



# Final report

## on the activity of the NiSIS task force on nature inspired robustness

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### Annex 1

K. Weller, M. Hecker, M.Pfaff: Robustness in Nature, Technology and Computation – A Survey with Special Emphasis on Immune Systems, report

### Annex 2

M. Hecker, K. Weller, M.Pfaff: Robustness Mechanisms of the Immune System and Autoimmune Disease Therapy Modelling – A Case Study on Rheumatoid Arthritis, report

### Annex 3

R.Brause: Modelling of Defence and Therapy of Sepsis, report + presentation

### Annex 4

R.Brause: Nature Inspired Robustness - a survey , report + presentation

# 1 The Task force on "Nature-inspired Robustness"

## 1.1 Introduction

This is a survey about the organizational principles that have given rise to the proven huge robustness and scalability in living systems (NiSIS' appendix I, p. 11).

There are many things in nature which we can admire from the engineering point of view and which gave rise to appropriate strategies for industrial products. One example is the analysis of the robust antibiotic defence mechanisms of earwax which offered blueprints for a spectrum of fungicides and anti-bacterial substances.

There are several aspects of "robustness":

1. One major aspect is in the sense of "**fault-tolerant**". This means that random faults or accidents in the considered system should not propagate and should not impede the desired system functions too much.
2. The second aspects means "**stability**" in a system inherent way. This means that the system should not be deviated by noise or random input, even if its internal components are slightly changed.

Principals for robustness can be learned for the information technology from the natural immune system. This was already done by artificial immune systems for defence against computer viruses and other intrusion attempts which reflect the principles above of parallelism and stable feedback.

However, we should also learn from dysfunctional states of the immune system. Thus, we focus first on severe sepsis where infections overcome the immune system, and, second, on autoimmune diseases such as rheumatoid arthritis, where the immune system destroys the body-own proteins and tissues. The two aspects of fault-tolerance and stability are problems in the modeling of specific biological mechanisms. Both immune system dysfunctions can be characterized by parallel actions of regulating circuits which are robust, although their dynamics may lead to undesired effects.

By modelling these two diseases and their therapeutic strategies (e.g. blocking of certain steps of the signalling pathways by anti-inflammatory or anti-rheumatic drugs anti-TNF alpha and anti-IL1b), we hope to learn how to improve the corresponding systems in information technology. This improved information technology systems should be also of technical interest, i.e. not only to improve therapy in these fields, but also to design organic computers which are less probable to fail.

## 1.2 Goals of the task force

The scope of the action of the task force is to provide a compilation of biological robustness mechanisms applied in the control of complex networks. The behaviour of cells under extreme environmental or processing conditions leads to the conclusion that for each particular process a specific solution space exists (window of operation). Fitting in this window represents a measure for robustness of each associated process.

Information technology target groups will benefit from the multitude of robustness mechanisms and handling of perturbations and from the assessment of influencing variables.

The action of the task force is addressed to the following target groups: software, process and control engineers in research and in different areas of application. It might be considered to include people involved in bioinformatics.

### **1.3 Activity record**

The presentation and founding of the Task force was during the 2nd European Symposium on Nature-inspired Smart Information Systems, 29/11/2006 – 01/12/2006 on Tenerife (Spain). A report of the kick-off meeting is enclosed.

As result of the initiative, a funding demand was initiated within the program "complex networks" of the Volkswagen-Stiftung, Germany, called "Constructing robust models of complex networks". Here, the topic of the demand was research on mathematical foundations of robustness in networks. Unfortunately, this initiative was not included in funding.

Additionally, teaching activity and research was triggered, e.g. by a seminar at the J.W.G. University "Robustness, Self-organization and Organic Computing" in summer 2007.

During 2007, four reports were prepared by different groups. The results were presented during the 3rd European Symposium on Nature-inspired Smart Information Systems in Malta at 28/11/2007.

### **1.4 Continuation of task force activities**

A concrete continuation of the task force initiative has been settled by the institute of informatics of the Johann Wolfgang Goethe-University, Frankfurt, Germany, and the Hans-Knöll-Institute Jena, Germany. Starting in February, 2008 a research initiative will try to include the robustness idea in the modelling tools for biochemical pathways (gene, protein and metabolic pathways). The enriched tools will be published and also be used by the working groups at Hans-Knöll-Institute and at BioControl.

