling pathways, we are able to define a distance measure that incorporates both differences in molecular components and in their interactions. 3. The final network representation can be reified to an object, in itself amenable to cybernetic studies on general properties of different communication systems, molecular and others.

4.2.8 A pi Calculus Model of the Na Pump

In their article 'A pi Calculus Model of the Na Pump' the authors apply Process Algebra to membrane transport and conformational change [38].

Integration of biological data, modelling and simulation of the biological systems become important research topics. Biology should adopt theoretical frameworks of physics, mathematics and computer science to challenge the enormous number of interacting molecules. Cell behaviour and molecular processes are usually described in biology by partial differential equations. These equations often fail to express molecular interactions or to represent systems with a small number of molecules. We propose a discrete mathematical tool called the π -calculus to model interactions and subsequent state transitions. The model provides a computational framework that allows an automated verification of system properties. This paper presents a discrete mathematical description of the ion transport across cell membranes in terms of the π -calculus process algebra. We motivate the use of the π -calculus as an adequate formalism for molecular processes by describing the dynamics of the Na pump. The Albers-Post mechanism is translated into an elegant π -calculus model outlining molecular interactions, conformational transformations, and ion transportation of the pumping process. We use a sophisticated software tool to verify some properties of the described system.

4.2.9 Automatically deriving ODEs from process algebra models

The article 'Automatically deriving ODEs from process algebra models' shows how to transform these equivalent model representations into each other [39].

4.2.10 BioAmbients

The article 'BioAmbients' introduces the BioAmbients calculus, which is suitable for representing various aspects of molecular localization and compartmentalization [40].

Abstract: Biomolecular systems, composed of networks of proteins, underlie the major functions of living cells. Compartments are key to the organization of such systems. We have previously developed an abstraction for biomolecular systems using the π -calculus process algebra, which successfully handled their molecular and biochemical aspects, but provided only a limited solution for representing compartments. In this work, we extend this abstraction to handle compartments. We are motivated by the ambient calculus, a process algebra for the specification of process location and movement through computational domains. We present the BioAmbients calculus, which is suitable for representing various aspects of molecular localization and compartmentalization, including the movement of molecules between compartments, the dynamic rearrangement of cellular compartments, and the interaction between molecules in a compartmentalized setting. Guided by the calculus, we adapt the BioSpi simulation system, to provide an extended modular framework for molecular and cellular compartmentalization, and we use it to model and study a complex multi-cellular system.

4.2.11 Seminaire Algorithmique et Biologie

The 'Seminaire Algorithmique et Biologie' is a Representation and simulation of molecular processes using stochastic process algebra [41].

Biochemical processes, carried out by networks of proteins, mediate the interaction of cells with their environment and are responsible for most of the

information processing inside cells. Recently, much interest has been focused on system level studies of such networks, and several approaches have been proposed for their representation and analysis. However, none of the existing approaches fully integrates dynamics, molecular, and biochemical detail.

We propose to model biochemical processes using the pi-calculus, a process algebra originally developed for describing distributed computer processes. In our model, biochemical processes are mathematically well defined, while remaining biologically faithful and transparent. To allow accurate quantitative modeling of biochemical networks, we employ a stochastic variant, the spi-calculus, where actions are assigned rates according to the rates of the corresponding biochemical reactions. Based on this model, we developed a new computer system, called BioPSI, for representation and simulation of biochemical networks.

The modular nature of the calculus allows incremental modeling of complex networks and alternation between different levels of complexity. This is instrumental for studying the modular design of biological systems. We have used the BioPSI system to study a recently proposed model of the circadian clock. Using the ability of the calculus to capture modular structures, we investigated the circadian machinery at two levels of abstraction. First, we modeled the molecular interactions explicitly. Second, we identified a functional module in the system - a hysteresis module - and described the system using this functional module. By using two BioPSI programs, we show that both levels of description are equally good at capturing the behavior of the system, and establish the function of the hysteresis module within the clock and in a wider cellular context.

We are currently extending our modular framework to represent various aspects of molecular localization and compartmentalization, including the movement of molecules between compartments and dynamic rearrangement of cellular compartments. We intend to incorporate the adapted calculus as part of the BioPSI system, to provide a fuller modular framework for molecular interaction, localization and compartmentalization.

4.3 Underpinning Mathematical Theories: Chemical Organisations

Robustness in Chemical Organizations [42] Abstract: Complex dynamical networks consisting of many components that interact and produce each other are difficult to understand, especially, when new components may appear. In this paper we outline a theory to deal with such systems. The theory consists of two parts. The first part introduces the concept of a chemical organization as a closed and mass-maintaining set of components. This concept allows to map a complex (reaction) network to the set of organizations, providing a new view on the system's structure. The second part connects dynamics with the set of organizations, which allows to map a movement of the system in state space to a movement in the set of organizations.

Theses of Chemical Reactions Theory

- Reaction network: set of species + reaction rules = directed graph = Petri net
- Reaction system: reaction network + dynamics
- Closed set: reaction inside the set produce exclusively species of the set
- Self-containing set: all species that are consumed can also be produced inside the set without losing any species of the set (regeneration)
- Organization:= closed and self-containing set of molecular species

- Organization structure: Hasse diagram of the Organizations of a reaction system

To be robust, a reaction system must be closed and self-containing, i.e. it must be an Organization, as a necessary condition. But not any Organization as a sufficient condition is robust. Regeneration is not a sufficient condition for robustness. Robustness means in addition insensitivity versus exogene and endogene perturbation with network extension and contraction included. In terms of organization theory this must mean that a changing reaction system to be robust must not only be but also remain an Organization under both growth and shrinkage. Chemical Evolution is movement in the space of Organizations since only Organizations can be robust and therefore keep alive long enough to replicate, propagate and survive.

4.4 Underpinning Mathematical Theories: Limit Cycles and Point Attractors

Bertalanffy's principle of equifinality in open non-linear systems seems to be another facet of robustness. It states, that these systems converge into the same final state in phase space irrespective of their initial state. It was published in his General System Theory [43].

Indeed, this property might be considered robustness versus different initial conditions. Moreover, this principle states that equifinality applies only to systems that are non-linear in their intrinsic dynamics and open to their environment. Both these properties are characteristics of living systems, and non-linearity is a kind of complexity.

Bertalanffy's principle of equifinality is to some extent an empirical finding, but it has its theoretical basis in Poincaré's theory on limit cycles and attractors of trajectories in phase space.

An application to life sciences can be found in 'Evolutionstheorie und dynamische Systeme. Mathematische Aspekte der Selektion' by Hofbauer and Sigmund who show that different variants of Eigen-Schuster's (non-linear) hypercycles have just this type of robustness and, therefore, can have come to exist by evolution [44].

A very interesting article on Robustness and Adaptation is the reprint of the Thesis 'An Organization-centric Approach to Viewing Adaptation in Complex Adaptive Systems' [45]. The author discusses in great detail interrelations between equifinality, limit cycles, point attractors and organizations.

4.5 Underpinning Mathematical Theories: Metabolic Pathway Analysis

Yet another approach to robustness is Metabolic Pathway Analysis of elementary modes (Stefan Schuster, Jena). Subject to his research is analysing the robustness of metabolic networks.

Metabolic Pathway Analysis (or Metabolic Network Analysis) has the following characteristics:

- Decomposition of the network into the smallest functional entities (metabolic pathways, elementary flux modes)
- Does not require knowledge of kinetic parameters
- Uses stoichiometric coefficients and reversibility/irreversibility of reactions

An elementary mode is a minimal set of enzymes that can operate at steady state with all irreversible reactions used in the appropriate direction. All flux distributions in the living cell are non-negative linear combinations of elementary modes. The structural robustness of metabolic networks can be defined in terms of elementary modes.

- Elementary modes are a suitable tool for analysing robustness because each elementary mode is non-redundant
- Number of elementary modes is a measure of redundancy

However, the number of elementary modes is not the best measure of robustness. A better measure of robustness is the fraction of elementary modes remaining functional after knock-out of one enzyme, averaged over all reactions whose enzymes can get knocked-out, one at a time, or, alternatively, its extension to multiple knockouts.

An inverse measure of robustness is network fragility. It can be computed via minimal cut sets. Minimal cut sets are sets of enzymes that have to be knocked out at least, to impede synthesis of a specified product. In a partially branched reaction way towards the specified product, the number of enzymes required depends on the number of branches. At non-branched locations where a single enzyme is sufficient the corresponding reaction is called essential.

- Minimal cut sets involving only one element correspond to essential reactions.
- Minimal cut sets can be calculated from elementary modes.

Clearly, if the cut sets of a particular product contain few elements the production of this product is fragile since its synthesis can be impeded by few enzymes knocked out. Therefore, the Fragility coefficient of an enzyme = reciprocal of average size of all minimal cut sets in which an enzyme is involved. Network fragility coefficient F = average fragility coefficient over all enzymes.

The Authors of Max-Planck Institut für Dynamik komplexer technischer Systeme write: Applying the elementary-mode analysis in the central metabolism of *E.coli* we could show that an integrative analysis of elementary modes can be used to reconstruct key aspects of cellular behaviour from metabolic network topology, namely to reliably classify mutant phenotypes, to analyse network robustness and flexibility, and to quantitatively predict functional features of genetic regulation. More generally, we conclude that robustness of metabolic networks is linked to redundancy, and that hierarchical genetic control supports this robustness by finding a trade-off between network efficiency and flexibility. Thus, elementary-mode analysis can provide a suitable method for the analysis of organization and functionality of metabolic networks requiring - in contrast to dynamic mathematical modeling - only network topology, which is well-known in many cases [46]. Conclusion: This concept allows to map a complex (reaction) network to the set of elementary modes as functional building stones, providing a new view on the system's structure. Redundancy in functional units alone favours robustness of a metabolic network, irrespective of the kinetic parameters of its dynamics. Any perturbation whatsoever that affects only the dynamics of a robust network but leaves the structure intact does not destroy the robustness of the network.

4.6 The Dialectic Mutual Relation between Robustness and Adaptability

By now it should be clear already that robustness requires flexibility, adaptability. At first glance, robust seems to be the opposite of adaptive, since sometimes robust is considered to be a synonym of rigid. This paradox, however, is only apparent. By contrast, a rigid system would fail in unknown situations or even get destroyed rather than succeed in maintaining its function.

Robust is by no means the same as rigid. Robustness, in a sense, is both prerequisite and consequence of Adaptability, and Adaptability is both prerequisite and consequence of Robustness.

Conclusion: Changing systems must be robust to be able to adapt. Changing systems must be able to adapt to be robust. This can be exemplified for several instances. Table 1 shows the corresponding aspects of Robustness and Adaptability for the example of Smart Adaptive Systems (SAS). Table 2 shows the corresponding aspects of Robustness and Adaptability for the example of Software Tools

Table 1 – Adaptability vs. Robustness of SAS as Simultaneous Aspects

SAS	Adaptability	Robustness
Type I	of response behaviour to environment changes	in functioning despite of environment changes
Type II	of problem-solving ability to a different problem	in finding a solution despite of problem changes
Type III	of response behaviour to environment changes, even without user interaction	in functioning despite of environment changes, even without user interaction
Type III	of problem-solving ability to a different problem, even without user interaction	in finding a solution despite of problem changes, even without user interaction

Table 2 – Adaptability vs. Robustness in Software Tools as Simultaneous Aspects

Software Tool	Adaptability	Robustness
Editor	to process different texts/codes	in functioning for any text/code
Compiler	to compile different source programs	in syntax error check ability for any code
Debugger	to run different programs in extended mode	in detecting and indicating execution errors
Development Studio	to cope with different development strategies	in enabling correct program development
Neural Network	to be trained with different signals/ to recognize different patterns	in mapping input neurons to output neurons
Fuzzy System	to process any non-precise or non-complete data	in providing rules and allowing inference
Machine Learning	to process populations of any rules	in extraction of relevant rules by awarding right prediction
Evolutionary Computing (GA)	to optimise different object functions	in finding the optimum for any object function
Simulation Model of Evolution Artificial (Molecular) Evolution Evolutionary Design	to design environmental conditions advantageous for species of predefined functionality so as to make them survive by mutation and selection as the fittest individuals in a propagating population	in global establishment of the quasi-species carrying the desired functionality in the propagating population, although mapping of structure to function is unknown
Computer-Assisted Technical Development Rational Design	to develop some device or algorithm by tentative modification guided by intellectual intervention.	in finally obtaining predefined functionality, based on knowledge or conjecture
Process Control by PID Loop Controller	to apply the proportional-integral-derivative algorithm to several different univariable, linear, time-constant processes	in maintaining desired process behaviour and output
Process Control Model free Adaptive Controller	to update controller's tuning parameters and strategy during its operation, based on rules or lookup tables of relationships between controller input and process output or using dynamic neural networks, to accommodate process changes	in regulating process behaviour and output, even for varying process behaviour in time and in absence of any quantitative process model

Process Control Model based Predictive Controller	to configure and tune programmable controllers using GUI, involving internal model, reference trajectory, control calculation, and self- compensator	in intelligent supervision opening the way for preventive process maintenance
Statistical Regression Analysis Data Evaluation, Curve Fitting Parameter Estimation, Sensitivity Analysis, Experiment Design	to model any system providing the measured data, by problem-specific computation of calculated data for least square regression	in determining model parameter values from appropriately designed experimental data allocation
Database	to store and query any reality sector in a database application	in finding relevant relations among database variables by queries
Data Mining	to cluster any data and extract rules among clusters	in providing cluster and rule results for reliable prediction, independent of data material

4.7 References Chapter 4

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5 Case Studies - Examples of Applications

5.1 Robust Artificial Systems

The following books discuss robust performance of Artificial Systems even under perturbation and uncertainty.

