

Simulation of developmental regulatory networks

1 Title

1a) Project Title: Simulation of developmental regulatory networks.

1b) Project Acronym: 3D-RegNet

1c) Principal Investigator: J.A. Kaandorp

2 Summary

Genetic regulation plays a fundamental role in biological processes. Regulatory systems cannot simply be described as an assembly of genes and proteins and diagrams of their interconnections. Many analysis techniques, as for example cluster analysis, only provide ‘correlations’ between genes and do not provide insight into causal relations between the genes in a regulatory network. An important option for the analysis of regulatory control systems are simulation models in combination with optimization algorithms.

In this project we will develop a model for simulating regulatory networks that are capable of quantitatively reproducing spatial and temporal expression patterns in developmental processes. The model is a generalization of the standard connectionist model used for modelling genetic interactions. The model will be coupled with a biomechanical model of cell aggregates and used to study the formation of spatial and temporal expression patterns of gene products during development in cellular systems.

Mathematically speaking this amounts to continuum-discrete hybrid models where discrete, moving and deformable objects in which biochemical reactions take place exchange species with the surrounding environment modelled as a continuum in which species diffuse and decay.

A major issue are correct estimations of the parameter settings in the network model (the regulatory weight factors). Therefore the model will be used in combination with optimization algorithms (genetic algorithms and simulated annealing) to explore large parameter spaces of regulatory networks and to select specific spatial and temporal expression patterns.

2b) Abstract for laymen (in Dutch)

Genetische regulatiesystemen spelen een fundamentele rol in het besturen van allerlei biologische processen; een belangrijk voorbeeld is de genetische regulatie van het ontwikkelingsproces van een bevruchte eicel tot een volledig individu. Genetische regulatiesystemen kunnen in veel gevallen niet simpel beschreven worden door een verzameling genen en proteïnen. Veel analysetechnieken geven enkel correlaties tussen de genen en geven geen inzicht in causale relaties tussen de genen in een genetisch regulatienetwerk. In dit project willen we simulatiemodellen gaan ontwikkelen om regulatienetwerken die een rol spelen bij de ontwikkelingsbiologie te analyseren en zoektechnieken ontwikkelen, zoals genetische algoritmen, om relaties tussen genen in een netwerk te kunnen vinden.

3 Classification

‘From data to model’ and ‘from model to simulation’.

4 Composition of the Research Team

PhD student N.N. Dr. J.A. Kaandorp ¹	modelling regulatory developmental networks modelling morphogenesis in biology, computational biology, scientific visualisation	UvA.IvI (NWO-CLS) UvA.IvI
Prof. dr. P.M.A. Sloot	computational physics, particle based modelling, distributed computing,	UvA.IvI
PhD student N.N. Drs J.G. Blom ² Prof. dr. J.G. Verwer	software development, numerical analysis scientific computing, partial differential equations numerical mathematics	CWI (NWO-CLS) CWI.MAS CWI.MAS/IvA.KdV
Prof. Dr. W. E.G. Müller ³	molecular developmental biology	Mainz

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Kaandorp and Sloot will act as supervisor and thesis advisor, respectively, of the requested PhD position at the UvA.IvI. Blom and Verwer will act as supervisor and thesis advisor, respectively, of the requested PhD student at CWI.

The first two groups are located in the same building in Kruislaan 403–415 in the Amsterdam Science Park. The anticipated cross-fertilization through this project is expected to be highly profitable for both sides. The first group has already a collaboration with Prof. Dr. W. E.G. Müller since 1999 and participates in the FP6 network of excellence ‘GenBioMar’ (see embedding of the research groups).

5 Research Schools

ASCI: the Advanced School for Computing and Imaging
the Thomas Stieltjes Institute for Mathematics

6 Description of the Proposed Research

6.1 Introduction

Although the identification of genes, the understanding of genes and proteins and the description of metabolic pathways are very important issues, the next step is to obtain an understanding of the dynamics and the structure of metabolic pathways and regulatory networks. Regulatory systems cannot simply be described as an assembly of genes and proteins and diagrams of their interconnections. Many analysis techniques, as for example cluster analysis, only provide ‘correlations’ between genes and do not provide insight into causal relations between the genes in a regulatory network. At present microarray analysis produce information derived from mRNA abundance and only provide very limited information on the transcriptional regulation [13]. The development of the body plan is typically controlled by large networks of regulatory genes. Although there are many examples available how individual genes affect the developmental process, there are no cases available where a line of causality can be mapped from the genomic sequence to a developmental process [5].

