

Mathematics and Computation for the System Biology of Cells (Cell.Math.)

1 Title

- 1.a. Project title: Mathematics and Computation for the System Biology of Cells.
- 1.b. Project acronym: Cell.Math.
- 1.c. Principal investigator: M. A. Peletier

2 Summary

The aim of the project is to develop, implement, and validate mathematical and computational techniques for the systems biology of the cell. Biologists and mathematicians together will formulate realistic mathematical models of metabolic and regulatory networks including intrinsic spatial non-homogeneity. Depending on the cellular phenomenon considered, models and methods of appropriate temporal and spatial scales will be developed and can then be applied: models in the form of ordinary differential equations and methods for system reduction; multi-adaptive computational methods for partial differential equations (PDEs) for moderate spatial and temporal variability within a cell or an organelle; particle models describing the interaction of individual molecules and computational methods for the evaluation of the dynamic behavior; and methods for integration of these different approaches into a single simulation.

The planned outcome of the project are computational and mathematical algorithms, implemented in auto-adaptive computational models, and simulation results for the functioning of living cells.

Nederlandse samenvatting voor leken

Een belangrijk doel in de computationele biologie is het kunnen doorrekenen, in een computersimulatie, van een hele levende cel of zelfs een heel organisme. Uitgaande van de huidige stand der kennis is hiervoor meer werk nodig in twee richtingen: het verzamelen van meer en gedetailleerdere experimentele gegevens, en het ontwikkelen van technieken voor efficiëntere simulatie.

De laatste jaren maken de experimentele meetmethoden, mede door de ontrafeling van het genoom, een spectaculaire ontwikkeling door. Steeds meer aspecten van de levende cel worden voor metingen toegankelijk. De uitdaging is om de bijbehorende computationele technieken te ontwikkelen om de simulatie van een levende cel praktisch mogelijk te maken.

In dit voorstel zetten we een belangrijke stap in die richting. Ten eerste ontwikkelen we methoden om dynamisch en automatisch de grote chemische complexiteit van de cel te reduceren. Ten tweede gebruiken we op plaatsen met sterke lokale activiteit een deeltjesmethode om voldoende resolutie te krijgen. Ten derde ontwikkelen we methoden om deze verschillen in benadering in één simulatie te verenigen.

Met de technieken van dit voorstel komt de simulatie van een volledige levende cel een stap dichterbij.

3 Composition of the research team

<i>Name</i>	<i>Research interests</i>	<i>Institute</i>	<i>Hours per week</i>
Ph.D. student 1	Biology/Mathematics	VU.ALW/CWI	40
Ph.D. student 2	Computational biology	UvA.IvI	40
Ph.D. student 3	PDEs, Scientific Computing	CWI	40
drs. J. G. Blom	Scientific Computing	CWI	4
dr. C. Francke	Biology	VU.ALW	6
dr. W. Hundsdorfer	Numerical mathematics	CWI	2
dr. J. A. Kaandorp	Computational biology	UvA.IvI	4
dr. M. A. Peletier	Mathematics	CWI/TUe	4
Prof. dr. A. C. M. Ran	Analysis, Control theory	VU.FEW	2
ing. W. Reijnders	Biology	VU.ALW	8
Prof. dr. ir. J. H. van Schuppen	Control theory	CWI/VU.FEW	4
Prof. dr. P. M. A. Sloot	Computational physics	UvA.IvI	2
Prof. dr. J.L. Snoep	Microbiology	U.Stellenbosch/VU.ALW	1
Prof. dr. J. G. Verwer	Numerical mathematics	CWI/UvA.KdV	2
Prof. dr. H. V. Westerhoff	Biology	VU.ALW/UvA.SILS	4

J. H. van Schuppen and H. V. Westerhoff (Ph.D. student 1), P. M. A. Sloot and H. V. Westerhoff (Ph.D. student

2), and J. G. Verwer and H. V. Westerhoff (Ph.D. student 3) will act as formal thesis advisors (promotor) for the doctoral degree of the Ph.D. students for whom financial means are requested in this proposal.

