Dr. Primoz Ziherl

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Dear Dr. Ziherl

On behalf of workshop organizers, I am writing to thank you for QuantTissue and ESF support of the “European Training Workshop on Collaborative Multiscale Modeling of Biological Development and Disease” which was hosted at Lorentz Center in Leiden, Netherlands. The Workshop organizers were Dr. Maciej Swat (Indiana University), Dr. James A. Glazier (Indiana University), Dr. Roeland Merks, (CWI,Netherlands), Dr.Herbert Sauro (University of Washington). The presented report gives you an overview of workshop activities, achievements and impact on tissue modeling field. We were very pleased with the outcomes of the workshop and we are confident that ESF and QuantTissue investment in this type of scientific training events will improve collaborations among European institutions and lead to significant scientific advancements.

Sincerely,

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Report: European Training Workshop on Collaborative Multiscale Modeling of Biological Development and Disease

Scientific Summary

The workshop brought together 30 scientists interested in biomedical modeling of tissue development, homeostasis and disease. The research interest spectrum was quite broad from few cell systems to organ and organism level modeling. Although the workshop was focused on modeling about 30% of participants identified themselves as core experimentalists. This was very encouraging given that one of the goals of the workshop was to facilitate discussion and collaboration between experimental and modeling research groups. There was also a good mix between senior and junior scientists.

The workshop had several focus areas:

1) Expose participants to cell-based quantitative tissue modeling.
2) Encourage discussions between scientists to start new research collaboration. To facilitate that, each participant gave 15 minute talk on his/her research
3) Collaboratively work on select modeling projects.

Unlike traditional workshops where people spend most of their time listening to talks, this workshop assumed that participants would try to complete modeling project within 6 days. This was quite ambitious and challenging given that some of the participants were relatively inexperienced modelers and that number of possible modeling projects that could be of interest to participants could easily be greater than the number of attendees.

Despite these initial challenges organizers decided to stick to the project-based format. As it turned out all most participants were happy with such workshop style and managed to accomplish more work than they initially anticipated. The key to workshop's success was to ensure that there were enough modeling experts who would help participants with their projects. After each participant gave a talk, the organizers divided attendees into workgroups. Each workgroups consisted of 1-5 people sharing similar modeling interests.

The participants were allowed to change working groups during the workshop or participate in more than one working group. This created great research opportunity for junior participants who wanted to get exposure to multiple research topics. Because the level of participants sophistication varied the organizers ensured that people who needed additional introduction to modeling concepts had an opportunity to get it. The lack of formal lectures was slightly inconvenient from organizers' stand point because they were forced to repeat similar material few times. However, given limited duration of the workshop squeezing formal lectures into workshop agenda would be quite challenging.

The organizers closely monitored progress of the working groups (on a daily basis) and made sure that all groups advance their models.

Overall the level of participant involvement was excellent. Although the workshop officially ended at 6 pm many participants worked longer hours trying to complete as much work as possible.

Scientific Content

The workshop focused mainly on multi-cell tissue modeling in the context of development homeostasis and disease. The participants divided themselves into the following working groups:

1) Angiogenesis/Vasculogenesis working group
2) Osteoarthritis working group
3) Gastrulation working group
4) Heart tube formation working group
5) *Arabidopsis thaliana* morphogenesis working group
6) Cancer cell metabolism working group

Each working group was matched with at least one expert modeler who was helping participants advance their projects. Because certain modeling themes/solutions could be shared between working groups there was fair amount of open discussions going on between members of different groups. The reminder of this section summarizes work done by each modeling team during the workshop.

Angiogenesis/Vasculogenesis working group: Angiogenesis, the formation of new blood vessels from pre-existing ones, is a hallmark of diverse malignancies. Since the early 70's, inhibition of angiogenesis has been considered a promising treatment strategy, providing the opportunity for intervention in tumor growth. Over the last decades considerable progress has been made in the development of therapies that target tumor angiogenesis. VEGF signaling can markedly enhance angiogenesis. Therefore, this pathway has been the target for many anti-angiogenic drugs, e.g. Avastin (anti-VEGF antibody) and Sutent (receptor tyrosine kinase inhibitor of VEGFR). However, both of them exhibit limited therapeutic effects, due to an induction of evasive drug resistance. Moreover, besides their limited activity, currently available angiogenesis inhibitors show severe side effects in patients, and may even induce metastasis. Improvement of anti-angiogenesis treatment is therefore urgently needed. A better understanding of the effects of these drugs on the formation, support of existing, and the recovery of vascular networks after drug turnover, is therefore needed. To gain this understanding this group employed a computational model of angiogenesis to study the effects of different anti-angiogenic agents and treatment schemes.