5.1.1 Control of Uncertain Sampled Data Systems [47]

Dynamical systems evolve in continuous time. Contrasting this, in feedback control the vast majority of complex systems are controlled using sampled observations of system behavior taken at discrete time instants.

Presumably, this book is important for reversed engineering of genetic Networks from Gene Expression Data of Microarrays, if control of genetic networks is intended.

5.1.2 Control under Lack of Information [48]

This book is devoted to problems of control in dynamical systems in situations of uncertain information about the disturbance or in conditions of conflict. The problem consists in the choice of control (input) that ensures the best possible result (output) even in conditions of the most unfavourable possible disturbance. The method is Differential Game theory. The application domain is: Control of genetic networks

5.1.3 Nonlinear and Adaptive Control Design [49]

This innovative book breaks new ground in nonlinear and adaptive control design for systems with uncertainties. Introducing the recursive backstepping methodology, it shows for the first time how uncertain systems with severe nonlinearities can be successfully controlled with this new powerful tool.

W.Levine (Ed)

5.1.4 The Control Handbook [50]

This book has textbook character and is highly worth recommending.

5.2 Robust Immune System

Virtual Immune Systems are computer-based simulations and visualizations of immune system functions.

Artificial Immune Systems are imitations of immune system functions in algorithms such as those for defence from virus attacks against computers or computer networks, or else algorithms for data analysis and pattern recognition in data. In fact, two of the most important immune system properties are protection against destruction of functions and the ability of pattern recognition.

Imitation of the Immune System is a further domain of Computational Biology using Nature-inspired algorithms, next to Genetic Algorithms as imitation of chromosomal heredity, Artificial Neural Networks as imitation of information processing in the Central Nerve System, Fuzzy Logic and Bayesian Inference as imitation of human reasoning. (Missing is still the imitation of heartbeat to enable rhythmic information flux processing through algorithmic networks, and the

imitation of kidney function for elimination of undesired, senseless, or sub-optimal solutions during information processing)

Obviously, there is a relation between virtual and artificial immune systems. Algorithms that stand the test in computer simulations of the virtual immune system by correct reflection of its functions in the simulation model, are candidates for the imitation of immune system functions by artificial immune systems in Computational Biology. In particular, the robustness of the virtual immune system can be tested during simulation and then be transferred to the algorithms of the artificial immune system.

5.2.1 Cellular Automata Immune Model

The 'Cellular Automata Immune Model' is a nice example of computer-assisted model simulation and visualization of immune system functions based on Cellular Automata [51]. The model is a generalization of the well known Game of Life by Conway. In contrast to Game of Life, in the simulation model IMMSIM several types of particles are considered in many different kinds of interaction, where different particles play the roles of different immune system components and their known interactions are imitated algorithmically.

The advantages of this approach are three-fold

- Imitation of the complex immune interactions is much easier than by mathematical models
- Visualization provides high evidence
- The simulation model can be operated interactively such that the influence of both model assumptions and control measures can be studied.

At the present state of development, IMMSIM takes into account B cells, T cells, Macrophages, Antigenes, Antibodies, Lymphokines. Different components can be added if desired. IMMSIM performs a realistic description and illustration of humoral aspects of the immune system and enables the study of clonal selection.

A typical computer experiment proceeds in the following three steps

- Choice of initial population of antigen-presenting cells (APC), B cells, and T cells
- Design of the infection schedule
- Start of simulation run

5.2.2 Computer Immune System

The following description of an Artificial Immune System is given at [52]: Natural immune systems provide a rich source of inspiration for computer security in the age of the Internet. Immune systems have many features that are desirable for the imperfect, uncontrolled, and open environments in which most computers currently exist. These include distributability, diversity, disposability, adaptability, autonomy, dynamic coverage, anomaly detection, multiple layers, identity via behaviour, no trusted components, and imperfect detection. These principles suggest a wide variety of architectures for a computer immune system.

5.2.3 A Vision of an Adaptive Artificial Immune System

'A Vision of an Adaptive Artificial Immune System' is a talk by Stephanie Forrest that stresses diversity and decentralization as sources of robustness [53].

Natural immune systems are sophisticated information processors. They learn to recognize relevant patterns, they remember patterns that have been seen previously, they use combinatorics to construct pattern detectors efficiently, and they use diversity to promote robustness. Further, the individual cells and molecules that comprise the immune system are distributed throughout our bodies, encoding and controlling the system in parallel with no central control mechanism.

The talk describes recent progress on several related projects which are incorporating principles and mechanisms from immunology into computer security. It will emphasize recent work on network-based intrusion detection in which normal behaviour (self) is characterized using TCP/IP packets. Several immune-inspired mechanisms are employed to create a distributed and robust approach to network security, and an outline of future extensions to make the system more immunological is given.

Textbooks on Artificial Immune Systems are also available.

5.2.4 Artificial immune systems [55]

5.2.5 Artificial immune systems and their applications [56]

5.3 Robust Immune Mechanisms in Health and Disease

5.3.1 Autoimmune Disease

A direct application of immune research in medicine is the paper by Hecker [57].

The aim of this investigation is to understand the reason why some patients of rheumatoid Arthritis (RA) respond to a particular autoimmune disease therapy (Biologicals that counter the immune system imbalance through blocking immune cytokines that play an important role in the pathogenesis) but some others do not.

The investigation is based on separate reverse engineering for reconstruction of the dynamic gene regulatory network out of time-series gene expression data from responders or non-responders, respectively.

Clearly, to ascertain discernibility a robust estimation of the gene regulatory network with limited connectivity and low model prediction error is absolutely required. To overcome the common parameter uncertainty problem in regression analysis for many parameters at limited sample size, the authors used LASSO regression. LASSO (Least Absolute Shrinkage and Selection Operator) regression is a modified Least Squares Parameter Estimation Technique for models linear in their parameters. In LASSO an additional penalty term in the least squares equation leads to parameter space shrinkage such that most entries in the Matrix W of mutual transcription strength control parameters of the genes become zero, rendering the connectivity limited and the Matrix W sparse.

LASSO itself was further modified to integrate previous knowledge in molecular terms supplied by gene regulatory databases. Hence, the proposed approach is a robust data and knowledge based algorithm. The authors found that the distinct therapeutic outcome correlates with an early differential expression of many genes coding for cytokines and other immune.system-related proteins.

On the basis of this modelling the authors proposed that the biological ethanercept is not able to control the disease in non-responders because of a differential gene expression regulation of the therapeutic target TNF-alpha. Thus, the result of the investigation is not so much the elucidation of immune mechanisms but rather the identification of the therapeutic target. The reason for its different gene expression regulation is unfortunately still obscure. However, the authors promise efforts to render the therapy successful for each patient.

5.3.2 Cognitive Immune System Model

The paper 'Modelling the Cognitive Immune System Theory with a Learning Classifier System' by Voigt is a reinterpretation of John Holland's Learning Classifier Algorithm in Machine Learning into terms of Cohen's Cognitive Immune Systems Theory [58]. The authors describe how the characteristic features of the theory, namely degeneracy of recognition and context of immune reactions, can be realized in this modified Learning Classifier System. Furthermore, they introduce the representations of the immune agents, the phases of activity that take place in the applied evolutionary mechanism. The computational immune model has been implemented and the various parameters of its operational cycle are presented.

The starting point for developing Artificial Immune System (AIS) was when people began to formalize their descriptive approaches. AIS became a new field of research where principles and mechanisms of the immune system were applied as problem solving methods to different kinds of problems.

The computational systems developed in AIS were based on the leading theories in the field of immune systems, namely Burnet's Clonal Selection Theory and Jerne's Network theory. In recent years I. Cohen has suggested a new approach which is based on the Network Theory but goes far beyond it. Cohen considers the immune system as a cognitive system that can learn, which can sense certain environmental aspects, build up an internal representation of them, and make decisions about actions that are required to keep the homeostasis of the individual. Special features of this theory are the degeneracy of recognition events, which is in sharp contrast to the assumption of monospecificity in clonal selection, and the embeddedness of immune activities in a context that is created by immune agents. Degeneracy of recognition means several equivalent functionalities rather than several copies of the same functionality:

Autoimmune diseases are not mentioned in this paper. However, it might be investigated by varying parametrization of the implemented computational immune system whether phases of activity can be generated that correspond to false recognition of self as non-self.

5.4 Robustness in Systems Biology

Systems Biology Projects at the MPI for Molecular Genetics in Berlin integrate experimental and modelling efforts. Two of them, that concern Model Discrimination in Cellular Biology, especially take into account the issue of robustness [59].

Biological problem	Modelling techniques
Discrimination of internal regulatory circuits from response to external signals (robustness vs. sensitivity of metabolism).	- Simulation of ODE systems - Analysis of perturbation experiments
Analysis and quantification of redundancy and robustness in the cellular network (in particular in signalling pathways).	- Boolean and discrete-valued networks - Simulation of ODE systems - Analysis of perturbation experiments

5.5 Evolution, Robustness, Regeneration

5.5.1 Computing robustness in biology

An extremely interesting article on computing robustness in biology can be found at [60]. *Robustness and fragility may hold the key to advances in biology and medicine*, says Brian Cogan. One of the key sentences in this article reads like this:

One could say that robustness allows evolution to happen and that evolution favours robustness. It refers both to recent research of the Santa Fe Institute [61] and to an article by Nyquist [62].

5.5.2 Robust Design – a repertoire of biological, ecological, and engineering case studies

The contributors to this study of robustness as a complex systems design principle explore the features of phenomena that are responsible for robustness or fragility [61]. The papers address the tension between stasis and response to change; opportunities for innovation; vulnerabilities to collapse; effects of interactions among different subsystems; and the role of adaptation and learning. The authors assess the extent to which knowledge about robustness can be used to gain a better understanding of biological, ecological and computational systems.

5.6 Robust Tissue Engineering

How might regeneration have come into existence? One possible answer is: by evolution. Prior to this question, however, is the question on how might tissues have come into existence?

Have tissues evolved out of biotope populations of unicellular protozoa due to selection pressure that favoured survival of heterogeneous assemblies of cells interacting and communicating in division of labour, rather than survival of unicellular species? This question seems to be open. If so, however, then regeneration of tissue instead of propagation of cells might contribute to the robustness of tissues.

A definite answer to this question is an essential prerequisite to Nature-inspired robust tissue engineering.

To realize the full benefits of tissue engineering, novel bioreactors are essential for the controlled fabrication of reproducible and robust tissue.

5.6.1 Enabling Technologies for Tissue Engineering and Regenerative Medicine

The Department of Health and Human Services consisting of the participating organizations: National Institutes of Health (NIH), National Institute of Standards and Technology (NIST), National Science Foundation (NSF) calls for contributions on 'Enabling Technologies for Tissue Engineering and Regenerative Medicine' and considers the following research areas important to achieve at robust tissue engineering:

- Predictive computational models for engineering functional 3-dimensional (3D) tissues
- 3D fabrication technologies for tissue engineering
- Novel bioreactors to precisely control the chemical and mechanical environment for functional 3D tissue growth or to rapidly expand functional

stem cells and robust evaluation methods to determine environmental requirements

- Quantitative, non-invasive tools to monitor structure, composition, and function of engineered tissues in real time
- Technologies for manufacturing of tissue engineered products including preservation, sterilization, packaging, and transport, and methods for quantitatively evaluating cell and tissue health and phenotypic stability throughout the process.