4 Classification

This project fits into two of the three categories: in 'from data to model' and 'from model to simulation'.

5 Research school

The Advanced School for Computing and Imaging, the Thomas Stieltjes Institute for Mathematics, the Dutch Institute of Systems and Control (DISC), and BioCentrum Amsterdam.

6 Description of the proposed research

6.1 Motivation

It is often said that with the deciphering of the genome sequences of autonomous living organisms, life itself has become defined. Together with the progress along the lines of transcriptomics, proteomics and metabolomics, this might suggest that it now becomes possible to understand 'Life' in molecular terms. However, 'Life' is not defined by the DNA sequence alone, but also by the structures and physico-chemical principles by which the encoded information is converted into cellular action.¹ The cellular executors, which include the 'proteome', 'metabolome', and so on, form a highly complex and interconnected network of chemical reactions [16]. In addition, the spatial organization of the cell is another player in this game, being at the same time responsible for essential system characteristics such as compartmentalization, and subject to the continuously changing state of the cell. The ultimate bioinformatics endeavour of understanding the implications of the genome for the living cell faces the challenge of also taking these structural and physico-chemical aspects of life into account.

Although there is substantial understanding of many of these additional aspects, through much experimental and theoretical work, it is unclear whether we know sufficient to understand (even approximately) the functioning of the living cell as a system of interacting molecules. The Silicon Cell (SiC) [28] initiative aims to give the proof of the pudding, i.e. to either show that we do know sufficient to understand (even approximately) functioning of (parts of) the living cell, or if we do not know sufficiently, to pinpoint where the essential lack of understanding resides. The method to be followed is one of systems biology, i.e. by putting all available information together in a numerical analogue of the living cell. This information combines all relevant information about the metabolic and genetic network with all relevant physico-chemical information and all relevant (bio)physico-chemical principles.

Of course, it will not be possible *now* to compute the complete behaviour of the living cell. Yet, around the world interest is gathering for a systematic approach of this goal. Accordingly, SiC starts from five tenets. (i) At present much molecular information, including the massive amounts stemming from genomics, is virtually sterile with respect to the understanding of biological function. Only such calculations as proposed here can make this knowledge useful, giving enormous added value. (ii) Where the calculated behaviour does not coincide with the parallel experimental observation, this will lead to new discoveries and new insights. In the complex system of the living cell, this is in fact one of the few ways to discover key properties. (iii) The complexity of the living cell is high, but not infinite. Ultimately the cell will become calculable. (iv) The expertise available in the Netherlands (particularly in the research consortium proposed here) is unique in that it ranges from the molecular level to the physiology level (which has virtually disappeared in the USA), to mathematics (partial differential equations (PDEs), control and system theory), and includes quantification. (v) Many of the present problems in biotechnology and medicine relate to the complexity of living systems. Engineering of living cell factories is limited due to the fact that living cells invoke strong and semi-intelligent homeostatic responses. Many of the remaining important diseases (e.g., cardiovascular, cancer) are due to the failure of complex regulatory networks. Such systems are too complex to address by common biochemical intuition and require computation-assisted human intelligence.

6.2 Aim of the project

This proposal is built around the concepts of *simplification* and *integration*. Simplification is essential: a straightforward simulation of a model comprising a significant part of current biochemical knowledge would be too computationally demanding to be practical; when in the future much more complete information will be available,

¹These have mockingly been described as 'Life's *other secret*' [29]

such simulations will even be impossible. Techniques for modularization, model reduction, flexible gridding and time discretization, and various other measures (see the work packages below) will be developed and applied to render the computations more efficient.