To model the action of Avastin and Sutent the group used simulations of a chemotaxis-driven model of vascular network formation where network formation, is driven by an autocrine gradient of growth factor, in combination with contact-inhibited

To model Avastin, an antibody that binds to and neutralizes VEGF, they applied a washout or depletion of VEGF for a fixed period of time to mimic instant scavenging of the growth factor by the antibody. They observed that VEGF washout merely resulted in a period of stasis, with no lasting effects. When VEGF secretion was reapplied, network formation continued as in the original model without treatment simulations. The group also studied the effects of VEGF decay rate to simulate a more gradual depletion of VEGF. As the decay rate increases, the network becomes more sparse and the branches thin. For very high decay rates the cells disassociate. To simulate Sutent, a receptor tyrosine kinase inhibitor that, among others, blocks VEGFR-2, they gradually

decreased the strength of chemotaxis to VEGF, in order to simulate a limited responsiveness of the cells to the growth factor due to impaired function of the receptor. They observed that the effects of this treatment were less dramatic than the Avastin treatment. During the simulation the meshes of the vascular network collapse. For the extreme case of no chemotaxis, the network collapsed completely.

For further studies the group will conduct simulations taking into account cell proliferation and cell death. The cell cycle of each cell will be controlled via intra-cellular signaling pathways which will be modeled using the Systems Biology Markup Language (SBML) – based model within CompuCell3D.

Osteoarthritis Working Group: Osteoarthritis (OA) is a degenerative joint disease affecting a large proportion of the elderly population, for which there are no disease modifying therapies available. The primary cause of joint degeneration in OA is the inappropriate degradation and remodeling of articular cartilage. Whilst we know which factors are involved in cartilage degradation, knowledge of the initiating events and disease course is lacking. A range of factors including biochemical, mechanical and environmental are thought to be involved. At present mathematical modeling in this area is mainly restricted to mechanical models of the joint or non-spatial models of the biochemistry.

Models of the cartilage during OA should be inherently multi-scale in nature. Molecular cytokines, with a half-life of minutes, mediate degeneration of the whole joint over a period of decades. Both physical and biochemical factors are crucial. For these reasons, the CompuCell3D and SBW modeling environments are particularly well suited for this type of research.

The working group combined both mechanical and biochemical modeling approaches to build a spatial model of the biochemical network in cartilage, with particular focus on cytokine activity. During the course of the workshop the group produced a model of cartilage in Compucell3D consisting of two cell types, representing the tissue, and diffusing interacting chemical fields representing the biochemical pathways. The key finding was that inappropriate levels of cytokines led to cartilage degradation and that spatially the cartilage breakdown closely resembled that seen in OA histology. Additionally, they were able to apply mechanical forces to the tissue and assess the effect of this on the biochemical fields.

The model produced in the workshop was a proof of concept model and will be extended with more detailed models of relevant pathways. Realistic parameter values and timescales can increase our understanding of the causes and possible therapies in OA, particularly in early OA where there is little clinical data.

Chick Gastrulation Modeling Group: The group modeled cell movements during primitive streak formation in the chicken blastodisc. Three mechanisms involved in the breaking of symmetry in the anteroposterior (AP) axis have in the past been stated: i) oriented cell division; ii) chemotaxis; and iii) convergent-extension. Although evidence shows that primitive streak formation is not due to oriented cell division, recent studies provide evidence for convergent-extension. Group's work placed emphasis on convergent and extension movements resulting in primitive streak elongation, a process that had not been explored theoretically. The group proposed that the convergent-extension movements result from cell-intercalation driven by surface tension minimization. They first created a new model for cell intercalation based on cell orientation. This was followed by modeling the whole chicken blastodisc where they introduced this function. As a result the cells started to intercalate at the midline and

extend along the AP axis, closely resembling cell and tissue movements of the real primitive streak.
The group continues making minor adjustments to the model, tuning the parameters and reproducing classical perturbation experiments while further developing and exploring the intercalation model itself. They aim to publish at least two papers from this work: a methods paper where the new intercalation model is introduced and a second one where the primitive streak formation is modeled.

Heart Tube Formation Working Group: This working group developed a simple model where differential cell growth leads to bending of the heart tube. The key discovery made by this group was that labile adhesion, alone, was not sufficient to maintain heart tube shape and it was necessary to model cells as elements connected by elastic constraints between their centers of mass. Because their simulation was quite big in terms of lattice space required they were able to run only simplified 2D simulation. The full 3D simulation required computer more powerful than a laptop. The group will continue running their simulations and if the results are encouraging they will be published.

Arabidopsis Working Group: This working group focused on modeling auxin gradient observed in the plant root, which is dependent on a PIN efflux network. In addition to this they modeled the auxin signaling pathway using Jarnac from the Systems Biology Workbech package (SBW) and put auxin signalling pathway model in each of the CompuCell3D model cells.

In contrast to animal development, plants have the capability to develop new organs during non-embryonic stages. This is due to presence of stem-cell niches, which contain undifferentiated cells that continuously produce new cells for the growth of the plants. In particular, the root stem-cell niche (RSCN) is located at the tip of the root and it is composed of the quiescent center and initial or stem cells surrounding it. The RSCN is morphologically simple. These properties make it an excellent system for the study of cellular organization and development.