In addition to experimental observations, simulation models are an important option to obtain an understanding of regulatory networks. Recently, Salazar-Ciudad et al. [21] [22] have used a continuum model (see also the section ‘Comparison with research elsewhere’) to model regulatory networks to (1) compare diffusion and direct-contact induction processes as mechanisms of pattern formation, (2) identify the possible range of behavior of real gene networks, and (3) suggest causal mechanisms to generate known patterns. This shows that this type of continuum models can successfully be used to study a variety of different properties of gene regulatory networks. With these models it can be demonstrated that different types of body segmentation during the development of insects, a process which is basically controlled by an identical set of genes, can be explained by ‘rewiring’ the regulatory network. Potentially these models seem to be a suitable tool to study the evolutionary relationships between developmental pathways in invertebrate animals. An important limitation in existing studies is that cells are modelled as static discrete lattice sites on a grid. For example in the work by Salazar-Ciudad et al. [21] [22], the *Drosophila* embryo is represented by a linear cellular automaton, while in the actual developing organism the spatial and temporal patterns of gene products during development will be formed in an aggregate of cells with a usually highly complex geometry.

Currently the genetic regulation of development in a number of model organisms is known in great detail, as for example: *Drosophila*, sea urchins, *Caenorhabditis elegans*, ascidians. Although the emphasis has been on the regulatory networks in bilaterians [4], recently much information has become available on the genetic regulation of growth and form in sponges [14] and cnidarians [15]. Within the metazoans, sponges and cnidarians represent the phyla with the simplest body plan and a relatively simple regulatory network controlling the development. This makes these organisms an excellent case study for understanding morphogenesis and the physical translation of the genetic information into a growth form, using a combination of a biomechanical model of cell aggregates and a model of the spatial and temporal expression of developmental genes.

In sponges, two morphogens crucial in the morphogenesis of an individual sponge have very recently been identified. One morphogen regulates the formation of the canal system in sponges [14]. The expression of this morphogen is the highest around the exhalant pores. The expression of this morphogen is considerably lower in other parts of the sponge body. Therefore, there is reason to assume that a gradient of the expressed protein exists - highest at the exhalant pore and lowest at the sites more remotely located with respect to the exhalant pore - which differentially activates the cells. The formation of the skeleton in sponges proceeds in a number of steps in which a catabolic enzyme is involved. It is hypothesized that the arrangement of spicules in the skeleton, their pattern formation, is directed by a gradient of these catabolic enzymes.

In this project we are planning to develop a generalized model of regulatory developmental networks, which is capable of simulating spatial and temporal expression pattern in cell aggregates. The model will be initially developed based on the information available on the regulatory networks in the early development of *Drosophila*. The advantages are: the network is known in great detail, the spatial and temporal expression

patterns can be simulated in a very simple geometry (an embryo sac with a radial symmetry and with nuclei, which can be assumed to be non-moving). The simple geometry allows for extensive testing of our models in 1D, 2D and 3D. In the final phase we want to test our generalized model of a regulatory network in a non-trivial geometry of a multi-cellular organism, by combining the regulatory model with a simulated cell aggregate. In this phase we will use the body plan formation in a sponge as an example. The main advantages are: the regulatory system and the body plan are largely known and relatively simple in sponges; there is for example no tissue differentiation in sponges.

6.2 Research questions

Biological questions The aim is (i) to find causal relations between genes in regulatory networks and to understand the dynamics of these networks, through modelling and optimization techniques; (ii) to quantitatively reproduce and understand spatial and temporal expression patterns in developmental processes in simulations and to compare these with actually observed patterns; (iii) to understand the physical coupling between an aggregate of cells and the body plan formation in regulatory systems.

Model questions The first issue is to develop a model or regulatory network which can be used to study spatial and temporal expression patterns. A second major issue in modelling genetic regulation systems, is the correct parameter setting (an estimation of the regulatory weight matrix in the network). We will apply optimization algorithms (simulated annealing and/or genetic algorithms) to explore large parameter spaces so as to select for certain spatial and temporal expression patterns. The third model question is to develop a suitable model of a cell aggregate which can be combined with a model of the regulatory system to study spatial and temporal expression patterns and which is sufficiently realistic to enable comparison with actual expression patterns.