5.7 Self-repairing Systems

Self-Repairing Computers. By embracing the inevitability of system failures, recovery-oriented computing returns service faster [63].

5.7.1 Exploiting Architectural Design Knowledge to Support Self-repairing Systems

'Exploiting Architectural Design Knowledge to Support Self-repairing Systems' is an article on self-repairing computational systems [64]. Abstract: In an increasing number of domains software is now required to be self-adapting and self-healing. While in the past such abilities were incorporated into software on a per system basis, proliferation of such systems calls for more generalized mechanisms to manage dynamic adaptation. General mechanisms have the advantage that they can be reused in numerous systems, analyzed separately from the system being adapted, and easily changed to incorporate new adaptations. Moreover, they provide a natural home for encoding the expertise of system designers and implementers about adaptation strategies and policies. In this paper, we show how architecture description languages and tools can be extended to provide such generalized dynamic adaptation mechanisms.

5.7.2 Robust, self-repairing systems

'Pattern formation for multi-robot applications: Robust, self-repairing systems inspired by genetic regulatory networks and cellular self-organisation' is an article on Nature-inspired self-repair, self-assembly, and pattern formation in multi-robot systems. Abstract: This work concerns a biologically-inspired approach to self-assembly and pattern formation in multi-robot systems. In previous work the authors have recently studied two different approaches to multi-robot control, one based upon the evolution of controllers modelled as genetic regulatory networks (GRNs), and the other based upon a model of self-organisation in aggregates of biological cells mediated by cellular adhesion molecules (CAMs). In the current work, a hybrid GRN-CAM controller is introduced, which captures the advantages, and overcomes the disadvantages, or both of the original controllers; it combines the adaptability of the evolutionary process with the robustness of an underlying self-organising dynamics. The performance of the new controller is investigated and compared with the previous ones.

For example, one experiment involves the evolution of a robot cluster that can stably maintain two different spatial patterns, switching between the two upon sensing an external signal. Another experiment involves the evolution of a cluster in which individual robots develop differentiated states despite having identical controllers (which could be used as a starting point for functional specialisation of robots within the cluster).

The results show that the combined GRN-CAM controller is more flexible and robust than either the GRN controller or the CAM controller by itself, and can

produce more complex spatiotemporal behaviours. The GRN-CAM controllers are also potentially portable to robotic systems other than those for which they were evolved, as long as the new system implements the underlying CAM model of self-organisation. Some technical issues regarding the implementation of the GRN and joint GRN-CAM systems are also discussed, including the use of 'smart mutation' operators to improve the speed of evolution of GRNs, and evolving the rate of dynamics of the GRN controller to suit the particular task in hand.

5.8 Sustainability in Models of Society and Environmental Protection

In the context of sociological models of direct or cooperative democracy in the society and in ecological models of environmental protection there appears the notion of sustainability. There is much temptation to consider the relation between sustainability and robustness. Indeed the meaning of both these notions is very close.

These models reflect opinion and attitude of Alternative Nobel Price Winners of whom Hans Peter Dürr is a member. They prefer learning from Nature to 'improving', repressing and dominating her. They understand that Nature consists of systems that are self-maintaining since they do not consume more than they invest. To respect natural rules of limitation means in political practice a profound reconstruction of Society, rather than minor corrections, and careful treatment of Nature. To render man-made systems sustainable, Dürr writes, they have to be organized in cycles and networks and open to constant change. However, the robustness of complex systems, such as Nature and Society, is not without limits. Therefore, Nature and Society may become dysfunctional or get collapsed if they are affected by stress that exceeds their adaptability. The reason, however, is different for Nature and Society. Due to scientific and technological progress of mankind, Nature, although robust, is at present confronted to attacks she has never seen before and that obviously outperform her adaptability. In contrast, Society, as a man-made system, is not yet robust enough to stand the challenges of current economy and ecology.

Dürr pleads for respecting the insights of modern science showing that the complex system of the living world requires careful treatment. Economy and technology must be structured in a transparent modular and fault friendly fashion rather than being giant like, monolithical, global and, therefore, error-prone and scarcely accessible to control. According to the principle of subsidiarity, in modular systems the partial tasks of the system behaviour are partitioned such that in division of labour each task is performed by the module that is most competent for. Fault localization and repair is much easier in modular structures. Robustness of the system must not be based on competition of isolated components but rather on their cooperation and mutual support. This kind of systems is capable of self-organisation, self-maintenance, creativity to react to crises and of conflict resolution.

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6 Robust Algorithms

The web page 'Thesilog: Robust Algorithms' is an on-line discussion on Robustness of Algorithms in general [66]: Not very seriously, I have thought about robust algorithm, i.e. an algorithm that is insensitive to its changes. Is it possible?! To answer this question, I must know what is an algorithm and what can be considered as an algorithm...

6.1 Robust Statistics, Robust Regression

The most important problem with previous approaches is that they can not cope with outliers. A solution to this problem was proposed by Fischler and Bolles [67]. Their algorithm is called RANSAC (RANDOM SAMPLING CONSENSUS) and it can be applied to all kinds of problems [68]. There exist Robust Algorithms in several distinct research domains. A general definition of algorithm robustness, presumably, can not be given.

6.2 Robustness and Artificial Intelligence

6.2.1 Application of Artificial Intelligence Techniques

Application of Artificial Intelligence Techniques. to Obtain Robust Dynamic Equivalents [69]. Summary: This paper presents an application of artificial neural networks (ANN) to power systems. ANN are tested to construct dynamic equivalents, which is considered a hard task in the context of power systems. The main objective is to reproduce the complex voltage at frontier nodes. The simulation results prove the applicability and robustness of this innovative approach.

6.2.2 Robust Back Propagation Learning [70]

6.2.3 Robust wavelet neural networks

Function approximation using robust wavelet neural networks [71]. Summary: Wavelet neural networks (WNN) have recently attracted great interest, because of their advantages over radial basis function networks (RBFN) as they are universal approximators but achieve faster convergence and are capable of dealing with the so-called 'curse of dimensionality'. In addition, WNN are generalized RBFN. However, the generalization performance of WNN trained by least-squares approach deteriorates when outliers are present. In this paper, we propose a robust wavelet neural network based on the theory of robust regression for dealing with outliers in the framework of function approximation. By adaptively adjusting the number of training data involved during training, the efficiency loss in the presence of Gaussian noise is accommodated. Simulation results are demonstrated to validate the generalization ability and efficiency of the proposed network.

6.3 Robustness in Bayesian Inference

The notion of robustness also applies to Bayesian Inference.

6.3.1 Robustness and Model Comparison [72]

6.3.2 Analysis of prior distributions and prior robustness

Chapter 3 of the book 'The Bayesian Choice: A decision theoretic Motivation' is called 'From Prior Information to Prior Distribution' and contains the Analysis of prior distributions and prior robustness [73].

6.3.3 Asymptotic global robustness in Bayesian decision theory

Asymptotic global robustness in Bayesian decision theory [74]. Abstract: In Bayesian decision theory, it is known that robustness with respect to the loss and the prior can be improved by adding new observations. In this article we study the rate of robustness improvement with respect to the number of observations n . Three usual measures of posterior global robustness are considered: the (range of the) Bayes actions set derived from a class of loss functions, the maximum regret of using a particular loss when the subjective loss belongs to a given class and the range of the posterior expected loss when the loss function ranges over a class. We show that the rate of convergence of the first measure of robustness is \sqrt{n} , while it is n for the other measures under reasonable assumptions on the class of loss functions. We begin with the study of two particular cases to illustrate our results.

6.3.4 Robustness in Multivariate Regression Models

Classical and Bayesian Inference Robustness in Multivariate Regression Models [75]. We consider a one-to-one correspondence between points $\mathbf{z} \in \hat{\mathcal{A}}^n - \{0\}$ and pairs (\mathbf{y}, r) , where $r > 0$ and \mathbf{y} lies in some space Y , through $\mathbf{z} = r\mathbf{y}$. As an immediate consequence, we can represent random variables \mathbf{Z} that take values in $\hat{\mathcal{A}}^n - \{0\}$ as $\mathbf{Z} = R\mathbf{Y}$, where R is a positive random variable and \mathbf{Y} takes values in Y . By fixing the distribution of either R or \mathbf{Y} while imposing independence between them, we generate classes of distributions on $\hat{\mathcal{A}}^n$. Many families of multivariate distributions (e.g., spherical, elliptical, l_q spherical, v spherical, and anisotropic) can be interpreted in this unifying framework. Some classical inference procedures can be shown to be completely robust in these classes of multivariate distributions. We use these findings in the practically relevant context of regression models. Finally, we present a robust Bayesian analysis and indicate the links between classical and Bayesian results. In particular, for the regression model with iid errors up to a scale, we provide a formal characterization for both classical and Bayesian robustness results concerning inference on the regression parameters.

6.4 Robust Learning

6.4.1 Robust Learning with Missing Data

The paper 'Robust Learning with Missing Data' introduces a new method, called the robust Bayesian estimator (RBE) [76]. Abstract: This paper introduces a new method, called the *robust Bayesian estimator* (RBE), to learn conditional probability distributions from incomplete data sets. The intuition behind the RBE is that, when no information about the pattern of missing data is available, an incomplete database constrains the set of all possible estimates and this paper provides a characterization of these constraints. An experimental comparison with two popular methods to estimate conditional probability distributions from incomplete data – Gibbs sampling

and the EM algorithm – shows a gain in robustness. An application of the RBE to quantify a naive Bayesian classifier from an incomplete data set illustrates its practical relevance.

6.4.2 Coherent Concepts, Robust Learning

The Authors of the paper 'Coherent Concepts, Robust Learning' establish the connection between coherency and robust learning [77]. Abstract: We study learning scenarios in which multiple learners are involved and 'nature' imposes some constraints that force the predictions of these learners to behave coherently. This is natural in cognitive learning situations, where multiple learning problems co-exist but their predictions are constrained to produce a valid sentence, image or any other domain representation. Our theory addresses two fundamental issues in computational learning: (1) The apparent ease at which cognitive systems seem to learn concepts, relative to what is predicted by the theoretical models, and (2) The robustness of learnable concepts to noise in their input. This type of robustness is very important in cognitive systems, where multiple concepts are learned and cascaded to produce more and more complex features. Existing models of concept learning are extended by requiring the target concept to cohere with other concepts from the concept class. The coherency is expressed via a (Boolean) constraint that the concepts have to satisfy. We show how coherency can lead to improvements in the complexity of learning and to increased robustness of the learned hypothesis.

6.4.3 Robust Learning from Bites for Data Mining

Robust Learning from Bites for Data Mining [78]. Summary: Some methods from statistical machine learning and from robust statistics have two drawbacks. Firstly, they are computer-intensive such that they can hardly be used for massive data sets, say with millions of data points. Secondly, robust and non-parametric confidence intervals for the predictions according to the fitted models are often unknown. Here, we propose a simple but general method to overcome these problems in the context of huge data sets. The method is scalable to the memory of the computer, can be distributed on several processors if available, and can help to reduce the computation time substantially. Our main focus is on robust general support vector machines (SVM) based on minimizing regularized risks. The method offers distribution-free confidence intervals for the median of the predictions. The approach can also be helpful to fit robust estimators in parametric models for huge data sets.

6.4.4 Research on robust learning

Pittsburgh Science of Learning Center (PSLC) supports research on robust learning and is creating a research facility, LearnLab [79]. PSLC's LearnLab is a national resource for learning research that includes:

- Authoring tools for online courses, experiments, and integrated computational learner models
- Support for running in vivo learning experiments
- Longitudinal microgenetic data from entire courses
- Data analysis tools, including software for learning curve analysis and semi-automated coding of verbal data.

6.4.5 Robust Learning and Segmentation

Robust Learning and Segmentation for Scene Understanding [80]. Abstract: This thesis demonstrates methods useful in learning to understand images from only a few examples, but they are by no means limited to this application. Boosting techniques are popular because they learn effective classification functions and identify the most relevant features at the same time. However, in general, they overfit and perform poorly on data sets that contain many features, but few examples. A novel stochastic regularization technique is presented, based on enhancing data sets with corrupted copies of the examples to produce a more robust classifier. This regularization technique enables the gentle boosting algorithm to work well with only a few examples. It is tested on a variety of data sets from various domains, including object recognition and bioinformatics, with convincing results. In the second part of this work, a novel technique for extracting texture edges is introduced, based on the combination of a patch-based approach, and non-parametric tests of distributions. This technique can reliably detect texture edges using only local information, making it a useful preprocessing step prior to segmentation. Combined with a parametric deformable model, this technique provides smooth boundaries and globally salient structures.

