

Towards a Dutch international Silicon Cells initiative

1. Aims and opportunities

System Biology developments

This memorandum aims to boost the Dutch momentum behind what should become an international program in an area of molecular system biology that is entitled Silicon Cells (SiC). This initiative should result in a major proposal in the framework 6 program of the European Union, in the European Science Foundation, and in the Human Frontier and Science Program. The wider ambition is to set up an international program in which the activities in Europe, The United States, Japan and South Africa are harmonized. For *E. coli* this is taking shape through the International *E. coli* Alliance (EclA; www.sciencemag.org/cgi/content/full/297/5586/1459a).

The Netherlands has a long scientific tradition in cell physiology. Through a combination with molecular biology and thanks to enabling technologies such as integrative genomics and bioinformatics, this now metamorphoses to what may be described as molecular system biology. Molecular system biology delineates complex biological systems both quantitatively and dynamically in terms of chemical conversions and physical interactions. The ultimate aim is to incorporate all processes in the living cell, to the extent that everything is networked with everything else. This should provide a basis for the true understanding of the complex network of processes that we tend to call 'Life'.

From System Biology to the Silicon Cell

Thanks to the opportunities offered by modern genomics, biological research has entered a new phase. Groups inside and outside The Netherlands have begun to put System Biology on an entirely new footing. Where previously System Biology employed modeling to examine which system properties might occur in Biology, now one can 'simply' calculate which system properties actually occur in biological systems. This is accomplished by making a computer replicon of (part of) a living cell. For each macromolecular process, such a replicon contains a mathematical rate equation describing the relevant kinetic, thermodynamic and structural properties. The set of equations for all components of the cellular system are then integrated by numerical procedures to calculate what the computer replicon, *i.e.* the Silicon Cell, should be expected to do under the given conditions. At the moment this can only be accomplished for cellular subsystems of limited complexity, such as glycolysis and EGF-initiated signal transduction; for most parts of living cells the components are incompletely known molecularly under the relevant *in vivo* conditions. In view of the many data that emerge ever more rapidly from the functional genomics programs, the possibilities are increasing rapidly however. The first Silicon Cell activities (cf. www.siliconcell.net) have been in the areas of signal transduction and metabolic networks, in relatively simple and well-known autonomously living cells (*E. coli*, yeast). Dutch groups play a leading role in this field. One of the initiators of this note was among the few European speakers on the International Conferences on Systems Biology in Pasadena (2001) and Stockholm (2002) and is co organizer of the 2004 ICSB in Heidelberg.

The existing SiC's are collected in a live 'modelbase', *i.e.* a web site where anyone from anywhere in the world can interrogate the SiCs for their behavior if kinetic parameters, or environmental conditions are changed (www.jij.biol.vu.nl) . The driving force behind this live model base is another Dutch scientist with appointments both in Amsterdam and at the University of Stellenbosch, South Africa.