Numerical questions The main issue here is to implement the hybrid discrete-continuum model as efficiently as possible, especially since it will be used as the core of the optimization algorithms. Furthermore is it important to discriminate between the modelling error and the numerical model error. The last one can and should be estimated.

6.3 Research program: methods and objectives

Modelling paradigms In this project we will develop a model for genetic regulation. This model will be a generalization of the model by Mjolsness [16] and Salazar-Ciudad et al. [21, 22]. The main difference with their work is that we do not plan to model the cells as static discrete lattice points on a grid but as independent objects. For this purpose we will use a biomechanical model of the cell aggregate based on the work of Palsson [17].

In the genetic regulation model we will include:

- Discrete cells. Cells are modelled as independent objects that can absorb and exude chemical substances from the extracellular space. At this moment we make no assumptions yet about the shape of cells. In the initial phase of the project cells are treated as point shaped sources and sinks on the extracellular matrix.
- The extracellular matrix. Gene products are allowed to diffuse through the extracellular matrix. Furthermore, cells can absorb chemicals from and exude chemicals into the extracellular matrix.
- Genetic regulation. We model genetic regulation as a set of differential equations. This model closely resembles the continuum model using weight matrices first introduced by Mjolsness et al. [16]. Proteins are capable of activating and inhibiting each other. Also, a distinction is made between proteins that stay within the cell and only function for intracellular regulation and proteins that can diffuse into the extracellular matrix and that are used for regional specification.
- Gene products. Protein levels are maintained within each cell, where they are assumed to be homogeneously distributed. Some protein levels are also maintained in the extracellular matrix, where they are allowed to diffuse. We assume that these gene substances do not go into direct chemical interaction with each other. By doing this, we prohibit the formation of Turing reaction-diffusion patterns. Thus, in our model chemical patterns can only arise through genetic regulation when cells absorb and exude chemical substances from and into the extracellular matrix.

The model for genetic regulation will be coupled with a biomechanical model of cell aggregates, adopting ideas from Palsson [17]. In this biomechanical model spatial and temporal morphogen gradients stemming from the genetic regulation simulation can influence the states of the cells within the cell aggregate, and lead to: (i) cell migration, (ii) cell-layer-contraction, (iii) adhesion, (iv) growth, (v) secretion of skeletal elements, and (vi) programmed cell death.

Mathematical model In the model a distinction is made between diffusing and non-diffusing (transcription factors) gene products. In the simplest version of the hybrid discrete-continuum model described above the cells are modelled as static points. The non-diffusing gene products may react within the cell and decay with rate λ , while the diffusing gene products diffuse through the extracellular matrix with diffusion constants D and decay also with rate λ . The equations describing the concentration of the diffusing gene products in the extracellular matrix are given by a parabolic system of PDEs (partial differential equations)

$$\frac{\partial \rho_j(\mathbf{x}, t)}{\partial t} = D_j \Delta \rho_j - \lambda_j \rho_j + \sum_{i=1}^{N_c} S_j(\mathbf{x}, t, \mathbf{r}_i, g_{ij}, \rho_j), \quad t > 0, \quad \mathbf{x} \in \Omega \quad (1)$$

with $\rho_j(\mathbf{x}, t)$ the concentration of the j -th diffusing gene product $j = 1, \dots, N_p$ at time t and at spatial point \mathbf{x} in the extracellular matrix, and with N_c the number of cells. The exchange of the diffusing gene products between the cells and the extracellular matrix is modelled as (point) source terms S which can, e.g., describe an instantaneous levelling of the concentration inside cell i at position r_i and the concentration at that position in the extracellular matrix of a specific gene product.

The genetic network inside is for all cells $i = 1, \dots, N_c$ given by a system of ODEs

$$\frac{dg_{ij}(t)}{dt} = \Phi(W \mathbf{g}_i(t)) + S_{ij}(t, g_{ij}, \rho_j), \quad \text{for } j = 1, \dots, N_p, N_{p+1}, \dots, N_g \quad (2)$$

with g_{ij} the concentration of gene j in cell i and N_g the total number of genes involved. Φ is a sigmoidal function which saturates at high and low values of the argument. The weight matrix W describes the regulatory effects of one gene on another.

A more general model will also include cell movement described by ODEs

$$\frac{d\mathbf{r}_i(t)}{dt} = \sum_{k=1}^{N_c} F_{ik}(\mathbf{r}_i, \mathbf{r}_k, \dot{\mathbf{r}}_i, \dot{\mathbf{r}}_k, \mathbf{g}_k, \boldsymbol{\rho}), \quad (3)$$

where F can contain as well active and static passive forces as dynamic forces (like chemotaxis) between the cells or between the cells and the extracellular matrix.