There are also potential opportunities to continue the activities of the task force within a wider context within the European Union's 7th RTD Framework Program. Here, a STREPS initiative is under way which builds on the fact that the information and communication technology for Health Unit has been supporting and promoting research and efforts towards a paradigm shift in healthcare delivery. This includes the shifts

- a) from "reactive" to preventive healthcare and
- b) from "hospital-centred" to person-centred health systems.

Here, disease prevention and early diagnosis for people at risk can be implemented by a personal test for the robustness ability of the patient suffering by septic shock. Therapy should then be adjusted to the given gene interaction network in order to reflect the personal situation properly.

## 1.5 Deliverables

The primary goal of the task force was implemented by providing a compilation of biological robustness mechanisms. This goal is accomplished by the following reports which have been attached to this task force report:

- 1) A general survey entitled "Robustness in Nature, Technology and Computation – A Survey with Special Emphasis on Immune Systems" was made by BioControl and the Leibniz Institute for Natural Product Research and Infection Biology. This is Appendix 1.
- 2) More specifically, a report on "Robustness Mechanisms of the Immune System and Autoimmune Disease Therapy Modelling – A Case Study on Rheumatoid Arthritis" was also prepared by the same authors. This is Appendix 2.
- 3) The robustness of the immune system is also the cause for a high mortality in septic shock. The background and the state of the art for tackling this problem is given in the report "Modelling of Defence and Therapy of Sepsis" of Appendix 3.
- 4) In general, there are several robustness principles developed in the technical domain by human beings and in the biological domain developed by evolution. In the report of R. Brause entitled "Nature Inspired Robustness - a survey" in Appendix 4 this is surveyed. The conclusion claims for several new initiatives in bioinformatics and mathematics.

## 1.6 Conclusion

The task force started with the aim of providing a link between robustness found in nature and desired robustness properties of technical systems. Throughout the general survey and specific content research documented in the deliverables it turned out that a robustness of desired level is not present in most natural systems. Only higher biological organisms are able to cope with severe structural deficiencies; only they provide enough redundancy and structural flexibility for compensating the cut of regulatory branches.

An explicit comparison of cell robustness mechanisms and robust mechanisms in the technical domain revealed (Appendix 4) that several mechanisms have counterparts in each domain, e.g. repair mechanisms and masking of failures by structural redundancy. Nevertheless, there are also robustness mechanisms in nature which can not be copied by technical systems like the probabilities for reproduction or life span limitation of units.

The most interesting robustness feature evolved in the modelling of the immune system, either for immune diseases like rheumatoid arthritis or septic shock (Appendix 2 and 3). Here, an ill-directed immune system with all its inherent robustness can hardly be corrected by therapy. A successful therapy have to be based on a model of the network which takes its robustness into consideration, i.e. makes a robust, redundant model and not the most simple one. In order to face this demand, new mathematical attempts for formulating redundant, robust differential equations have to be developed - a challenge to be solved only by coordinated attempts on national and European level.

## 2 Report on the kick-off meeting

Rüdiger Brause, J.W.G.-University, Germany

1<sup>st</sup> of December, 2006 Puerto de la Cruz, Tenerife, Spain

### 2.1 Introduction

Beside the initial task force group members also other individuals of the symposium were invited to join the task force. The following persons joined the meeting:

Rüdiger Brause (University Frankfurt/Main, Germany)  
Benjamin Garrnett (Temple University of Philadelphia, USA)  
Alexander Gegov (University of Portsmouth, United Kingdom)  
Reinhard Guthke (Hans-Knöll-Institute Jena, Germany)  
Michael Hecker (Hans-Knöll-Institute Jena, Germany)  
David Irons (University of Sheffield, United Kingdom)  
Derek Linkens (University of Sheffield, United Kingdom)  
Michael Pfaff (BioControl Jena GmbH, Jena, Germany)  
Daniel Vogt (TU Chemnitz, Germany)

As introduction, two presentations were held. The first was by Rüdiger Brause, entitled "Robustness in immune system modelling and sepsis therapy" and claimed that in modelling of immune reactions the property of robustness which is often found in nature should be incorporated in order to reflect the variance in observations. This will lead to better models which should advance septic shock therapy.