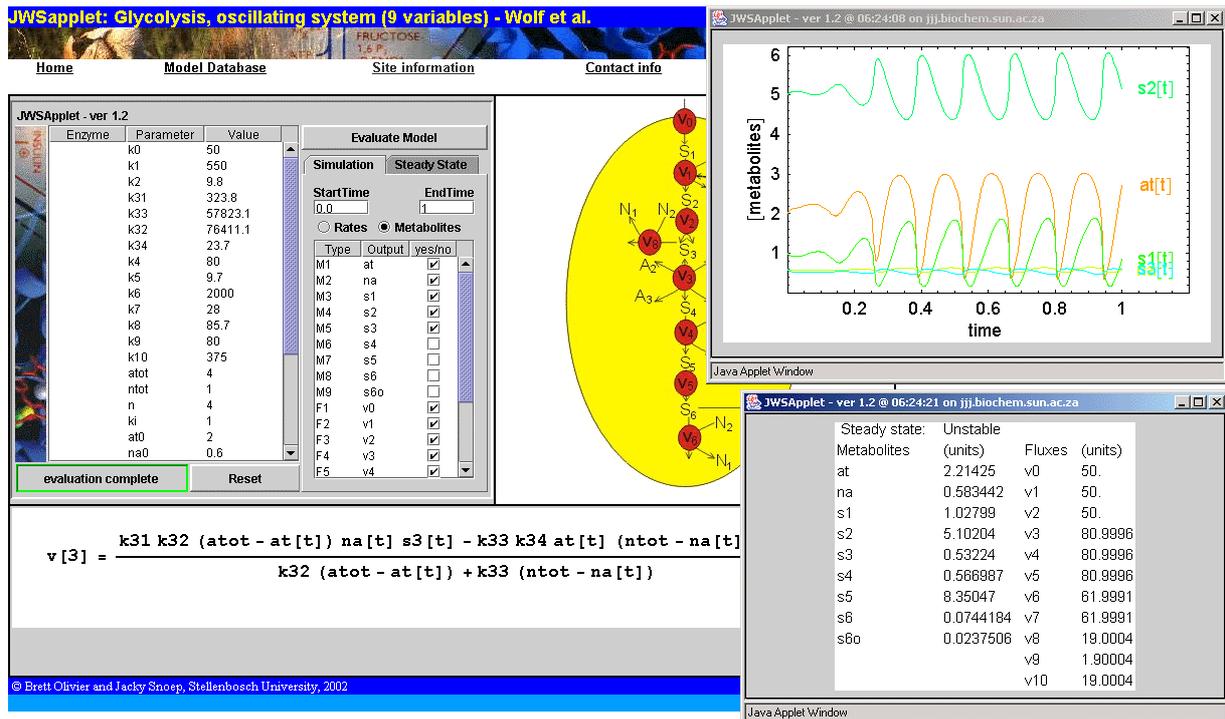


Figure 1. A screenshot from the Silicon Cell modelbase; cf. www.jjj.bio.vu.nl

As a response to the first call of the EU-FP6 program a Specific Support Action has been requested to enable the setting up of a European System Biology network at various levels, scientifically, educationally and organizationally. The third call of the program is likely to offer ample opportunities for a Silicon Cells Network of Excellence, which The Netherlands may help pull off. As a matter of preparation a European workshop/think tank will be organized in which the format of the initial European Silicon Cells program will be pinpointed. Aim of the present memorandum is to solicit the assistance of the most relevant Dutch scientists, institutions and companies for this Silicon Cells' initiative, such that we can gather momentum in the European arena as 'The Netherlands, incorporated'.

2. Silicon Cells: molecular system biology

Notwithstanding the great successes of molecular biology and cell biology, we are still not able to understand scientifically how a living cell functions. Whilst we know many components of the living cell, the dynamic wiring of the cellular network is only now being determined. In order to comprehend cell functioning including the basis of its typical mixture of robustness and adaptation, the protocols according to which macromolecules enter in interactions should be mapped. As many parallel and cross-connected interactions are at play at various time scales (from nanoseconds inside macromolecular complexes to hours at the level of gene expression), *computation-assisted* approaches are essential.

Molecular System Biology is the scientific area that focuses on this interplay between (mostly large numbers of), by themselves often relatively simple, physical and chemical processes that results in the complex behavior of living organisms. For the Silicon Cell initiative this is the Living Cell.

The Silicon Cell approach integrates bioinformatics, genomics, proteomics, and metabolomics with the more classical approaches in the biomolecular sciences. At stake is the area where quantitative experimentation in the living cell integrates with the mathematical modeling of how those molecular processes bestow that cell with its life-specific properties. The word 'Silicon' in Silicon Cell refers to the ultimate aim of obtaining a replicon of the living cell in the computer. Making the predictions of these replica correspond with the results of new cell physiological experiments, will be the ultimate and hard quality criterion of this program. At first the program will have to be limited to signal-transduction and metabolic networks. However, in the coming five years a rapid development is expected towards spatially resolved supernetworks that will ultimately comprise all processes and dynamic structures in the living cell. Large complexes of transcription factors, as well as structure formation on membranes and in 'cytosol' are on the immediate agenda.

It is important to emphasize the complementarity between the classical system biology and molecular biology on the one hand, and the Silicon Cells/molecular system biology on the other. The classical system biology saw the biological system as a black box and determined experimentally the transfer functions between input and output. The macromolecular mechanisms responsible for these transfer functions were not addressed. This estranged classical system biology from physics and chemistry. Molecular biology (and biochemistry and biophysics) tended to consider macromolecules independently of one another, and fell short understanding how macromolecules attain function in the dynamic and reciprocal contexts of the living cell. These limitations were motivated by the phenomenon that unknown components continued to appear *deo ex machina*, such that explanations could never be made conclusive. The complete genome sequences of living cells and the coupled functional genomics programs remove these limitations more and more. The system biology proposed here, and most strongly so, the SiC, has the ambition of explaining the system behavior of a limited number, well characterizable living cells on the basis of the dynamic behavior of the macromolecules, with as hard criterion the successful prediction of cell behavior under physiological, biotechnological and pathological conditions.