Moreover, the numerical model should be flexible enough to treat the cells as deformable objects, e.g. using visco-elastic properties as in Palsson's model. Also the introduction of 'rules' that describe cell division, cell death, and the deposition of skeleton elements should be allowed.

Numerical aspects Although the numerical solution of reaction-diffusion equations like Eq. (1) and ODEs like Eq. (2) separately is rather standard, the coupling of the two in one hybrid discrete-continuum system, the combination with cell motion (Eq. (3)), and especially the incorporation of cells as deformable objects subject to rules, makes the development of a numerical model a true challenge. The fact that the numerical model will be the core of a parameter search implies that myriad runs will be executed and therefore efficiency and robustness are of utmost importance in the design and implementation of the algorithms. Aspects that need to be addressed involve, a.o.,

- Time integration. In this project we look for equilibria of the solutions. Therefore it is important that the limit behavior of the mathematical model is maintained in the numerical model so that an implicit time integrator seems to be the most adequate (damping of spurious oscillations). However, for the problem at hand, a standard implicit time integration of the fully coupled system is not feasible. Therefore some special purpose time stepping technique needs to be developed, most likely with some form of splitting. It should be noted that not the - possibly stiff - diffusion is the expensive part but the computation of the reactions in the - large number - of cells.
- Splitting. Operator splitting, and to a lesser extent implicit-explicit time integrators and approximate-matrix factorization, can effectively decouple equations (1), (2), and (3). The solution of such a decoupled system is not only much simpler but allows also different solution methods per process, a flexible implementation of the 'rules' needed for the motion of the cells, and dynamic grid generation (see below). But of course a price has to be paid in the form of less stability and an additional split-error which might result in a too large restriction on the time step to be efficient.
- Choice of grid. A straightforward *Cartesian grid* implies that the extracellular concentrations need to be interpolated at the position of the cells and that the exuding gene products from the cells need to be distributed over the extracellular variables. The interpolation should have a sufficiently high order (at least C^1) and should be monotone to avoid artificial extrema. The distribution process should be mass-conservative. This problem of transfer of variables from cells to grid and vice-versa holds for all grids which do not have at most one biological cell per grid cell or point. A possibility to avoid this transfer of variables is to use a *dynamic Voronoi mesh* where the biological cells are the point sites of the planar Voronoi diagram and the Voronoi edges form the mesh. This approach is currently studied in one of the projects in CWI/MAS by

J.K. Krottje, see also under ‘Embedding in Research Groups’. Although the computation of such a mesh is only of $O(N \log N)$ complexity ([6]) the number of cells, thus N , is large ($O(10000 - 100000)$) and if the cells are not static a new mesh would be needed every time step.

At the moment it can not be foreseen whether adaptive gridding will be necessary. That will depend on the significance of the influence of the gradient in the diffusing gene products in the extracellular matrix. A first prototype for the *Drosophila* model with static cells indicates that for this organism a uniform grid is the most efficient.

- Cell versus supercell. A clustering of cells into one ‘supercell’ could be an option to make the process more efficient both for the computation of the chemistry in the cells, as is done for instance by Dallon and Othmer[3], and for the computation of a Voronoi mesh. However, it requires an estimation of the modelling error made in that way.
- Parallelization. Initially parallelization will be done within the optimization process, i.e., an instantiation of the numerical model (individual) will be executed sequentially on one processor. But in the final phase, when cell motion and deformability are incorporated, that might no longer be feasible when simulating a realistic sponge case. Therefore in all algorithmic development and implementation stages parallelization issues will be taken along.
- Last but not least: Error estimation. It is important to discretize the differential equations sufficiently accurate to assure that numerical errors are not larger than the modelling errors. The size of the numerical errors therefore should be estimated to get insight in the reliability of the numerics.

Model optimization In the first phase we will verify and test our genetic regulation model by comparing our simulated results to regulatory networks results which are known into very much detail and which are characterized by a relatively simple spatial and temporal pattern formation. As a proof of concept we will use the pattern formation in the early development of *Drosophila*.

