

Final report on the activity of the NISIS NiMOC Task Force “Multitasking of Liver Tissue”

1. Participants:

Initial participants:

- Sebastian Zellmer, University of Leipzig, Germany (responsible)
- Rolf Gebhardt, University of Leipzig, Germany
- Davide Anguita, University of Genova, Italy
- Reinhard Guthke, Hans Knoell Institute Jena, Germany
- Christian Hummert, Hans Knoell Institute Jena, Germany
- Derek A. Linkens, University of Sheffield, U.K.
- Michael Pfaff, BioControl Jena GmbH, Germany

Additional participants

- Rüdiger Brause, University of Frankfurt, Germany
- George Coghill, University of Aberdeen, U.K.

At the “kick-off”-meeting of the task force R. Brause from the University Frankfurt (Germany) participated and joined the task-force. Coming from the field of computer sciences his questions about similarities between liver cells and computers started a vivid discussion. The discussion, which had to be stopped due to time limitations, showed that the interaction of scientists from live science and engineering sciences can be very fruitful and has a high innovative potential.

2. Main task force activities

In the following the individual tasks, planned and fulfilled within the task-force are summarized and references to published data are given.

1. Generation of definitions (decided at the kick-off meeting):

Already during the first meeting of the task force it occurred that the members do have a different understanding and different views on the same subject. This was basically due to the fact that the members had different backgrounds (e.g. biochemistry, computer science, engineering, etc.). This was a challenge for the task force and it was decided to generate a set of definitions in order to have a common language and to identify, whether there are similarities between the liver cells and computers. More than 20 definitions were generated starting from “biochemical reaction” and “cell” to stream” and “virtual task pool”. The final set of definitions was incorporated into the NISIS glossary for general use (<http://www.nisis.risk-technologies.com/Collaboration/Default.aspx>).

2. Selection of heterogeneously expressed genes in liver tissue using gene arrays:

Affymetrix gene array experiments were used to identify heterogeneously expressed important regulatory factors within the liver. More than 270 probesets were identified, which are heterogeneously expressed between periportal and pericentral hepatocytes. These probesets consisted of genes encoding for enzymes, regulatory factors and proteins with unknown function. Several new and previously unknown genes were identified, which will be the basis of further metabolic and signalling investigations.

3. Immunohistochemical (IHC) proof of the expression of the protein

Immunohistochemistry (IHC) was used to prove the heterogeneous expression pattern of some selected genes. The SOCS (suppressors of cytokine signalling) proteins were chosen as important target genes. As an internal control the glutamine synthetase was stained. It is well known that the latter occurs only in a small subset of cells surrounding the central veins. In order to have a broader data set the expression pattern of SOCS and its receptor (growth hormone) was studied in several different liver tissues from different mice.

The SOCS proteins are important for the regulation of cytokines. The latter are factors responsible for proliferation, regeneration and some metabolic functions of liver tissue. The SOCS proteins represent a negative feed-back function in the regulation of cytokines. Since the growth hormone receptor shows a homogeneous distribution within the liver parenchyma and its negative feed-back regulator SOCS shows a heterogeneous distribution, regulatory mechanisms could be based solely on the different expression pattern.

Results of these data were presented at the 3rd European Symposium on Nature-inspired Smart Information Systems (Zellmer *et al.*, 2007a).

4. Disturbance of the cells/tissue by external factors (e.g. cytokines).

In order to proof the heterogeneous expression of SOCS hepatocytes were isolated from mouse liver and cultivated according to a SOP. In order to set up an optimal stimulation protocol different cytokines (IL-6 and GH) were used for the stimulation. In addition, the induction of SOCS at different concentrations and time points was investigated.