6.5 Robustness – Fuzziness – Fault Tolerance

6.5.1 Key challenges in the fault-tolerant control

Key challenges in the fault-tolerant control problem are to design: (a) a sufficiently robust controller which is reconfigurable, (b) a robust fault diagnosis scheme and (c) a suitable reconfiguration mechanism [81]. This very interesting site describes the following Projects:

- Fault-tolerant control
- Non-linear Observers
- Neural Network Observers
- Identification, Modelling & Canonical Structures for Neuro-Fuzzy Networks
- Comparison of Fuzzy Modelling Approaches

6.5.2 Robustness of fuzzy control rules [82]

6.5.3 Robustness of fuzzy decision trees

An article on improved robustness of fuzzy decision trees can be found at [83]

6.5.4 Improvement of robustness through incorporating fuzziness

The article 'Improvement of robustness through incorporating fuzziness' deals with improvement of flexibility and robustness through incorporating fuzziness [84].

6.6 Robustness and Adaptation in Data Mining

6.6.1 Robust Cluster and Rule Based Prediction out of Data

Data Mining is a means of knowledge discovery by recognizing patterns, regularities or interdependences in data material, for the purpose of prediction. Data Mining is data-driven analysis in the absence of any model of the system producing the data. The results are in terms of cluster partitions of the objects

carrying the data (e.g. patients in health care applications) and in terms of prediction rules connecting clusters of objects with respect to different variables in a heterogeneous data material.

Thus, this treatment of Data Mining consists of three steps:

- Data-based clustering of training data
- Cluster-based rule extraction and rating
- Cluster and rule-based prediction for unseen test data

For prediction to be reliable both cluster partition and rules have to be robust versus use of different methods of clustering and different methods of rule extraction and rating. In addition, they have to be robust versus different numbers of objects (e.g. patients) involved in Data Mining. In Quality Management this proof is called validation.

In contrast, Data Mining itself has to be adaptive so as to allow use of different methods of clustering and rule extraction and rating as well as involvement of different data volumes.

In the absence of any model, the only possibility to prove the correctness of Data Mining results is their coincidence or at least compatibility (of highest rated rules) when obtained using different Data Mining methods and different data volumes. In this sense, data and methods have to be adaptive, but results have to be robust.

6.6.2 Adaptation in evolution and in development

The notion of adaptation, central to Evolution Theory, deserves some attention when transferred to technical development, i.e. to design of devices or algorithms to obtain some predefined functionality, in particular reliable prediction in decision support systems.

While adaptivity is desirable during evolution or development, at the end of the process, in contrast, it is desired that the obtained functionality be robust. For this reason, robustness of a device or an algorithm, although surprising at first glance, may be seen as an aspect simultaneous to adaptivity when viewed from the standpoint of the user instead of that of the developer. The developer has to provide the user with the opportunity to change methods and data volumes so that the user can trust in robust results.

Tables 1 and 2 try to illustrate the simultaneity of both adaptivity and robustness and to show how they are mutually conditional. Adaptivity and robustness are not in contradiction to each other, rather they are in a complementary relation. Data analysis methods have to be adaptive for the results to prove robust. Results have to be robust for adaptive methods to meet the predefined functionality.

Table 2, in addition, shows that the specific meaning of both adaptivity and robustness heavily depends on the context, i.e. on the particular type of software tool and its predefined functionality.

The focus is database application, data mining, and decision support by prediction. In the particular case of a decision support system, developer's and user's points of view have to be separated to show how adaptivity of the software is needed to provide the user with robust results of prediction, as shown in Table 3.

Table 3 – The components of a decision support system

	Adaptivity	Robustness
Data	⊗	∅
Methods	⊗	∅
Results	∅	⊗

Two notions of robustness in data mining may be distinguished: Firstly, robustness of rule base as the model of the system and secondly, robustness of prediction for unseen data, i.e. test data

6.7 Robustness of Reverse Engineering for Reconstruction of Gene Regulatory Networks

6.7.1 Robustness Aspects in Context of Gene Regulatory Networks

- Robustness in context of gene regulatory networks has two aspects
- Robustness of the networks themselves
- Robustness of the results of reconstruction from data

6.7.2 Methods of Model Building for Data-based Reconstruction

Methods of model building for data-based reconstruction of gene regulatory networks may be grouped as follows:

- Directed Graphs
- Bayesian Networks
- Differential Equation Systems
- Stochastic Models
- Boolean Networks
- Rule-based Models
- Learning Algorithms
- Artificial Neural Networks

6.7.3 Network reconstruction in a theory of the cell

MTC, Virtual Genetics Lab AB, Fogdevreten 2, Karolinska Institutet, Stockholm, Sweden writes: *A theory of the cell has to include dynamics, regulation, homeostasis, feedback, cycles, clocks, scale free nets, robustness, signalling cascade. Mathematical models have to explain this repertoire by Boolean nets, regulatory networks and their reconstruction as well as their robustness, differential equations.*

6.7.4 Robust and adaptable behaviour of cells

Peter Hagedorn from Risø National Laboratory, Denmark writes: The robust and adaptable behaviour of cells and tissues depends on the operation of complex regulatory biochemical networks. Elucidation of the structure and functioning of such networks poses major experimental and theoretical challenges.

6.7.5 Generic and robust Network modeling

The Neural Computing Research Group (NCRG) at Aston University describes the background of its project: The principal aim for data analysis and modelling is to develop methodologies and tools that are generic and robust, that is, the conclusions drawn from studying particular systems should be applicable to a wide range of microarray studies. Following data capture, image analysis, normalisation, data correction and pre-processing, the starting point for data analysis and modelling is a gene expression matrix (GEM) corresponding to n genes in its rows and m samples (conditions or time points). The purpose of microarray data analysis is two-fold: to investigate the organisation (interrelationships) of genes and/or the dynamic behaviour (interactions) of genes. While the former employs pattern recognition techniques for gene classification, the latter requires parametric modelling to represent gene networks.

6.7.6 Robustness and stability of gene expression patterns under noise

Tianhai Tian and Kevin Burrage from the University of Queensland describe their Stochastic Neural Network Models for Gene Regulatory Networks. In particular, they study robustness and stability properties of gene expression patterns under the influence of noise: *Recent advances in gene-expression profiling technologies provide large amounts of gene expression data. This data raise the possibility for a functional understanding of genome dynamics by means of mathematical modelling. As gene expression involves intrinsic noise, stochastic models are essential for better descriptions of gene regulatory networks. We will present stochastic models by introducing stochastic processes into neural network models that can describe intermediate regulation for large scale gene networks. Poisson random variables are used to represent chance events in the processes of synthesis and degradation. For expression data with normalized concentrations, exponential or normal random variables are used to realize fluctuations. Using a network with three genes, we show how to use stochastic simulations for studying robustness and stability properties of gene expression patterns under the influence of noise, and how to use stochastic models to predict statistical distributions of expression levels in a population of cells.*

6.7.7 Robust statistical methods for Gene expression in medicine

The IMA Workshop 'Statistical Methods for Gene Expression: Microarrays and Proteomics' concentrates on robust statistical methods [85]. Various microarray technologies for measuring RNA transcript abundance have created some challenging statistical problems. There are many sources of variation in a typical experiment and these can be accounted for using statistical design and analysis-of-variance methodology; but careful attention has to be given to the high-dimensionality and complicated interactions. Statistical methods invoked early in the data analysis pipeline can remove systematic errors and improve subsequent inferences. Robust statistical methods are important to account for influential observations that may be hidden in massive data sets. A wide range of supervised and unsupervised learning methods have been considered to better organize data, be it to infer coordinated patterns of gene expression, to discover molecular signatures of disease subtypes, or to derive various predictions. Related efforts aim to reconstruct regulatory networks from large sets of expression data. Theoretical problems arise in statistical inference when attempting to address thousands of gene-specific hypotheses at once, such as the problem to bound the

rate of false detections of differential expression. Further, research in statistical computing concerns infrastructure to enable efficient and flexible calculations with large expression data sets. The workshop will consider these and other pressing problems generated in current research.

Reconstruction of regulatory networks generally takes into account the investigation of robustness. As a standard approach, reconstruction of regulatory networks contains the following steps of analysis : draft construction of regulatory networks e.g. by Singular Vector Decomposition or Robust Regression, optimization of the network structure by pruning, growing and evaluation of alternative structures, dynamic analysis of robustness and critical states of the network, validation of the network by database search and further empirical data.

The extent of coincident substructures among different hypothetical network structures in a comparative structural analysis is the measure of robustness of the reconstruction approach.

Robust data analysis requires new methods for clustering, visualisation, reverse engineering, and time series analysis [86].

6.8 Robustness – Evolutionary Game Theory

6.8.1 Robustness and Conceptual Analysis in Evolutionary Game Theory in Sociology

A variety of robustness objections have been made against evolutionary game theory [87]. One of these objections alleges that the games used in the underlying model are too arbitrary and oversimplified to generate a robust model of interesting prosocial behaviors. In this paper, I argue that the robustness objection can be met. However, in order to do so, we must attend to important conceptual issues regarding the nature of fairness, justice, and other moral concepts. Specifically, we must better understand the relationship between moral concepts and formal characterizations of games.

6.8.2 What have we learned from Evolutionary Game Theory so far?

'What have we learned from Evolutionary Game Theory so far' is a paper by Weibull [88]. Abstract: Evolutionary theorizing has a long tradition in economics. Only recently has this approach been brought into the framework of non-cooperative game theory. Evolutionary game theory studies the robustness of strategic behaviour with respect to evolutionary forces in the context of games played many times in large populations of boundedly rational agents. This new strand in economic theory has lead to new predictions and opened up doors to other social sciences. The discussion will be focused on the following questions: What distinguishes the evolutionary approach from the rationalistic? What are the most important findings in evolutionary game theory so far? What are the next challenges for evolutionary game theory in economics? An evolutionary strategy is an evolutionary stable strategy ESS if it is robust against evolutionary pressure from any foreign strategy of invaders into the population.

6.8.3 Evolutionary game theory and multi-agent reinforcement learning

Abstract: In this paper we survey the basics of reinforcement learning and evolutionary game theory, applied to the field of multi-agent systems. This paper contains three parts. We start with an overview on the fundamentals of reinforcement learning. Next we summarize the most important aspects of evolutionary game theory. Finally, we discuss the state-of-the-art of multi-agent

reinforcement learning and the mathematical connection with evolutionary game theory. This article has textbook character.

6.8.4 Evolutionary Game Theory (EGT) developed by theoretical biologists

Evolutionary Game Theory (EGT) was developed by theoretical biologists, especially John Maynard Smith (cf. Maynard Smith 1982) as a formalization of the neo-Darwinian concept of evolution via natural selection. It builds on the insight that many interactions between living beings can be considered to be games in the sense of Game Theory (GT) every participant has something to win or to lose in the interaction, and the payoff of each participant can depend on the actions of all other participants. In the context of evolutionary biology, the payoff is an increase in fitness, where fitness is basically the expected number of offspring. According to the neo-Darwinian view on evolution, the units of natural selection are not primarily organisms but heritable traits of organisms. If the behavior of organisms, i.e., interactors, in a game-like situation is genetically determined, the strategies can be identified with gene configurations.

Robustness against small amounts of mutation means that there is an environment of x such that all trajectories leading through this environment actually converge towards x . In the jargon of dynamic systems, x is then asymptotically stable or a point attractor. It can be shown that a (possibly mixed) strategy is an ESS if and only if it is asymptotically stable under the replicator dynamics.

6.9 Self-configuration, Self-repair, Self-healing

6.9.1 The relation between self-organisation and robustness

The relation between self-organisation and robustness is described in a paper developed at a Workshop in Helsinki [90]. One of European industry's biggest problem is low Overall Equipment Effectiveness (OEE). Increasing OEE would have tremendous economic impact. ICT systems and embedded systems technology is capable of producing large increases in productivity.

The workshop will include presentations covering perspectives from different aspects. Users, researchers and developers, technology and systems providers and operators. The workshop will address issues related to how self-healing and self-diagnostic systems and supporting technologies can contribute to increased OEE values .