A major issue in modelling the genetic networks are the correct parameter settings in the weight matrices used in the differential equations. In this project we will apply optimization algorithms, as for example genetic algorithms ([21] [22]), to explore large parameter spaces and select for certain spatial and temporal expression patterns. The optimization process, using genetic algorithms, can be initiated with a population of equal networks (equal entries in the regulatory weight matrices W in Eq. (2)). New configurations in the optimization process can be introduced by point mutations (changes in an element of W), duplications, recombinations (interchanging W elements between genes) and the acquisition of new interactions (a zero element of W acquires a small positive or negative value). In subsequent steps in the genetic algorithm the fitness of individuals can be evaluated by the degree of similarity between the spatial or temporal pattern, produced by the individual, and an imposed optimal pattern. The similarity or distance d_{jk} between the optimal pattern j and an individual k can - for the static case - be measured as:

$$d_{jk} = \sum_{i=1}^{N_c} |\phi_j(i) - \phi_k(i)| \quad (4)$$

where $\phi_l(i)$ is a measure of the state of a discrete unit i (at location r) in individual l , e.g., $\phi_l(i) = \sum c_j g_{ij}$. For moving cells a distance function needs to be developed.

A disadvantage in genetic algorithms is the ad-hoc choice of mutation and recombination operators. To avoid this problem another attractive, but computationally more expensive, optimization method is simulated annealing. Here ‘temperature’ dependent changes in the regulatory matrix W can be made in a Metropolis process.

Simulation In a later phase of the project we will couple the model of genetic regulation with a biomechanical model of a cell aggregates. As a proof of concept we will use a simple example of a developmental process, viz. the regulation of skeletal secretion and body plan formation in sponges. In this case study we will closely collaborate with the group of Prof W.E.G. Müller (Institut für Physiologische Chemie Johannes Gutenberg-Universität Mainz) and with other participants within the FP6 Network of Excellence on marine genomics.

6.4 Scientific relevance

In this project a powerful tool will be developed to find causal relations between genes for all kinds of regulatory gene networks even when the matrix itself or the reaction kinetics is not (fully) known. The match can be against real spatial and temporal patterns or quantitative measurements carried out for metabolic networks. This will make it possible to interpret spatial gene expression patterns and to understand the regulation of metabolic networks.

On the numerical side the answer to the research questions as stated in 6.3 ‘Numerical aspects’ will be generally applicable in hybrid discrete-continuum models (axon growth, aggregation of *Dictyostelium discoideum*, colloidal fluid simulations, etc.)

6.5 Comparison with research elsewhere

A number of different models has been proposed to capture the notion of gene networks, although most of these models were originally created for reverse engineering genetic networks [2], [20] [19].

To date, the most frequently used is the Boolean network model, introduced by Kauffman [12] and used - among others - by Jackson ([9]), to show that pattern formation in both space and time is possible when using active feedback loops and limited communication among cells. Discretising gene expression levels results in significant loss of information. Furthermore, there are some concepts in control theory, indispensable for genetic regulatory systems, that either can not be implemented using discrete variables or that have radically different dynamic behavior (amplification, subtraction and addition of signals, maintaining equilibrium using negative feedback and smoothly varying the period of a periodic phenomenon like the cell cycle).

More recently, continuum models, also referred to as connectionist or additive models, are being used in the groups of Salazar (Complex Systems Research Group, Universitat Politecnica de Catalunya, Spain) and Newman (New York Medical College). These models closely resemble neural-like connectionist architectures [16] or biochemical networks of interacting chemicals [10] [11]. Reinitz and Sharp [20] have used this model to reproduce the formation of stripes of expression of the pair-rule gene *eve* in the *Drosophila* embryo.

For modelling cellular development a number of approaches have been used recently. One approach is to simulate the cells with a cellular automaton representation, based on the model by Glazier and Graner [7], a model related to the large-Q Potts model (a generalisation of the Ising spin model). This model is since the 1990s extensively used in the group of Hogeweg (University of Utrecht) to model biological cellular processes (see for example [8]). In order to generate cellular patterns in this model, it must first undergo a grain size growth process, through slow cooling. This process has no biological significance and is only a characteristic of the large-Q Potts model.

A comparable hybrid-continuum model has been studied by Othmer in collaboration with Dallon [3] and Palsson [18] for the simulation of *Dictyostelium discoideum*. In these projects the modelling aspect was prominent and not so much the development and implementation of efficient computational tool suitable for large scale 3D computing.