An effective use of these techniques will, however, require that they be adaptive; variations in spatial, temporal, and chemical complexity are handled most efficiently if the simplification techniques can be adjusted accordingly. Thus the problem presents itself of *integrating* different model descriptions and numerical approximations into an aggregate simulation without sacrificing reliability. The dynamic heterogeneity of the living cell and the flexibility of the simplification techniques imply that the degree and type of simplification will vary in space and time, thus placing further constraints on the integration.

Motivated by this introduction, we set ourselves the following goal for this proposal: To develop mathematical and computational techniques for the efficient treatment of ‘Silicon Cell’ models. Explicitly, we develop methods for simplification, modularization, and integration:

1. system reduction techniques for ordinary differential equations (ODEs) of the type that arises in chemical networks (simplification and modularization in the chemical ‘dimension’);
2. particle-based methods for modelling of features with high spatial variability or low number of molecules;
3. multi-adaptive numerical methods for the efficient solving of PDEs with varying spatial and temporal scales;
4. methods that allow 1–3 to be integrated into a single simulation, in order to take advantage of simplification and modularization wherever and whenever possible.

We will use existing and new realistic models of regulatory and metabolic networks for development, validation, and benchmarking of these methods.

Points 1–3 roughly coincide with work packages WP1–3 below. The aspect of integration is addressed in all of the work packages.

6.3 Work packages

6.3.1 WP1: Towards functional models and control analysis of interconnected metabolic and regulatory networks

The aim of Work Package WP1 is to formulate realistic biological and mathematical models of metabolic and regulatory networks and to develop theory and algorithms for system reduction and for control of dynamic systems for such networks. The novelty of WP1 lies in the development of theory for system reduction and control of positive polynomial and rational dynamic systems, mathematical theory which thus specifically targets the dynamical systems of the type encountered in chemical networks [14, 17]. In doing so we additionally expect to merge existing mathematical and biochemical control theories.

Recent studies in the Westerhoff group were restricted to hardly interconnected single metabolic modules in steady state [31, 25, 7, 10, 26, 2, 12]. Now that more and more experimental data becomes available, also on transcription regulation, a more comprehensive quantitative model of metabolism becomes feasible. We will therefore now construct a much extended model that contains sugar transport by the PTS [26, 2, 12], glycolysis, the tricarboxylic acid cycle (TCA-cycle) and ammonium assimilation [10] and also includes regulation of transcription, translation, and aspects of signal transduction. The basic structure of the network will be derived from databases like KEG (www.genome.ad.jp/kegg/) and BIOCYC [6]. Then, for every component the literature will be searched for data on possible additional interactions, kinetic parameters (such as K_m ’s, K_a ’s, and K_d ’s), and physiological concentrations. Of course, the data have been obtained under varying physiological conditions and thus have to be judged with care and expertise to make the model consistent. If necessary, parameters will be determined using standard assays on cell-free extracts, or otherwise estimated from homologous pathways and changes in free energy.² The model will be formulated such that it can be expanded whenever appropriate.

Our approach to the system reduction problem is to apply an algebraic decomposition of the system, to apply a truncation technique for each of the units in the algebraic decomposition, and to bound the approximation error in terms of an appropriate norm. This approach will be carried out for the following classes of dynamic systems: (1) positive linear systems, (2) polynomial positive systems, and (3) rational positive systems that are characteristic

²The experimental work will not be carried out by the personnel to be hired on this grant but by a technician already working in the Westerhoff group.

of biochemical systems. The algebraic approach is based on the relation of a positive system with an underlying graph. The graph has a decomposition into strongly connected classes. With each of the irreducible subgraphs one associates the corresponding subsystem. The feedbacks in these irreducible subsystems involve intricate forms of feedback that have to be exploited for system reduction. Depending on the dynamics of the subsystem, one can formulate a truncation operation on the dynamics and bound the error of approximation. Depending on the choice of the norm, different algorithms are obtained and different approximation bounds are to be derived. The applicant J.H. van Schuppen has worked out this approach for positive linear systems in terms of the L_1 norm and a paper is in preparation. For polynomial and rational positive systems this approach has to be worked out and this seems nontrivial. References on the algebraic decomposition include [9, 21].