5. Analysis of the disturbed tissue by gene array experiments and IHC

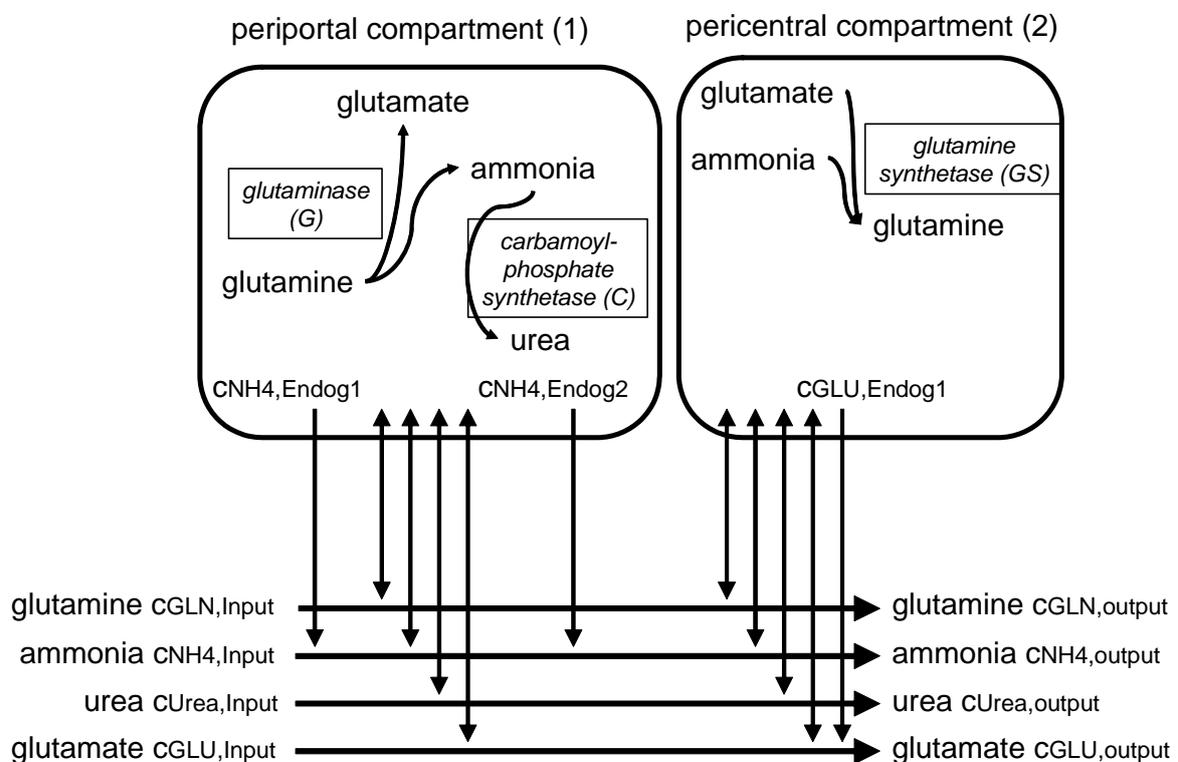
Using quantitative RT-PCR the expression of SOCS was investigated after stimulation of hepatocytes with GH. Also, IHC was performed on samples stimulated with IL-6. This allowed the visualization of the induction of SOCS. Some of the data were presented at the 3rd European Symposium on Nature-inspired Smart Information Systems (Zellmer *et al.*, 2007a). A manuscript is in preparation.

6. Development of a model describing the multitasking capabilities of one metabolic pathway:

In a close and very fruitful cooperation between the biochemists of the University of Leipzig and the engineers of BioControl Jena GmbH, a 2-compartment model of the liver was generated. Especially the combined input of the cell biologists/biochemists

and the engineers resulted in a rapid generation of the model. The developed 2-compartment model of liver is able to describe one of the main function of liver tissue, the detoxification of ammonia, the degradation/synthesis of glutamine and the synthesis of urea. The data of the model show a very high correlation to experimental data published by Haussinger (1983). The model also allows to simulate situations, in which some of the detoxifying reactions are inhibited. Therefore, the model has the potential for direct medical applications. Further applications are currently exploited. Comparison of the 2-compartment model with a similar 1-compartment model showed, that the 2-compartment model performs much better in the detoxification. Therefore, the engineering approach proved, to our knowledge for the first time, that nature had to evolve a 2-compartment model for an efficient detoxification of toxic ammonia.

This part of the task force demonstrated that the combination of biological knowledge with engineering tools has a huge potential, is innovative and opens new views.



The results of the modelling approach were presented at the 52nd IWK (International Scientific Colloquium), held at the University of Applied Sciences in Illmenau (Toepfer *et al.*, 2007a). The abstract can be obtained at http://www.db-thueringen.de/servlets/DerivateServlet/Derivate-12346/IWK_52_2_107-112.pdf. In addition, data were presented at the 2nd Conference Foundations of Systems Biology in Engineering (Zellmer *et al.*, 2007c) as well as on the 3rd European Symposium on Nature-inspired Smart Information Systems (Toepfer *et al.*, 2007b).

7. Comparison of the signal transduction pathway to modern scheduling strategies

During the generation of the 2-compartment model it occurred that there are similarities in metabolism and data processing in modern information technology. In the liver toxic ammonia enters the tissue and is detoxified first by a high capacity and low specificity system (urea synthesis). Then, before leaving the liver tissue a low capacity and high specificity system (glutamine synthetase) removes very efficiently remaining ammonia.

A similar construction can be found in the generation and optimization of spam filters, for example. Incoming spam-mails are removed first with a high capacity and low specificity filter system. This reduces the amount of mail to a broad extent. In a second step the remaining mails are screened for content (low capacity but high specificity) in order to identify remaining spam.

This example shows, that the generation of models inspired by natural systems is not a one-way track and that efficient technical solutions can be drawn from systems already evolved by nature.

3. Additional activities, related to the task-force:

Glutamine synthetase is a well known heterogeneously expressed gene in liver tissue. A model of the signalling cascade was presented at the **NISIS / JCB / DFG International Spring School and Workshop on Data Mining and Modelling in Systems Biology** (Zellmer *et al.*, 2007b).

Summary

The task-force on “Multitasking of liver tissue” made NISIS more visible within the group of people working at the border of biological and engineering science. This was especially obvious at the conferences in Illmenau (52nd IWK) and at the conference in Stuttgart (FOSBE 2007), where the 2-compartment-model was presented outside of NISIS. In addition, within NISIS, the contact of engineers and biologists resulted in intensive discussions, which made the generation of a set of definitions necessary. The latter can be helpful for people entering the field. The generation of the 2-compartment-model was very successful and it will be the basis for an extended model. The latter will incorporate more data and also data after liver intoxication. The model will be extended and possible medical applications are likely. Also, the investigations on the SOCS proteins were very promising. These studies opened a new view on the field of cytokine signalling in liver tissue, which will be investigated further.

References

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