6.6 Embedding in Research Groups

The two PhD projects will be carried out in close collaboration, one within CWI’s research cluster MAS (Modeling, Analysis and Simulation), the other within the section Computational Science of the University of Amsterdam. In the latter group a prototype of a model of the regulatory network of the early development of *Drosophila* has been developed by T. Krul, J.A Kaandorp and J.G. Blom [23]. The prototype is based on the work by Mjolsness [16] and Salazar-Ciudad et al. [21] [22].

Both groups participate in the Amsterdam Silicon Cell consortium (cf. [1]), which is a collaboration between research groups from different disciplines (mathematics, computer science, physics and biology). The other partners are VU.IMBS (Westerhoff) and UvA.SILS (van Driel).

The Section Computational Science participates in a FP6 Network of Excellence proposal entitled ‘Advanced Genomics in Biodiversity of Marine Organisms (Acronym GenBioMar): Genomic approaches for understanding of marine biodiversity and evolution and protection and sustainable exploitation of marine genetic resources. Through this network of excellence we can easily collaborate with developmental molecular biologists in Europe. For biological input and model validation we will collaborate with the group of Prof. dr. Müller (Johannes Gutenberg Universität Mainz). Research on natural solver techniques (for example particle-based modelling, genetic algorithms, simulated annealing)⁴. as computational models for dynamical complex systems belongs to one of the major research themes within this group.

The research group at CWI has extensive expertise in the analysis and computation of (time-dependent) partial differential equations. The project fits in the research theme ‘PDEs in the Life Sciences’⁵. One of the current projects in this theme is the development of a computational model for axon guidance⁶, which also is a hybrid continuum-discrete model[24] (PhD student J. Krottje, Prof.dr. J.G. Verwer). Although the problems are not altogether comparable, the proposed project will certainly benefit from the knowledge acquired in this project.

⁴See <http://www.science.uva.nl/research/scs/>

⁵See <http://www.cwi.nl/projects/pdels/>

⁶See <http://www.cwi.nl/projects/pdels/frame.shtml?Axon>

7 Work Program

PhD 1: Section Computational Science, University of Amsterdam

Yr1: development of the genetic regulation model (based on early development in *Drosophila*, including optimization methods)

Yr2: Further development of the optimization methods. Development of a prototype of the biomechanical model of a cell aggregate.

Yr3: Further development of the cell aggregate model, application of the genetic regulation model and the aggregate model in the sponge case study. Writing journal papers.

Yr4: Writing PhD thesis

Suitable courses on distributed / grid-computing; scientific visualisation and virtual reality will be selected.

PhD 2: CWI/MAS

Yr1: Literature study on numerical methods and basic principles of biological model. Attending PhD courses on numerical methods. First prototype of numerical code for *Drosophila* (static points).

Yr2-3: Attending PhD courses on numerical methods. Numerical research on interpolation and distribution, splitting techniques, grid choice. Development and implementation of algorithms. Writing CWI reports meant as preprints for journal papers and as part of the thesis.

Yr4: Polishing algorithms and software with respect to efficiency, robustness, documentation, etc. Simulating realistic case-studies. Completing the thesis.

8 Expected Use of Computerfacilities

The models will be developed initially on workstations and on the locally available distributed computing environments, the Beowulf cluster at the university of Amsterdam and Medusa at CWI. Furthermore we expect that advanced visualisation 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 visualisation equipment, the PC based virtual reality environment using one projection screen (DRIVE) at the Section Computational Science and the Cave Automated Virtual Reality Environment at the Academic Computing Services of Amsterdam (SARA). In the final phase of the project we might call upon NCF for the use of Teras at SARA.

9 Literature

Five key references of the Research Team

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10 Requested Budget

We apply for 2 OiO positions with benchfees.

$$\begin{array}{rclcl}
 2 \text{ OiO positions} & 2 \times & \in 135.762 & = & \in 271.524 \\
 2 \text{ OiO benchfees} & 2 \times & \in 4.538 & = & \underline{\in 9.076} \\
 & & & & = \in 280.600
 \end{array}$$

We request funding for additional travelling and accommodation:

$$\begin{array}{l}
 2 \times 1 \text{ week visit dr. Logg (numerics, multi-adaptivity)} \in 2.000 \\
 2 \times 1 \text{ week visit Prof. Müller (molecular developmental biology)} \in 2.000 \\
 2 \times 1 \text{ week visit NN} \in 2.000 \\
 \text{Workshop (based on 10 participants)} \in 6.000
 \end{array}$$