Biochemists and biophysicists have developed a Metabolic Control Theory/Analysis (MCA) for biochemical networks [14, 32]. This has been extended to signal transduction and gene-expression networks [18, 15]. This extension is particularly relevant for the present proposal as it made use of the known hierarchical organization of cell biology to simplify the control analysis. By making use of properties of homogeneous functions and of the stability of biological steady states theorems could be formulated and proven that relate extents of control by individual processes of physiological properties such as growth rate to each other and to enzyme properties. For the complex networks of cell biology, MCA has been simplified by modularization [27, 18, 32, 19]. In cases of flux connections the modularization was reached for modules that have few degrees of freedom [27]. This modular and multi-level MCA has already been quite successful and will continue to be helpful as the knowledge of intracellular networks extends and its complexity must be reduced. However, since MCA did not stem from the mathematical discipline of control theory, it is likely that it could be made even more powerful by implementing findings and procedures from mathematical control theory and by mathematizing it. In this project we shall first rederive the theorems of MCA using methodologies stemming from mathematics. Then we shall seek to generalize the theorems to other cases and other dimensions (e.g. from the temporal to the spatial dimension; two of the participating groups already have a manuscript on preliminary work submitted). And subsequently, we shall try to marry the theorems to the numerical procedures used to calculate the behaviour of living cells, with the aim of optimizing those procedures; at present the theorems are not used as constraints in most such calculations.

6.3.2 WP2: Development of a particle-based model for simulating reaction-diffusion at irregular surfaces

In this work package we will develop a three-dimensional particle model for bulk and surface reaction-diffusion. Examples of relevant systems are reactions at the surface of cellular membranes, chromatin aggregates, DNA, and scaffold proteins; in the context of this proposal we will concentrate on the interaction of several relevant transcription factors with the DNA and on the binding and aggregation of signaling molecules at the membrane as a result of ammonium or carbohydrate transport (like sequestration of GlnK [11], inducer exclusion [24], the recruitment of the transcription factor MLC [23], or chemotaxis [30]). Information on the spatial distribution of the components, on the interactions of the relevant transcription factors and on the membrane-associated processes will be extracted from the literature in a similar fashion as described under WP1. For the reaction-diffusion behaviour we will use a Lattice-Boltzmann approach (LBE) or, if fluctuations and correlations cannot be neglected, a Lattice Gas Automaton (LGA). An important challenge is the matching of microscopic coefficients to macroscopic measurements; in addition, the inclusion of a large number of reactive species in an LGA model presents practical difficulties.

The particle models developed in this work package are destined to be modules in a larger simulation: Most of the cell will be described by a PDE (or even an ODE), but parts of the cell will be represented by a particle model where this is necessary to obtain the required resolution. At the interface between the PDE-based and particle-based regions concentrations and fluxes should be continuous at the macroscopic level. We will investigate two representations of this model coupling, one with a surface interface and one with a zone of overlap.

For the ultimate goal of a self-organizing simulation, which treats different parts of the cell with different methods according to local requirements, a measure is needed to quantify the degree of local spatial heterogeneity and therefore the degree of necessity of a particle-based representation. To determine such a measure we will make comparisons of the performance of PDE and particle-based methods using the case study of protein patches in membranes. In the PDE-based approach a fine grid near the membrane-bound protein will be required, while in the particle-based modelling techniques (LBE and LGA) the reactions in the cytosol will be computationally expensive. We expect to deduce a quantitative relation between the degree of protein aggregation and the relative advantage of a particle-based method.