3. Why should The Netherlands play a leading role in this?

The Netherlands have a long tradition in physiology, excellent molecular biological and biochemical expertise, excellent modeling and computational capabilities, distinctions in the area of Silicon Cells, the tendency not only to compete but also to synergize, as well as a biotechnologically innovative industry.

4. Why we should act quickly; rapid international developments

The United States and Japan already house major initiatives aiming to help calculate processes in living cells. The Cell Signaling consortium of Alfred Gilman focuses on collecting the quantitative experimental data necessary to make a computer model of cell signaling systems. Leroy Hood and Bernard Pallson are setting up entire institutes to do system biology. The *Virtual Cell* initiative makes available programs and software that can be used by others for modeling intracellular processes. SiC differs from all these initiatives in that it aims at computer replica, including the values of the kinetic parameters, rather than at general purpose modeling software, or phenomenological proofs of principle. The Japanese E-cell program is not as publicly available, but may be closer to SiC: It does relate to the biochemical and physical reality of the living cell, albeit that it aims more at a phenomenological than a mechanistic descriptions.

Also in Europe the System Biology challenge is felt. The German Ministry for Education and Science (GMBF) has initiated a 50 M€ system biology program, which focuses on the hepatocyte. The Max-Planck Gesellschaft has founded institutes on system biology and complexity. Dutch scientists are involved as evaluators in many European System Biology

initiatives. They often lecture at meetings initiating national European System Biology programs. Why should the Dutch System Biology program not play a major role in Europe?

5. Industry

In the first (sequencing) phase of the genomics programs, international big industry was largely absent. New companies entered the vacuum, and some of these grew to substantial sizes before being bought up by the traditional industry. System biology may differ. Merck (a.g.), Bayer, Merck, Sharp and Dohme and Smith Kline Beecham appear highly interested in the German hepatocyte program and in the Silicon Cell and IECa initiatives. DSM, Unilever, and Organon are highly interested in System Biology, the former two certainly with respect to *S. cerevisiae*, the latter with respect to human whole-body system biology.

Again however, importance exceeds the interest of any single industry (just like the human genome sequence did). In the German initiative, a 'man-on-the-moon' inspiration suggests that it should be possible to make a silicon hepatocyte. Perhaps this will take another 10 years, but the ability to calculate the effects and conversions of many drugs in the liver, as well as liver regeneration after hepatitis and alcohol abuse, may well be worth the tremendous effort.

It should be clear that the economic importance of the SiC initiative is substantial both for the near and the more distant future. Results of this type of system biological approaches will strongly impact the biomedical, pharmaceutical and biotechnological industry. Ultimately they will transform the medical world from a largely empirical to a calculation-based operation.

6. The multidisciplinary Silicon Cells initiative relates to existing Dutch research programs

The Silicon Cells initiative closely corresponds to and integrates with Dutch research priorities in the areas of bioinformatics, genomics, 'biology inspired physics', computational life sciences, 'molecule to cell', and nanotechnology. At the same time the Silicon Cell initiative will address medical aspects. It relates to the Leiden-VU-TNO-EUR program on Medical Systems Biology. The initiative concerns a multitude of disciplines such as mathematics [statistics, logics, numerical mathematics], informatics [including artificial intelligence], physics [biophysics, complex systems, fluorescence, optics], chemistry [analytical, biological, pharmacological], biology [molecular biology, physiology, ecology, genetics, neurobiology], medical sciences [tumor cell biology, multifactorial diseases, population studies], sociology [the sociology of molecules, science and society] and philosophy of science. This is an additional reason why the topic system biology may be entertained by a wide science base in the Netherlands.

7. State of affairs as of April 2003

A number of concrete steps have been set to organize System Biology in the Netherlands

- A web site (www.systembiology.net/sbni)
- A two-day workshop in February 2003 under the auspices of NOW-ALW, defined the contours of Dutch System Biology
- A Dutch industrial platform has been set up
- The Dutch have contributed to two relevant FP6 first call proposals; one a specific support action and the other a system biology demonstration program
- preparations towards the European Sciences Foundation
- The various areas within NWO are being approached
- The initiative group SBNI has been installed

A second workshop is being prepared for the fall of 2003.