To tackle the challenge of self-diagnosing and self-healing automation systems the ICT system must meet the requirements and provide the necessary support to implement for example model-based diagnostics, fault prediction tools and decision support tools. It is also envisioned that an ICT system must be self-diagnosing and self-healing to provide the necessary robustness. One important goal is the development of a Scalable Self-Organizing Sensor Network.

6.9.2 Self-healing systems, Self-repairing systems

Self-Healing Systems. Scientific American has a fascinating five page article on recovery-oriented computing; self-repairing Computers. This gives a nice review of the motivations behind self-healing systems, as well as the technology [91].

6.9.3 Research Perspectives in Self-Healing Systems

In self-healing systems, where it is important to monitor and check system behavior at runtime, runtime verification can provide new and relevant solutions and mechanisms in order to generate test oracles in an automated manner and to

use these test oracles for monitoring the program during execution. The use of invariants in self-healing systems is a promising solution for the monitoring phase [92].

The term autonomic computing introduces a new interesting and promising research field. Self-adaptive software requires non-functional requirements such as high dependability, robustness, adaptability and availability.

6.10References Chapter 6

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7 Appendices: Comparison of Approaches to Robustness

7.1 Books, Projects, Papers

7.1.1 Approach via multivariable digital non-linear control [93]

7.1.2 Robustness, Modularity and Evolutionary Design of Living Systems

'Robustness, Modularity and Evolutionary Design of Living Systems' is the title of a DFG project started in 2003 [94]. The central goal of the collaborative research centre is the development of theoretical concepts, mathematical models, and methods for data analysis that can be used to elucidate the 'design' principles of living systems, and to analyse their functional relevance. In order to achieve this goal, theoreticians and experimentalists jointly conduct a number of coordinated projects in which they explore the structural properties of cellular signalling pathways, regulatory and neuronal networks, and organismic interactions. The long-term plan is to develop a comparative and integrated understanding of the ways in which living systems solve the problem of robustness and adaptability, the role modularity plays in this context, and what favours and constrains the evolution of these properties. The individual projects study various components of the nervous, immune, and reproductive systems, and the regulation of cell differentiation and gene expression. Some projects focus on the development of pathologies that illuminate the limits of robustness.

7.1.3 Papers on Robustness in Systems Biology Issue 1

Already the first Volume of a new Journal on a new research direction, *Systems Biology* Issue 1, contains several articles on Robustness, under the aspects of both system robustness and algorithm robustness.

Liu et al.: *Copasetic Analysis: A Framework for the Blind Analysis of Microarray Imagery*:

This is integrative software for microarray data analysis. It consists of several different interactive algorithms of artificial intelligence with expert knowledge included. Robustness of results is tested at different signal to noise ratios.

Schuster et al.: *Analysis of Structural Robustness of Metabolic Networks*:

The number of elementary flux nodes of cellular metabolism is not an appropriate measure of structural robustness versus environmental influence on cells. Rather, measures of robustness should be based on relative diminution of the number of modes at knock-out of a particular enzyme. Three of them are tested at both fictive and realistic examples of metabolic networks. It is shown quantitatively that *E. coli* which must adapt to different conditions is more robust than erythrocytes are, living under homeostatic conditions.

Jacobsen et al.: *Identifying Mechanisms Underlying Complex Behaviors in Biochemical Reaction Networks*:

The authors use a modularization approach. They decompose an extensive system of ordinary differential equations with known parameters as a model of a

network with sustained oscillations and multi-stability into several subsystems in order to identify the mechanisms that cause sensitivity, robustness, and specific functions. They analyse the interaction between the sub-systems that produce an observed cellular behaviour.

7.1.4 Experiment design, parameter estimation, robustness analysis

The 'Expression of Interest' 'System-Theoretical Analysis of Genomic and Signalling Models' is an integrative discussion of experiment design, parameter estimation and robustness analysis [95].

The goal of the Integrated Project is the development of design and analysis methods specially suited for mathematical models in systems biology. Some of them help modellers choosing a good type of model for their problem, other methods make it possible to understand complex dynamic phenomena like crosstalk, feedback regulation and robustness.

7.2 Vision and Outlook

7.2.1 Nature-inspired evolutionary algorithms

In context of Nature-inspired evolutionary algorithms, of particular interest is the role of self-organizing principles for evolutionary computation. Self-organization is fundamental to the developmental process at all levels: molecular, genetic, and cellular. With new reports of the number of genes in the human genome being revised downwards, the role of self-organization in complex webs of gene regulation is all the more salient. Given these new findings, perhaps the self-organization of genotypic instructions that transform genotype to phenotype is a key missing ingredient necessary for unleashing the evolution of complex and scalable solutions with emergent phenomena such as: scale-freeness, adaptability, innovation, evolvability, and robustness.

7.2.2 Developmental Algorithms

Natural evolution and developmental biology have produced adaptable and self-repairing systems of great complexity. Therefore, it is anticipated that models of biological cells and multicellular development are another source of knowledge that will aid us in making evolutionary algorithms more scalable. Regardless of the developmental model or generative representation chosen – cellular automata, genetic regulatory networks, L-systems, etc – we must understand exactly what gives such systems their computational power and exactly how they affect evolvability.

7.2.3 Robotics and evolutionary computation

Particular areas of current explosive growth in scientific understanding relevant to the success we see in biological systems include the study of *interaction, development, symbiosis* (and its evolutionary extreme, symbiogenesis), *embodiment, epigenetics, and developmental robustness and plasticity, higher-level units of individuality (with heritability of fitness), evolutionary developmental morphogenesis with genetic regulatory control, and massively parallel and distributed multicellular networks* with special connectivity characteristics. Current practice in robotics and evolutionary computation is benefitting from ever deeper understanding of these principles and mechanisms underlying the success of life-on-earth, as generalized to other domains by Artificial Life.

7.2.4 Robustness through collective intelligence

Recently, ant algorithms and swarm intelligence systems have been offered as a novel computational approach that replaces the traditional emphasis on control, preprogramming, and centralization with designs featuring autonomy, emergence, and distributed functioning. These designs are proving flexible and robust, able to adapt quickly to changing environments and to continue functioning even when individual elements fail.

7.3 Recent Research Contributions Relevant to Robustness

The definition of the three Focus Groups in NiSIS is considered a clever approach to learning from Nature since it guides reasoning on Nature's principles that render living systems flexible, robust, fault-tolerant, noise-resistant, adaptive, evolvable in propagating populations.

7.3.1 Network Design and Robustness Issues

The Systems Theory Group, Dept. Mathematics, Universiteit Maastricht, UM is competent in network design and robustness issues. It is known for General simulation framework for network systems, Piecewise Linear Dynamic Modeling and Identification of Gene-Protein Interaction Networks, Identifiability and controllability of natural information processing networks under chaos and noise, Network Modelling and Simulation from sparse, incomplete and uncertain data, Qualitative Network Modeling, The Group studies the role of chaos and stochastic fluctuations in robustness and self-organized control in networks, reverse engineering from microarray data, Robust network design.

Piecewise linear state space models of gene protein networks are treated in the paper on Robust Identification of Piecewise Linear Gene-Protein Interaction Networks by Westra and Peeters [96]. The treatment follows the dynamic state space approach with special interest in state space partition for local linearization, punctuated equilibria and sparse hierarchical interaction. It focuses on exact computation of the interaction matrix in reverse engineering from microarray time series data and its robustness to intrinsic and extrinsic noise. The algorithm is explained in mathematical detail. Design principles of robustness and control are derived from Nature.

7.3.2 The final aim of NiSIS

The final aim of the NiSIS project is understanding the principles and properties of living systems, such as dynamics, networks, flexibility, resilience, recovery, robustness, self-organisation, multi-scaled interconnection and communication, simplicity of basic elements, emergence, modularity, decentralization, fault-tolerance, noise-resistance, adaptation, evolution in propagating populations, and their implementation into both computational algorithms and artificial Smart Information Systems/Smart Adaptive Systems via real world applications.

7.3.3 Decentralized Modeling and Decentralized Thinking

Robustness studies are part of Modelling decentralized structures. 'Decentralized Modeling and Decentralized Thinking' is a verbal consideration on decentralization principles and decentralization modelling, with references to self-organization as organization among individuals without any organizer, and to randomness and order [97].

'Bird Flocks and Zebra Stripes' [98] is a rather nice introduction to populations as biological decentralized structures, including Self-Organization, Self-Organized Patterns, Evolution, Adaptation, Emergence, Robustness etc.

7.3.4 Robustness through Sparseness in Network Models

Data-based Extraction of Hypotheses about Gene Regulatory Networks in Liver Cells by Guthke et al. is a paper on data-based network reconstruction [99]. Hypotheses about the signalling pathways after LiCl stimulation of liver cells were generated by clustering and network reconstruction from gene expression time series data. Due to the large number of potential interaction partners the selection of appropriate network nodes was the crucial step in the data analysis. This selection was performed by filtering differentially expressed genes at different sampling time points. The links between network nodes were revealed by the NetGenerator algorithm that minimizes both the model fit error and the number of non zero parameters in the linear kinetic equations of gene expressions under the restriction of available biological knowledge. Kinetic clustering of gene expression time series revealed 10 different kinetic types associated with individual subsets of differentially expressed genes and a representative gene. Model validation was performed by adding normally distributed noise to the measured data. This type of modelling control reveals at the same time controlled networks robust to noise.

7.3.5 Robustness through Metabolic Control

Analysis of Metabolic Control Strategies by Bayer is a verbal paper on principles of adaptability and robustness of biological systems [100]. Due to their complexity, cells have evolved multiple regulatory networks to control metabolism, growth and replication. Hierarchical organisation, modularisation, redundancy by development of alternative pathways and feedback control circuits are mentioned as key elements, mechanism and strategies to achieve both adaptability and robustness. Issues discussed in detail are key elements of (transcriptional) regulation, such as Sigma-factors, transcription factors; regulatory strategies, such as two- component regulatory systems (phosphorylation/dephosphorylation), regulatory motifs and models; definition of robustness, basis mechanism that confer robustness to biological and engineered systems. Analytical platforms providing insights on molecular level will improve the monitoring of individual components and thereby facilitate comprehension of their interplay.

7.3.6 Robustness through collective intelligence

Applied Nature Inspired System: A Survey by Lhotska et al. reviews examples of Nature-inspired software applications mostly drawing inspiration from collective behaviour of colonies with particular mechanisms of communication between individuals [101]. Nature-inspired modelling and simulation in general is aimed at understanding fundamental properties of natural systems such as dynamics, flexibility, robustness, self-organization, simplicity of (network) elements and decentralization without central control (in colonies and collectives). Search items chosen for Google are swarm intelligence, ant colony optimisation, particle swarm optimisation, artificial immune systems, swarm robotics. Both ant colony optimisation and particle swarm optimisation are algorithms mainly suited for optimisation problems, but also for clustering, data mining, and dynamic task allocation. Differences between particle swarm optimisation and genetic algorithms are explained. Swarm robotics is an emerging field of collective robotics. Artificial immune systems are population algorithms that mimic foreigner recognition, memory

and protection. Also they are applied to anomaly and fault detection, clustering, learning, optimisation. Many examples of application to problem solving are described, even prior to real world applications or technical implementations. Projects and conferences, software systems and journals are discussed. These algorithms are important especially for computation and telecommunication systems, also for social, ecological and economical systems, and of course for modelling optimisation and control of living systems.

7.3.7 Robustness through Decentralized Modeling, Division of Labour, Multitasking

Sebastian Zellmer's Task Force on Multitasking of Liver Tissue: The liver is the main organ of intermediary metabolism. Different bio-molecules are synthesized, degraded and modified at the same time in different compartments of hepatocyte tissue in the liver. Glutamine is synthesized by the enzyme Glutamine synthetase and is degraded by the enzyme glutaminase in a different compartment. Therefore, the liver has multitasking capabilities.

The enzyme glutamine synthetase, expressed in the compartment of a small subpopulation of hepatocytes, shows an expression pattern of static localization, and is, therefore, used as a model enzyme to investigate factors and signalling pathways of this expression pattern by data-based modelling from gene array data.

The liver can consequently be interpreted as a massively parallel processing computer (MPP) where each cell can be seen to represent a single processor. As knowledge of regulatory mechanism of metabolic pathways in multi-cellular organs grows, it becomes possible to transfer this knowledge to computer science to create intelligent MPP schedulers. Vice versa, known regulatory mechanisms in computer science may help analyse whether similar regulatory processes are being used in Nature, too.