6.3.3 WP3: Development of a PDE-based computational model allowing for modularization in space, in time, and in the chemical dimension

Whereas in WP1 and WP2 we adapt the mathematical model with respect to chemical complexity and temporal and spatial scales, in WP3 we focus on the integration of these varying model descriptions and on multi-adaptive numerical methods to address the problem of varying spatial and temporal scales to make the computations more efficient. The aim of WP3 is (a) development of novel numerical algorithms for biochemical reaction-diffusion problems with widely differing spatial and temporal scales, for problems where the chemical *scheme* is space dependent and where in part of the domain other, particle-based, solution methods can be used, (b) implementation of these algorithms in a computational model where flexibility and ease-of-use are the main requirements, and (c) error estimation to assure that numerical errors do not overshadow modelling errors.

We will combine three adaptive strategies. First, we will use an *adaptive spatial grid* (see, e.g., [1, 8]): high resolution where it is required to represent the solution or the domain and low resolution elsewhere. Secondly, we will use *multi-rate time stepping* as used e.g. in partitioned Runge-Kutta methods [13] and multi-adaptive Galerkin methods [20]. Multi-rate time stepping allows for different time steps in different parts of the domain in response to a disparity in time scales over the domain. This combined adaptive treatment of the spatial and the temporal aspect will be combined with *splitting* techniques, like operator splitting or a combined implicit-explicit time integrator or approximate matrix factorization [5]. To obtain flexibility in the computational model we will implement the spatial adaptivity using (predefined) grid patches, which allow per patch for different biochemical reaction networks and possibly also a different mathematical model. The multi-rate time stepping will be implemented with time slots for synchronization and to allow dynamic selection of the biochemical reaction network.

Work package WP3 will incorporate the modules developed in WP1 and WP2: (i) For each patch in the domain and for each time slot the dynamics of the biochemical reactions is decomposed on the basis of time scales. At the fast time scale the diffusion between grid cells and the integration of the fast dynamics can be carried out. At the slower time scale the slow dynamics can be computed; (ii) in places where either the continuum approach is not appropriate, e.g. near a membrane-bound protein, or where the required resolution is too high to handle with a PDE-based approach, the particle-based model from WP2 will be coupled to the PDE-based model developed in this work package. The convergence analysis of such hybrid methods is a non-trivial theoretical issue that may be neglected during an exploratory phase, but is essential for the development of trustworthy numerical algorithms and therefore will also be addressed during the project.

6.4 Anticipated long term impact of the research

The mathematical models of dynamic behavior of biochemical reaction networks will allow further study of the functioning of cells in organisms, the development of medicine and drugs, and control measures for food production. System reduction methods will make possible computation of reduced order systems and provide error bounds on the approximants. These methods will impact both on system biology of cells and on system theory of positive systems. The project will contribute to the development of hybrid numerical methods and computational models for multiscale problems. Such problems are at the forefront of the mathematical modelling research. It is a challenge to combine, as proposed here, the control theory approach for reducing the chemical network with the multi-adaptive PDE and particle-based approaches for simultaneously addressing the widely differing scales in the chemical, temporal and spatial dimensions. Exploration of this challenge will open up new possibilities for tackling highly complicated mathematical biological problems.

6.5 Comparison with research in this topic elsewhere

Related research on the combination of system biology with control and system theory is carried out in the research groups of R. Heinrich (Berlin), B. Kholodenko (Philadelphia), J-H Hofmeyr, J.M. Rohwer and J. Snoep (JJJ, Stellenbosch), E. D. Sontag (Rutgers University), and J. L. Gouzé (INRIA, Sophia Antipolis). Related research on the multi-adaptive solution of PDEs is carried out in the research group of J. Lang (Darmstadt, Germany) and in the group at Chalmers, Sweden (Eriksson, Johnson, Logg), and more specific on multi-rate time stepping in the groups at NTNU Trondheim, Norway (Kværnø, Owren, Nørsett), and Karlsruhe, Germany (Rentrop, Günther), and also in the group at Chalmers, Sweden. Research on particle-based methods which can be used to represent

reaction-diffusion is done in the research groups of B. Chopard (University of Geneva), S. Succi (Istituto per le Applicazioni del Calcolo, Rome, Italy), D. H. Rothman (MIT) and J. P. Boon (Université Libre de Bruxelles).