The second contribution was presented by Michael Hecker. He presented the results of modelling of the immune response to anti-rheumatic therapy. For a better understanding of the molecular processes leading to the distinct outcome of the anti-rheumatic therapy, he reconstructed genetic networks of responders and non-responders separately. He analysed the distinct models with respect to their stability. The inferred linear network models were found to be unstable under certain conditions. Reinhard Guthke claimed that robust models have to be non-linear.

## 2.2 Results

The kick-off meeting presented a good start. Beside additional interested persons several points were discussed in the opening session and interest were expressed. As result, the following work load distribution was fixed:

- Rüdiger Brause: Coordination and scientific support (Report)
- Michael Pfaff: Survey on Robustness in Immune System Models
- Michael Pfaff: Case Study “Modeling of Defense and Therapy of Rheumatoide Arthritis”
- Rüdiger Brause: Case study “Modeling of Defense and Therapy of Sepsis”

The studies and final reports are scheduled for November 2007.

The presentation slides are attached to this presentation.

## **3 Report on the concluding meeting**

27<sup>th</sup> of November, 2007 St. Julians, Malta

Rüdiger Brause, J.W.G.-University, Germany

### **3.1 Members**

Beside the initial task force group members also other individuals of the symposium were invited to join the task force. The following persons joined the meeting:

Monika Berendsen (Degussa GmbH)  
Rüdiger Brause (University Frankfurt/Main, Germany)  
Reinhard Dudda (Degussa GmbH)  
Reinhard Guthke (Hans-Knöll-Institute Jena, Germany)  
Peter Kaßler (Degussa GmbH)  
Kauko Leiviskä (University of Oulu, Finland)  
Joseph Lengeler (University of Osnabrück, Germany)  
Michael Pfaff (BioControl Jena GmbH, Jena, Germany)  
Jens Strackeljan (Otto-von-Guericke University Magdeburg, Germany)

### **3.2 Presentations**

After a short introduction by Rüdiger Brause, three presentations were held. The first was given by Michael Pfaff, entitled "Robustness in Nature, Technology and Computation – A Survey with Special Emphasis on Immune Systems" on behalf of Klausdieter Weller, who was not present. The contribution showed different aspects of robustness like structure (architecture) and function (algorithms) and attempts to contribute robustness to technical systems by imitating methods found in nature.

As second presentation, "Robustness Mechanisms of the Immune System and Autoimmune Disease Therapy Modelling – A Case Study on Rheumatoid Arthritis" was also presented by Michael Pfaff, this time on behalf of Michael Hecker. There is evidence that the inherent robustness mechanisms of the immune system persist in the disease state. As consequence, successful treatment is often impeded, particularly in the case of Rheumatoid Arthritis.

The third presentation was held by Rüdiger Brause, entitled "Modelling of Defence and Therapy of Sepsis" and claimed that in modelling of immune reactions the property of robustness (which is often found in nature) should be incorporated in order to reflect the variance in observations. This will lead to better models which should advance septic shock therapy by taking the robustness into account.

The fourth presentation of "Nature inspired Robustness: a conclusion" was held in the context of the task force workshop session "Immune system-inspired Health Monitoring of Machinery". The presentation of Rüdiger Brause concluded the three preceding presentations. It showed that there are many

robustness principles, invented in technical domains and by nature, all dedicated to special applications. There are several common robustness mechanisms used both in technics and nature like repair, redundancy fault masking or negative compensating feedback. Nevertheless, there are also robustness mechanisms of nature which have no counterpart in technics, like statistical selection of robust systems by codon bias and genetic bottlenecks (diploid-haploid-diploid phases) and anti-redundancy effects like limited life time.

### **3.3 Results**

As conclusion, the most inspiring aspect of robustness appears to be the modelling of robust biochemical genetic, protein or metabolic networks by including the robustness demand already on the creation stage. Instead of modelling a network in the most simple form, it should be architecturally modelled in a simple form using additional redundant elements which provide the robustness. For proper functioning, the dynamical modelling by differential equations have also to take the redundant elements into account. This means that research have to include new mathematical methods for redundancy robustness of differential equations, too.