The scope of the Task Force is to reverse engineer the signal transduction pathways of the heterogeneous expression of proteins within a liver lobulus from gene array data. Next, its response to hormone or cytokine stimulation will be monitored and evaluated by means of the NetGenerator Algorithm. A two-compartment model will be developed to simulate simultaneous synthesis and degradation processes of glutamine synthesis and degradation.

There are also similarities between the compartments of the lobulus and other compartemented structures. Larger warehouses receive goods in varying amounts and composition as the liver does. Supply, storage, modification, and delivery of goods take place simultaneously in warehouses as they do in the liver. Warehouse organisation requires complex regulatory schedules that may be similar to, and might help understand, those in liver tissue.

7.4 Personal Views of NiMOC Focus Group Members on Robustness

Among the members of the NiMOC Focus Group each one has his specific look at Robustness. Let them pass in review.

7.4.1 Robust Network Reconstruction

Robust network reconstruction by reverse engineering from time series microarray data (Reinhard Guthke).

Systems Biology / Bioinformatics

- Systems Biology approach to understand both infectious processes and the physiology of secondary metabolites from microarray gene expression data.
- Combination of in vivo, in vitro and in silico approaches to discover the structure and dynamics of biological systems by process data analysis and modelling
- Control and optimisation of experiments (model based experimental design), biotechnical product formation and medical processes in diagnostics and therapy.

Methods, Algorithms, Software

- New methods for pattern recognition, data mining, or statistical learning, found promising in other application areas.
- Comparison and ranking of methods based on quantitative results obtained for simulated and real data sets
- Development of improved methods that facilitate the practical analysis and enable the analyst to fully utilize the potential of the selected approaches; relieve the user of possibly critical heuristic decisions by automatic optimization of algorithmic settings
- Interdisciplinary application of the best methods and demonstration of their advantages to medical doctors.
- Primary focus on DNA microarrays and mass spectrometry data from inflammatory diseases and tumors

7.4.2 Robustness in terms of Molecular Biology

Karl Bayer understands robustness in terms of molecular biology.

Analysis of Metabolic Control Strategies

- Adaptability and robustness of biological systems
- Complexity of cells. Definition of robustness
- Multiple regulatory networks to control metabolism growth and replication
- Hierarchical organisation, modularisation, redundancy by development of alternative pathways and feedback control circuits
- Key elements, mechanism and strategies to achieve both adaptability and robustness
- Key elements of (transcriptional) regulation, such as Sigma-factors, transcription factors
- Regulatory strategies, such as two- component regulatory systems (phosphorylation/dephosphorylation),
- Regulatory motifs and models
- Basis mechanism that confer robustness to biological and engineered systems
- Analytical platforms providing insights on molecular level will improve the monitoring of individual components and thereby facilitate comprehension of their interplay

7.4.3 Robustness is self-organized control

Robustness is resistance against chaos and stochastic fluctuation (Ronald Westra).

Modelling and Identification of Gene-Protein Interaction Networks

- Piecewise Linear Dynamic Modeling and Identification of Gene-Protein Interaction Networks
- Identifiability and controllability of networks under chaos and noise
- The role of chaos and stochastic fluctuations in arising macroscopic complexity from microscopic interactions
- Dynamical systems approach on the role of chaos and stochastic fluctuations in robustness and self-organized control of biological systems
- The tendency of natural systems to punctuated equilibria in piecewise linear models with sparse and hierarchic interactions
- Reverse engineering and reconstruction of dynamic genetic networks from microarray data

7.4.4 Adaptation and Robustness are due to intelligent decision making

Adaptation and Robustness are due to intelligent decision making and intrinsic fuzzy logic of living systems (Jon Garibaldi).

- Modelling of human decision making, primarily in the context of medical applications.
- Fuzzy logic to model the imprecision and uncertainty inherent in medical knowledge representation and decision making
- Applied in areas such as the assessment of immediate neonatal outcome and more recently the detection of pre-cancerous changes in cells from FTIR analysis of cervical smears.
- Transfer of medical intelligent systems into clinical use
- Evaluating intelligent systems and mechanisms for their implementation, optimisation techniques such as simulated annealing and genetic algorithms, particularly when applied to the optimisation of decision making models, and in the study of adaptive and time-varying behaviour.

7.4.5 Robustness by simulation and modelling

Kauko Leiviskä looks for principles of robustness by simulation and modelling of living and artificial systems and of industrial processes.

Simulation and Modelling – Modelling tools

- Numerical methods for simulation
- Simulation tools and technology
- Visualization of modelling and simulation results
- AI in Simulation
- Parallel simulation
- Simulation of distributed parameter systems
- Training simulators and real-time simulation
- Simulation in control engineering
- Process plant simulation

Simulation and Modelling – Simulation in industry

- Simulation in pulp and paper industry
- Simulation in metallurgical industry
- Simulation in the energy sector
- Power station design
- Simulation in chemical engineering
- Simulation in biological and environmental engineering
- Simulation in electronic systems
- Simulation in electronic manufacturing
- Simulation in mechanical engineering
- Simulation of marine systems

7.4.6 Robustness and control of model building

Teresa Mendonca: Multiple strategies for on-line parameter estimation via a hybrid method: designed to model parameter estimation

- that combines the ability of neural networks to produce good initial parameter guesses for problems non-linear in their parameters with the fast convergence to the true values only when using good estimates.
- 1st strategy: general applicability
- 2nd strategy intended for models having a structure of several serial blocks.
- Nature-inspired component of the combined algorithm: Artificial Neural Network that assures control of model building.

7.4.7 Robustness of data-based modelling by means of intelligent technologies

Michael Pfaff: Intelligent Technologies cover

- Fuzzy Technology
- Neural Networks
- Machine Learning
- Data Mining
- Knowledge Based Systems

in order to carry out

- BioData Analysis
- BioProcess Analysis

and to provide

- BioProcess Optimization Software
- BioProcess Optimization Strategies

Problems related to bioprocess optimization are usually approached in three major steps:

1. Identification of Optimization Objectives
2. Bioprocess Analysis
3. Bioprocess Optimization

7.4.8 Robustness in terms of Systems Theory

Mannes Poel sees robustness in terms of Systems Theory, Control Engineering, Mathematical and Computational Physics, Operations Research, Stochastics and Statistics

- Telematics and Telecommunication Systems
- Microsystems technology and Micro-electronics
- Embedded Systems
- Systems Theory, Control Engineering and Mechatronics
- Biomedical Signal Processing
- Mathematical Physics and Computational Mechanics
- Multi-Media, Virtual Reality and Human Computer Interaction
- Systems, Information and Software Engineering
- Operations Research, Stochastics and Statistics
- Financial Engineering (FELab, CTIT)

7.4.9 Robustness of Multi-Scale Aggregation Models

Derek A. Linkens:

- Modelling Aggregation and Robustness
- Multiscale Modeling of Complex Systems
- Modelling growing structures, incorporating effects of recovery, static and dynamic re-configuration
- Composing aggregate models from theory-driven and data-driven components
- Components have their own internal dynamics but couple/interact locally and lead to aggregated global properties
- Aggregated behaviour provides robust properties and prediction.
- Reliable and robust performance against variability of parameters of model modules
- Self-organising adaptive behaviour based on steady state performance with extension to dynamic specification

7.5 NiMOC Grand Challenges in Robustness Research

7.5.1 Scalable Robust Self-organizing Sensor (SRSS) network project

The Scalable Robust Self-organizing Sensor (SRSS) network project is an effort by the Protean group at NRL to conduct research of communication protocols applicable to creating networks of distributed and self-organizing sensor devices [102]. However, much of the software developed in this project is applicable to a broad set of dynamic networks, aside from sensor networks.

7.5.2 Proofreading

Nature-inspired Modelling, Optimization and Control might learn some lessons from mechanisms of molecular biology that ascertain robustness by control of heredity genetics.

Fault detection, fault tolerance control, robustness control, e.g. in analogy to proofreading of replicated DNA and translated proteins, similar to self-healing; but proofreading in simple organisms like *Escherichia coli* is already a complex process with operation under constraints.

7.5.3 Balancing Robustness and Evolvability

A very interesting article on proofreading at several levels looking for a single unifying mathematical framework that can encompass such diverse examples of biological robustness is a paper by Lenski [103].

One of the most important features of biology is the ability of organisms to persist in the face of changing conditions. Consider the remarkable fact that every organism alive today is the product of billions of generations in which its progenitors, without fail, managed to produce progeny that survived to reproduce. To achieve this consistency, organisms must have a balance between robustness and evolvability, that is, between resisting and allowing change in their own internal states

One important question is whether there exists a single unifying mathematical framework that can encompass such diverse examples of biological robustness.

7.5.4 Biomass Inferential Sensor

'Biomass Inferential Sensor Based on Ensemble of Models Generated by Genetic Programming' is a book about an application to biotechnology.

A successful industrial application of a novel type biomass estimator based on Genetic Programming (GP) is described. The biomass is inferred from other available measurements via an ensemble of nonlinear functions, generated by GP. The models are selected on the Pareto front of performance-complexity plane. The advantages of the proposed inferential sensor are: direct implementation into almost any process control system, rudimentary self-assessment capabilities, better robustness toward batch variations, and more effective maintenance. The biomass inferential sensor has been applied in high cell density microbial fermentations.

7.5.5 Self-healing Mechanisms, Algorithms and Devices

Self-healing, i.e. diagnose and react to system malfunctions, including regeneration of system components (learned e.g. from the regeneration capacity of liver). Several different self-healing mechanisms are subject to research. There exists research on A Self-healing Mechanism for an Intrusion Tolerance System [104].

The SDH network self-healing mechanism is a very important content in research of SDH networks survivability and is also key to ensure network reliability. There exists research on Connector-based self-healing mechanism for components of a reliable system. Self-healing communication networks inspired by the regeneration capacity of the liver seem not to exist.

A self-healing hybrid sensor network architecture called SASHA is described, that is inspired by and co-opts several mechanisms from the Acquired Natural Immune System to attain its autonomy, robustness, diversity and adaptability to unknown pathogens, and compactness

7.5.6 Decentralized Control

Component-orientated control methods, algorithms, software are still in its early days yet. There exists, however research on Decentralized Control which is described as follows [105].

Several real-world large-scale systems can be viewed as interconnections of linear/nonlinear subsystems with constraints on information flow between the subsystems. We have addressed the decentralized control problem for large-scale systems under various sets of assumptions on the subsystem structures and interconnection topologies. We have also applied these results to a variety of large-scale systems including power networks, smart structures, and satellite formations. Our results on nonlinear control techniques have enabled us to weaken the required assumptions on the structures of the individual subsystems and also on the interconnection (or coupling) among the subsystems. We have also extended the results to include adaptations to compensate for unknown system parameters and also to provide robustness to uncertain terms and appended nonlinear dynamics. Furthermore, we have investigated techniques to achieve decentralized attenuation of disturbance inputs and provided explicit guaranteed bounds on the disturbance attenuation along with tuning strategies to achieve desired disturbance attenuation properties through the proper choice of controller parameters. Decentralization of the control may be achieved both through a centralized or a decentralized design of the decentralized controllers. In our research, both strategies have been utilized.

7.6 Emergent Phenomena/Complex Adaptive Systems

7.6.1 Emergent Robustness

A grand challenge already identified to become a central goal of research in FP7 is understanding robustness as an emergent phenomenon in large, open multi-agent complex systems and emergent computing.

7.6.2 Emergent Computing Workshop: Computation in Cells

The workshop focussed on molecular and cellular interaction networks as computational systems and addressed among others the topic: robustness in biochemical networks [106].

7.6.3 Centre for Emergent Computing

The drive behind the Centre for Emergent Computing is the desire to solve real problems that people care about [107]. Many industrial and commercial problems do not have perfect solutions that can be found in a reasonable time - we need methods that find acceptable solutions in the time available. Solutions are also required that are robust and which can evolve with changing circumstances. Many biological and social systems are very good at doing exactly this, and they can give us insight and inspiration into new methods of problem solving. Emergent Computing studies and uses biologically and socially inspired systems in which complex behaviour at the global level emerges from the interaction of large numbers of simple components.