The joint research of the applicants has a unique focus on the presented integrative approach needed to further the system biology of cells. With this focus the involved groups distinguish themselves from groups elsewhere which are active in the single fields of this proposal.

6.6 International contacts

Besides having collaborations with the groups of Heinrich, Kholodenko, Sontag, and Gouzé (mentioned above) the Westerhoff group participates in the *E. coli* consortium headed by Barry Wanner in collaboration with the group of P. Mendes (Blacksburg, U.S.A.) and the JJJ group in Stellenbosch. International contacts on the topic of control and system theory for biological systems exist with Sontag and Gouzé, and with G. Bastin (Université Catholique de Louvain); on the topic of particle-based methods in biology and physics with Chopard and Succi (mentioned above); on the topic of numerical algorithms with R. Weiner (Univ. Halle, Germany), B. Sportisse (INRIA, Paris), S.J. Ruuth (Simon Fraser Univ., Vancouver), J. Lang (DUT, Darmstadt, Germany), and A. Logg (Chalmers, Göteborg, Sweden).

6.7 The research team; imbedding of the proposal in current research

The research team has already successfully cooperated in a smaller project in the ICES-KIS2 WTCW Bioinformatics programme [22, 12, 2]³.

The Francke/Westerhoff group (<http://www.bio.vu.nl/hwconf/papers/index.html>) engages in the rare combination of experimental, computational and theoretical biological research that is useful for the programme proposed here. The preliminary computational biochemistry models mentioned in the work packages were developed in this group and have provided much of the experience and sense of possibilities necessary to put the SiC programme together. The *T. brucei* [7], *S. cerevisiae* [31, 25] and *E. coli* [26, 2, 12] systems are also studied experimentally, with additional focus on the systems that regulate and catalyze the energetics, ammonia assimilation (collaboration with K. Hellingwerf, UvA), DNA supercoiling and nucleoid structure (collaboration with C. Woldringh, UvA, T. Odijk, TUD, and D. Frenkel, AMOLF) in *E. coli* and on glycolytic dynamics and cell-cell communication in *S. cerevisiae*. Physiological studies in batch and chemostat accompany molecular biochemical analyses. The group also engages in the development and application of metabolic control theory and analysis, with special emphasis on gene expression regulation, signal transduction and dynamics.

The Van Schuppen/Ran group focuses on fundamental problems of control and system theory. It is known for its system theoretic approach to control and to identification. In addition, the CWI group has contributed to control of freeway traffic; and to system identification of compartmental systems for public health and environmental protection. In the latter context results were published on realization and identification of positive linear systems. Currently the group is involved in developing system theory for rational positive systems as models for biochemical reaction networks as occur in the investigation of Dr. B. Bakker of the group of H. Westerhoff. In addition, a master level course is offered in the Spring of 2003 on positive systems at the Mathematics Department of the Vrije Universiteit.

The group Sloot/Kaandorp focuses on research into developing and applying novel particle-based methods for mesoscopic physics, biological materials and solid modeling. This work draws on the groups experience with more traditional atomistic particle simulations. Developing high performance algorithms, particularly with regard to parallel computing, constitutes a significant aspect of this work. Research on lattice gas automata, the lattice Boltzmann model and other particle-based modeling methods as computational models for dynamical complex systems belongs to one of the major research themes of this group.