7.6.4 Inference of system models, under Uncertainty

'Complex System Research and Design in ICT' is a talk about Methodologies for robust computations on models with uncertainty [108]

7.6.5 Large Sparse Matrix Problems

Large Sparse Matrix Problems [109]: The goal of this series of conferences is to address the complex issues related to the solution of general sparse matrix problems in large-scale real applications and in industrial settings. The issues related to sparse matrix software that are of interest to application scientists and industrial users are often fairly different from those on which the academic community is focused. For example, for an application scientist or an industrial user, improving robustness may be far more important than finding a method that would gain speed. Memory usage is also an important consideration, but is seldom accounted for in academic research on sparse matrix solvers. As a last example, linear systems solved in applications are almost always part of some nonlinear iteration (e.g., Newton) or optimization loop. It is important to consider the coupling between the linear and nonlinear parts, instead of focusing on the linear systems alone.

7.6.6 Hierarchical structures from aggregation: emergence of higher level behaviour

As a lesson drawn from studying multicellular systems such as bioartificial liver cell systems, network properties at cellular level determine tissue properties of cell-cell interaction at the next higher hierarchical level. Based on this result, some even more general issues related to nature-inspired information systems can be addressed, such as predictability of complexity, robustness of behaviour and order in highly complex systems.

7.6.7 Simulating Emergent Properties in Complex Systems

Analytical model building and simulation complements the data-based approach to system identification of gene regulatory networks, i.e. reverse engineering and reconstruction from microarray data, and may guide simulation attempts.

Theory explains the mechanisms involved in interaction and how microscopic interactions can give rise to macroscopic complexity which is nothing else than a theory of emergence in complex systems. The theory also considers the huge degree of natural systems' robustness towards chaos and stochastic fluctuations, phenomena playing a vital role in their self-organized control. In biomedical systems self-organized control is closely related to healthiness while its failure is to illness.

The theoretical approach provides lessons from Nature on how to design network structures robust to noise and chaos and able to maintain self-organized control.

7.6.8 Principal Goals and Tools in Simulating Emergent Properties in Complex Systems

- The role of chaos and stochastic fluctuations in robustness and self-organized control in networks, reverse engineering from microarray data, Robust network design

- Attempts to obtain a definition of complex networks in terms of structure, dynamics, robustness, emergence
- Estimation and validation of robustness in multiscale simulation models in analogy to multigrid methods in numerics

7.6.9 Preconditioning techniques

Using preconditioning techniques in large sparse matrix problems in network modelling and simulation, considering robustness improvement, computation speed gain, memory usage, and linearization as a step in some non-linear iteration or optimization loop, as well as parallel processing and object-oriented programming [109].

7.6.10 Emergent Robustness in a Walnut

Mark Miller just published his dissertation: 'Robust Composition: Towards a Unified Approach to Access Control and Concurrency Control' informed by his years of work on the capability-secure E programming language [110]. Great stuff, very relevant to the future of highly distributed, concurrent and secure computing, i.e., the future of computing, and pretty readable too – I blinked and momentarily misread the heading 'Reference Graph Dynamics' (numbered page 66) as 'Reference Graphs for Dummies'. I've only skimmed the document, but Part III, *Concurrency Control*, looks the most interesting and hardest, while Part IV, *Emergent Robustness* should be accessible and thought provoking to anyone with marginal technical literacy [111].

7.6.11 Emergent robustness in competition between autocatalytic chemical networks.

Résumé/Abstract: The origin of auto-catalytic networks has been proposed as an initial step in prebiotic evolution. It is possible to derive simple models where auto-catalytic networks naturally arise from simple chemical mixtures. In order for such a system to develop, there needs to be some degree of stability, what is characterised as 'robustness'. We demonstrate that competing systems generate this robustness as they create a distributed network of catalytic pathways.

7.6.12 Robustness of multi-scale multi-tasking aggregated Systems

Three-dimensional Bioartificial Human Liver Cell Systems: Model for Dynamic Description and Prediction of Hepatozyte Function:

1. Theme and objective

The focus lies on investigating the liver cell system under physiological conditions by data mining and pattern recognition methods to obtain a rule based expert system as a semiquantitative model and a module for hybrid (e.g. fuzzy) mathematical modelling to predict the behaviour of the bioartificial system with disturbed input. The rule based systems and hybrid mathematical models involve previously unknown hypotheses, which will be verified by crucial experiments with the bioartificial human liver cell system designed by these models. The result is a robust, standardized and quantitatively and dynamically characterized bioartificial human liver cell system that can be used for research and therapy.

2. State of the art in science and technology

Systems Biology aims understanding of structures and of dynamic behaviours of the system such as cells and organisms, how to control the system and how to design the system such as bioartificial systems [112]. Methods were established to understand the design patterns and roles of feedback, redundancy, and modularity to attain a high-level of stability and robustness [113].

3. Expected results

The bioartificial human liver cell system with hepatocytes in their physiological environment including also other human liver cells will be developed and characterized in standardized manner using Mini-DNA arrays and other specific sensors together with a rule based expert system and hybrid mathematical, e.g. dynamic fuzzy models. These models formulate hypotheses for understanding of structures on genomic, metabolic and cellular as well as population level. The dynamic behaviours of the model will be compared with that of the experimental one to validate the hypotheses about the regulatory networks on epigenetic and metabolic level. The model will be used to understand the roles of feedback, redundancy and modularity, to control the bioartificial system in a desired state with a high-level of stability and robustness.

7.6.13 Sepsis – Data-driven approach to assist and specify metabolomic modelling

Common dynamic simulation of microarray, mass spectrometric and cytologic time series data will reveal conditions of the robustness, stability patterns and critical states of the predicted network. The final aim is understanding sepsis as emergent phenomenon in the complex immune system and control of the conditions of its emergence in sepsis therapy.

7.6.14 Work packages of multiscale modeling

Multi-scale modelling and simulation of artificial organ culture in bioreactors

Modelling to design and to control bioartificial systems, such as liver cell bioreactors for liver support therapy, are used more and more in medicine. These systems and processes have to be designed and controlled in optimal manner. Prerequisite to design and control of such complex systems and processes is appropriate modelling and simulation. Models should reflect the available knowledge and current information status. The optimality criteria are diverse, e.g. to stabilize the functional state (of the artificial organ) over long time, with minimum cost, with maximum robustness.

The modeling of bioreactor culture processes concerns different levels from balancing of certain ions, via protein-protein, protein-gene, protein-ligand interaction, gene-regulation and signal transduction, via cell-population of human cells in the bioreactor used for supportive therapy up to the device used for the therapy (multi-compartment bioreactor including pumps, membranes and biofilms, drug injection system or galenic systems that control the drug release) or devices for process monitoring. All these different systems have to be modelled at first in separate, modular manner. But they have to be merged and aggregated via certain interfaces and embedded in a more general modeling environment.

Four scales must be considered:

1. Microscale: gene regulatory and metabolic networks, data-based (microarray, mass spectrometry)
2. Mesoscale: intercellular interaction, signal transduction networks, data-based (cytological, receptor binding assay)
3. Mesoscale: culture medium chemistry, data-based (ingredient recipe) / knowledge-based (biochemistry)
4. Macroscale: multi-compartment cultural medium, knowledge-based (rheology, physicochemistry)

The modelling tools at these scales will be:

1. Reverse engineering to identify major expression products after signalling stimulation
2. Cellular automata to model organ cell population, receptor binding models to identify binding ligands
3. Molecular modelling, Quantitative structure activity relations to identify signalling ligands
4. Compartment model, Balance equations, biochemical rate equations, rheological equations, Finite Element components which use neuro-fuzzy hybrid models

Multi-scale modelling and simulation of fermentation of secondary metabolites or recombinant proteins

Modelling to design and to control bioartificial systems, such as microorganisms that produce recombinant human proteins or secondary metabolites are used more and more in biotechnology. These systems and processes have to be designed and controlled in optimal manner. The optimal design and control is based on models and simulation as a prerequisite. The optimality criteria for optimality are diverse, e.g. to maximize the productivity (of protein production) or to stabilize the functional state (of product delivery) over long time, with minimum cost, with maximum robustness.

The model focuses on fermentation either of secondary metabolites or of recombinant proteins. The modeling of these processes concerns different levels from the balancing of certain ions, via protein-protein, protein-gene, protein-ligand interaction, gene-regulation and signal transduction, via cell-population of bacterial cells in the bacterial culture up to the device used for fermentation (multi-compartment fermenter including pumps, membranes and biofilms, substrate injection system or galenic systems that control the product release) or device for process monitoring. All these different systems have to be modelled at first in separate, modular manner. But they have to be merged and aggregated via certain interfaces and embedded in a more general modeling environment.

Four scales must be considered:

1. Microscale: transformation of bacteria by plasmids cloned with eukaryotic fragments, data-based
2. Mesoscale: plasmid replication kinetics and cellular population growth, data-based

3. Mesoscale: gene expression of foreign protein by plasmids and release to cultural medium, data-based
4. Macroscale: multi-compartment cultural medium, knowledge-based (rheology, physicochemistry diffusion, population dynamics)

The modelling tools at these scales will be:

1. (Stochastic) transformation kinetics to obtain transformation yield
2. Hierarchical Cellular automata to model plasmid population growth in bacterial cell population growth,
3. Reverse engineering to identify foreign expression products after transformation stimulation
4. Compartment model, Balance equations, substrate feeding regime, rheological equations, Biomass growth equation, species diffusion equations, Finite Element components which use neuro-fuzzy hybrid models

Multi-scale modelling and simulation of host-pathogen interaction during infection

Modelling to design and to control virtual immune systems are gaining more and more interest in medicine. Virtual Immune systems are computer-assisted simulations and visualisations of immune system functions. To achieve optimum anti-infectious therapy, these systems and processes have to be designed and controlled in optimal manner. The optimality criteria are diverse, e.g. to stabilize the functional state (of the therapy) over long time, with minimum cost, with maximum robustness.

The model focuses on the modelling of host-pathogen interaction during infection as well as on the therapy infectious diseases. The modeling of these processes concerns different levels from protein-protein, protein-gene, protein-ligand interaction, gene-regulation and signal transduction, via cell-population of human cells in the organ of a patient. All these different systems have to be modelled at first in separate, modular manner. But they have to be merged and aggregated via certain interfaces and embedded in a more general modeling environment.

Four scales must be considered:

1. Microscale: interaction and function of the components of the innate immune system, unperturbed, data-based (immuno assays)
2. Microscale: response reactions after infectious stimulation, data-based (diagnostic and therapeutic assays)
3. Mesoscale: gene expression of immune proteins and release into blood, data-based (gene expression time series)
4. Macroscale: Health state of patient, data-based (clinical data)

The modelling tools at these scales will be:

1. Heterogeneous cellular automata modelling the diverse innate immune system components
2. Modified heterogeneous cellular automata with pathogene cells included ,

3. Reverse engineering to identify expressed immune proteins after infection stimulation
4. Compartment model of human body, drug application regime, Finite Element components which use neuro-fuzzy hybrid models

Multi-scale modelling and simulation of autoimmune pathogenesis in immune system

Modelling to design and to control virtual immune systems are gaining more and more interest in medicine. Virtual Immune systems are computer-assisted simulations and visualisations of immune system functions. To achieve optimum anti-autoimmune therapy, these systems and processes have to be designed and controlled in optimal manner. The optimality criteria are diverse, e.g. to maximize the productivity (of healthy immune constituents) or to stabilize the functional state (of the therapy) over long time, with minimum cost, with maximum robustness.

The model focuses on the modelling of autoimmune pathogenesis as well as on the therapy of autoimmune diseases. The modeling of these processes concerns different levels from protein-protein, protein-gene, protein-ligand interaction, gene-regulation and signal transduction, via cell-population of human cells in the organ of a patient. All these different systems have to be modelled at first in separate, modular manner. But they have to be merged and aggregated via certain interfaces and embedded in a more general modeling environment.

Four scales will be considered:

1. Microscale: interaction and function of the components of the innate immune system, unperturbed, data-based (immuno assays)
2. Microscale: spontaneous emergent transformation of some component into quasi pathogene, data-based (diagnostic and therapeutic assays)
3. Mesoscale: gene expression of immune proteins and release into blood, data-based (gene expression time series)
4. Macroscale: Health state of patient, data-based (clinical data)

The modelling tools at these scales will be:

1. Heterogeneous cellular automata modelling the diverse innate immune system components
2. Modified heterogeneous cellular automata with quasi pathogene cells included, pattern recognition
3. Reverse engineering to identify expressed immune proteins after emergent transformation
4. Compartment model of human body, drug application regime, Finite Element components which use neuro-fuzzy hybrid models

This multi-scale modelling and simulation approach involves across-scale modelling in time and space. It integrates data-based and knowledge-based modules.