The Blom/Peletier/Verwer group has a long-time expertise in designing efficient numerical algorithms for the solution of large reaction-convection-diffusion systems. On mathematically related problems like ground water flow, air quality modelling and climate modelling⁴ the group has made extensive contributions on the analysis and software development and more specifically on various adaptive grid techniques (moving-finite-element, static refinement using the cascade approach), tailored stiff chemistry solvers (TWOSTEP, Rosenbrock methods), splitting

³<http://www.cwi.nl/projects/pdels/frame.shtml?SpatEf>

methods (operator splitting, implicit-explicit methods, approximate matrix factorization), and parallel implementations. The group is currently focusing on mathematical problems from biology and medicine⁵.

7 Work programme

Programme: PhD student of WP1: Year 1: Courses in biology (BioCentrum Amsterdam) and within the research school DISC; literature study on cell biology, metabolic control analysis (MCA), system theory, and existing Silicon Cells. Year 2: Research on biological and mathematical models for metabolic and signaltransduction networks; implement modular MCA. Year 3: Study of system reduction and biological implications. Year 4: Writing the thesis and further work on open issues.

PhD student of WP2: Year 1: Courses in biology (BCA) and within ASCI; literature study on particle-based methods, cell biology, and existing Silicon Cells. First version of a reaction-diffusion simulation using lattice gases. Year 2-3: Developing a reaction-diffusion system based on lattice gases of steps in a metabolic pathway and coupling to PDE-based methods. First prototype of reactivity at cellular membranes. Comparison of PDE-based and particle-based approach on specified case studies. Year 4: Writing the thesis.

PhD student of WP3: Year 1: Courses in biology (BCA) and within Stieltjes; literature study on numerical methods, cell biology, and existing Silicon Cells. First prototype of adaptive grid/multi-rate time stepping code. Year 2-3: Attending PhD courses on numerical methods. Numerical research on multi-rate time stepping and splitting techniques. Development and implementation of algorithms. Comparison of PDE-based and particle-based approach on specified case studies. Incorporation in code of modules developed in WP1 and WP2. Convergence analysis of the hybrid PDE-based/particle-based method. Year 4: Polishing algorithms and software with respect to efficiency, robustness, documentation, etc. Simulating realistic case-studies. Completing the thesis.

Education: The Ph.D. students will take part in graduate courses offered by the research schools Dutch Institute of Systems and Control (DISC), Advanced School for Computing and Imaging (ASCI), and Thomas Stieltjes Institute for Mathematics, and of the BioCentrum Amsterdam. Each of the participating research groups has a seminar series. The Ph.D. students will be asked to take part in such seminars and to present lectures.

Communication and coordination: To coordinate the efforts in the different work packages monthly meetings will be organized with the Ph.D. students and both the mathematical and the biological members of the research team; in these meetings the team members will inform each other about their progress. Independently the three Ph.D. students will collaborate on a regular basis in their literature searches for pre-existing Silicon Cells and biochemical data, and assist each other in interpreting and manipulating the data.

8 Use of instrumentation

The models in WP2 and WP3 will be developed initially on locally available workstations and distributed computing environments, such as the Beowulf cluster at the University of Amsterdam. In a final phase of the project we may call upon NCF for the use of the SGI Origin 3800 (Teras) at SARA. Furthermore we expect that advanced visualization will play an important role in this project. For the visual exploration and comparison to actual data sets, we are planning to use the locally available visualization equipment, the PC based virtual reality environment using one projection screen (DRIVE) and the Personal Space Station (PSS) at the Section Computational Science and the Cave Automated Virtual Reality Environment at the Academic Computing Services of Amsterdam (SARA).

9 Major references by the research team

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⁵<http://db.cwi.nl/projecten/project.php4?prjnr=78>

⁵<http://www.cwi.nl/projects/pdels/>

10 Requested budget

Cost category	EUR
Personnel costs Ph.D. student (3x)	407.286
Bench fee Ph.D. student etc. (3x)	13.614
Total	420.900

Travel costs: The NWO bench fee is stated in the budget for the travel costs, both inside and outside The Netherlands, for subsistence, for registration costs of conferences and summer schools, and for a contribution to the printing of the theses.

Other references

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