In each of the four cases, the architecture of a prototype multi-modular model system must be designed and applied. Applying this architecture the aggregate behaviour must be studied, compared with the real observed behaviour and used to improve the architecture of the multi-modular model.

In all the four cases, Modules must be tested and simulated individually and after merging in common. Simulation results must be documented in terms of SBML.

There must be provided several variants of constituent model modules and user-defined composition of the entire model must be allowed . User-defined composition must be guided by SBML code in the background.

7.6.15 Work packages of dynamic Modeling and Identification of sparse gene-protein interaction networks

Based on the existing theory of dynamic Modeling and Identification of sparse gene-protein interaction networks, piece-wise linearization (PWL), development of a simulation framework has to ask for possibilities for tuning the model to represent different situations of network performance. Once the relevant parameters of interaction are known from modeling and identification, their influence on network behaviour can be studied by simulation. More generally, the influence of noise and stochastic fluctuations of tuned strength and the influence of tuned sparseness on network identifiability and controllability can be studied by simulation, as well as the role of noise in the network's self-organized control and robustness.

Five Work Packages with associated tasks might be isolated. Robust identification plays a major role at all scales. For each Work Package an Internet search study has been carried out.

WP1 – Tools for system modelling

Task 1 Single level PWL and state space modelling

Task 2 Multi-scale PWL modelling

Task 3 Mapping non-linear systems on multi-scale PWL state space models

Task 4 Modelling of mode switching

WP2 – Tools for system identification

Task 1 Identification of PWL systems with rich data

Task 2 Robust identification of hierarchic and sparse PWL systems with poor and incomplete data

Task 3 Relation with non-linear systems and multi-scale PWL state space models

Task 4 Identification of multi-scale PWL systems

Task 5 Validation of identification methods

WP3 – Testbed selection, implementation and evaluation

Task 1 Selection and preparation of reference and empirical annotated testbeds

Task 2 Implementation of testbeds in simulation environment

Task 3 Testing and validation of testbeds with special attention on emergence of complex behaviour and the role of intrinsic noise and chaos

WP4 – Integrated simulation environment

Task 1 Development and implementation of Integrated simulation environment using output of WP1 on model classes and identification tools

Task 2 Description of design strategies of emergent simulation models

Task 3 Methodology for generating a simulation model based on temporal data

WP5 – Multiscale analysis and identification of emergent properties

Task 1 Multi-scale correlation analysis through hierarchical clustering of time series

Task 2 Hierarchy detection through multi-resolution analysis of gene-protein time series using optimally designed wavelets

Task 3 Using network analysis and genetic programming to detect emergent complexity in simulated reference and real models

Desirable is the development of an integrative simulation platforms that enables simultaneous access, by means of a formal specification language, to data sets, simulation models and result documents for automated comparison.

Most desirable is the possibility to address several simulation issues subsequent to reverse engineering for identification, from microarray data of a particular system, at an integrative platform for modeling, identification and simulation.

Among methodological approaches to large sparse matrix problems in network modelling and simulation, it is preconditioning techniques that considers in particular network robustness

Using preconditioning techniques in large sparse matrix problems in network modelling and simulation, considering robustness improvement, computation speed gain, memory usage, and linearization as a step in some non-linear iteration or optimization loop, as well as parallel processing and object-oriented programming

7.6.16 Multiscale Simulation [114]

- Conventional Simulation: Nonlinear solver of individual phenomena.
- Holistic Simulation: Explore the complexity of interdependence between microprocesses and macroprocesses

7.6.17 Tutorial on Multiscale Simulation

Tutorial on Multiscale Simulation (T3005). Overview: This session is a tutorial on multiscale modeling, simulation, and analysis. Various techniques will be reviewed and examples from different applications will be discussed [115]. Most interesting in the present context is topic 3: Multiscale Analysis in Chemical, Materials and Biological Processes.

7.6.18 Towards the Multiscale Simulation of Biochemical Networks

The ICB Institute for Collaborative Biotechnologies develops tools for Multi-scale Modeling [116]: The multi-scale modeling component of this proposal will address simulation and analysis techniques for: (1) individual devices for 'sensing' and 'information processing' as described above; (2) the complex interactions with the biological systems (soldiers) that 'respond' and (3) the coordination and decision components that link a closed-loop 'sense and respond' system. In addition, these investigators will address high level systems integration issues that will lead to strategic iterations in sensor and information processing development, as the complex multi-scale networks are analyzed for their robustness and fragility attributes.

7.6.19 Some additional quotations on Robustness

Key Word	URL	Contents
RüdigerBrause Robustness	www.nisis.risk-technologies.com/(S(lskmorbmw2jdo55z0m5lj45))/filedown.aspx?file=117	Application for a Task Force Nature-inspired Robustness
	www2.informatik.uni-erlangen.de/Lehre/SS2006/CI/material/vorl7_ci.pdf?language=de	Immun_Heuristik.ppt
	www2.informatik.uni-erlangen.de/Lehre/SS2006/CI/material/vorl6_ci.pdf?language=de	Schwarm_Heuristik.ppt
Robustness	en.wikipedia.org/wiki/Robust	Robust - Wikipedia
	discuss.santafe.edu/robustness/stories/storyReader\$16	OVERVIEW
	www.cs.washington.edu/homes/gribble/papers/robust.pdf	Robustness in Complex Systems
Immune Robustness	www.mitpressjournals.org/doi/abs/10.1162/biot.2006.1.1.61	Self-Extending Symbiosis: A Mechanism for Increasing Robustness
	compbiol.plosjournals.org/perlserv/?request=getdocument&doi=10.1371/journal.pcbi.0020160	PLoS Computational Biology - Robustness and Fragility in
	discuss.santafe.edu/robustness/stories/StoryReader\$31	DISTRIBUTED FEEDBACK AS A SOURCE OF ROBUSTNESS IN THE IMMUNE SYSTEM

7.7 Understanding Robustness from First Principles of Non-Equilibrium Thermodynamics

7.7.1 Nonequilibrium Thermodynamics and Nonlinear Kinetics in a Cellular Signaling Switch

The importance of nonequilibrium thermodynamics in analyzing biological information processing and signal transduction [117]. We develop a rigorous nonequilibrium thermodynamics for an open system of nonlinear biochemical reactions responsible for cell signal processing. We show that the quality of the biological switch consisting of a phosphorylation-dephosphorylation cycle, such as those in protein kinase cascade, is controlled by the available intracellular free energy from the adenosine triphosphate (ATP) hydrolysis *in vivo*: $\Delta G = k_B T \ln([ATP]/K_{eq}[ADP])$, where K_{eq} is the equilibrium constant. The model reveals the correlation between the performance of the switch and the level of ΔG . The result demonstrates the importance of nonequilibrium thermodynamics in analyzing biological information processing, provides its energetic cost, establishes an interplay between signal transduction and energy metabolism in cells, and

suggests a biological function for phosphoenergetics in the ubiquitous phosphorylation signaling.

7.7.2 Inspiration from Nature By Understanding Complex Systems and Emergent Robustness from First Principles of Non-Equilibrium Thermodynamics

Like complexity research, NiSIS has three main goals

- To elaborate the concepts, methods and tools of self-organizing dynamical systems at all levels of description and in all scientific fields, especially newly emerging areas within Life, Social, Behavioural, Economic, Neuro and Cognitive Sciences
- To encourage novel applications of these ideas in various fields of Engineering and Computation such as robotics, nanotechnology and informatics
- To provide a forum within which commonalities and differences in the workings of complex systems may be discerned, hence leading to a deeper insight and understanding.

7.7.3 Non-Equilibrium Thermodynamics and the Production of Entropy

The book 'Non-Equilibrium Thermodynamics and the production of entropy – Life, Earth and Beyond' centres on the interaction of Biosphere and Geosphere, of vegetation and climate [118]. Nevertheless, this book gives a strong hope that an integral principle, Maximum Entropy Production (MEP), is at work in all open systems with large distance to thermodynamic equilibrium, i.e. those governed by non-linear thermodynamics like the Earth, thus in particular in living systems. The principles of Minimum und Maximum Entropy Production are explained as well as associated concepts of macroscopic reproducibility – the key concept behind thermodynamics and self-organized criticality.

This book contains, in addition to purely physical processes, attempts to integrate life as it enhances diabatic processes through evapotranspiration, higher surface roughness and higher emissivity. Life intensifies the global cycles of water, carbon and nitrogen. If all thermodynamic systems far from equilibrium are subject to MEP, Life on Earth included, it would also be a governing principle for the evolution and maintenance of the Earth system as well as the evolution and maintenance of Life. Life, Earth and Beyond do not only speak a common language, but are also governed by common principles and have a common Nature.

With respect to NiSIS, Nature-inspired Smart Information Systems or Smart Adaptive Systems, a fundamental analysis of living systems, of their evolution and maintenance, seems to be important. At present, living systems like gene regulatory networks, metabolic networks, signal transduction networks are analysed in two ways. Either, the analysis is based on microarray data or mass spectroscopic data and is done by data mining methods to yield data-based models. Or, the analysis is based on ad hoc kinetic models of these networks derived from molecular mechanisms of gene regulation and gene expression. Fundamental analysis of living systems, however, means to consider them as complex self-organized dynamical systems of many degrees of freedom in far from equilibrium conditions, and to use Maximum Entropy Production as a governing principle for the evolution and maintenance of living systems. This type of analysis would reveal the true reason why a particular living system is robust, reproducible

and adaptive and another one is not. This type of analysis would use criteria for living systems to exhibit these properties and behaviour.

Data-based modelling does not provide such criteria. Kinetics-based modelling detects a posteriori whether a particular kinetic model behaves robust but does not explain the reason why. Fundamental analysis in terms of Non-Equilibrium Thermodynamics, however, provides criteria for robustness, reproducibility and adaptability, essentially independent of a particular model parametrization. It furnishes a theoretical explanation for the interrelation of robustness, reproducibility and adaptability which is already obvious from common sense. When living in changing environmental conditions, a living system has to be robust versus perturbation in order to be reproducible, rather than to be subject to decay, unless it is adaptive to new environmental conditions.

To be instructive to technological design of Smart Information Systems or to design of computational algorithms, a living system has to be understood in terms of fundamental principles. In order to be inspirational, the design principles of a living system must be identified to be transferred and must be distinguished from the peculiarities of the inspired system.

Important issues are

- Multiscale Simulation
- Emergent Robustness
- Emergent Multitasking
- Understanding Complex Systems from First Principles of Non-Equilibrium Thermodynamics

Complex Systems of Biosphere, Geosphere, Technosphere, Sociosphere, and Cognosphere (the brain) are governed by common principles of entropy production in far from equilibrium conditions.

Common principles of entropy production in Non-Equilibrium Thermodynamics for complex systems enable inspiration from Nature for technology and for cognition.

The differences lay in the models of the natural phenomenon at one hand and the model of the inspired counterpart in information technology or algorithmic computation at the other hand. Examples of natural phenomena as sources of inspiration can be found both in Karl Bayer's Task Force on Analysis of metabolic control strategies and in Sebastian Zellmer's Task Force on Multitasking of Liver Tissue.

Complex systems comprise many interacting parts with the ability to generate a new quality of macroscopic collective behaviour through self-organization (emergent phenomena), i.e. the spontaneous formation of temporal, spatial or functional structures. As philosophers have told us since long ago, the whole is more than the sum of its parts. The recognition that collective behaviour can not be inferred from understanding the behaviour of the constituent parts, has led to various new concepts and tools of complexity research, such as self-organisation, complex systems, synergetics, dynamical systems, turbulence, catastrophes, instabilities, non-linearity, stochastic processes, chaos, neural networks, cellular automata, adaptive systems, genetic algorithms.

The topics treated are divers and the field of applications is very broad; it comprises complex systems of all spheres, both in the inorganic and the organic or living world., e.g. lasers, fluids in physics, electric circuits in engineering, growth of

crystals in chemistry, morphogenesis, metabolic control, and adaptation in biology, cancerogenesis in medicine, stock exchange rates in economics, formation of public opinion in sociology, brain function in neurology.

All these seemingly quite different kinds of structure formation have a number of important features and principles in common. These deep structural similarities can be exploited to transfer analytical methods and understanding from one field to another. Complexity is transdisciplinary.

7.8 References Chapter 7

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