The group will analyze the behavior of the coupled transport and signaling pathway models in order to reproduce experimentally observed behaviors and produce new predictions about possible missing components and unknown behaviors of the RSCN. This should improve the understanding how individual cells respond to auxin concentration and make decisions regarding cell division, growth or its differentiation state in the RSCN.

Cancer Cell Metabolism Working Group: The work-group investigated the effects of heterogeneity of metabolic rates in a 2D population of motile cells, where cells depend on a single, limiting nutrient to produce energy for survival, growth, and proliferation. The problem of heterotypic metabolism is closely related to understanding tumor behavior and tumor development. Normal cells consume nutrients at a relatively low rate, and convert them to energy (e.g. ATP molecules) efficiently through oxidative phosphorylation. The energy yield of the process is diminished by its low rate. Besides oxidative phosphorylation, tumor cells also process glucose in an inefficient, but fast way (aerobic glycolysis). This mode is used by cells when supplies of oxygen are low, and a large amount of energy is needed. A typical phenomenon in tumors is that cells do not return to the first mode of metabolism, even after the restoration of normal oxygen levels -- an effect discovered by Otto Warburg.

Understanding the dynamics of a tumor cell population in response to varying nutrient supply is crucial in planning anti-tumor therapies that aim at restricting metabolism. The goal of the work-group was to investigate the population dynamics and spatial patterning of a mixture of normal (low consuming) and tumor (high consuming) cells as a function of nutrient diffusion. The group aimed at constructing a re-usable and easily extendable model.

During the Workshop, the work-group learned the basics of using CompuCell3D and SBW. CompuCell3D was used to create a model of a 2D cell population. The substrate is provided uniformly by the stroma, a layer above the field of simulation. Persistent random walk of cells was implemented in a run-and-tumble fashion. Simplified cell metabolism was implemented in SBML, and linked to the CompuCell3D simulation.

Simulations of the model showed that the two different cell types are able to co-exists in the explored parameter regime. The model proved to be sensitive to nutrient supply, and metabolic efficiency, but less sensitive to variations in nutrient diffusion and cell motility parameters. From the preliminary simulations it has become clear, that the stochastic nature of the model requires more experiments. A further exploration of the parameter space will also provide a better overview of the system. After exploring the simple system, the model can easily be expanded to include a more sophisticated cellular metabolism, in the form of standard SBML modules.

Assessment of the results

The Workshop was highly successful, judging by the feedback from the participants. The organization was flawless with no logistic glitches of any kind. The Lorentz Center Staff organized excellent social program which allowed participants to engage in discussions in a less formal atmosphere. This had tremendous impact on formal part of the workshop. Once people got to know each other better they were able to communicate and work more effectively. The hotel and facilities at the Lorentz Center were excellent. Everybody seemed to appreciate the efforts that Lorentz Center put into organizing this event.

We hoped that this Workshop would significantly raise the profile of QuantTissue Consortium and Lorentz Center in the area of biomedical modeling, computational tissue biology. Given the level of interest from scientists around the world we feel confident that we were able to convey the message that there exist significant involvement of European organizations (QuantTissue, ESF) in quantitative modeling of development and disease of tissues.

We were very pleased with the talk by invited speaker Carl-Philip Heisenberg. It was very stimulating talk especially that the topics he discussed (force-based approach to tissue dynamics during zebrafish gastrulation) were directly relevant to workshop main themes. In particular he has presented an approach based on Cellular Potts Model (a model that CompuCell3D implements) to study impact of tensile forces on germ layer organization during gastrulation. One of the working groups was modeling gastrulation in chick embryos so Carl-Philip's talk was directly relevant to this group.

This workshop was quite experimental and the organizers were somewhat skeptical whether project-based workshop format would work out. The big concern was that level of familiarity with cell-based modeling would vary among different participants and it would lead to some attendees feeling left out. Since we could not accommodate lectures in the workshop schedule we had to ensure that people who needed to be brought up-to-speed in modeling topics had an opportunity to learn the material as quickly as possible.

For this reason we invited modeling experts who served as instructors for workshop participants. Each time a workshop participant would struggle with completion of particular tasks or needed one-on-one coaching, instructors were available to help.

At the conclusion of the workshop all working groups had made significant advancement in their projects. It was somewhat surprising to organizers to see so much progress being done at the workshop given relatively short duration of the workshop and the fact that several groups started coding the simulations from scratch. The gastrulation working group was able to finish the project completely and they are ready to submit the paper based on their model. This group, however, started working on the project earlier so it would be unreasonable to expect other groups show same level of accomplishment during just few days.

Besides working in groups participants had ample opportunities to talk to each other and discuss possible new collaborations. Many participants who were graduate students, were able to talk senior researchers and get advice, suggestions or feedback on their research. Such informal conversations have often significant impact on student's careers. Having access to experienced researchers other than student's own advisor allows students to get different perspective on their research , get advice for future research and consequently help students make more informed decisions when they transfer to post-doctoral positions.

Finally, during the workshop we had several short brainstorming sessions on how to improve modeling software. Although most of the suggestions applied mainly to CompuCell3D and SBW many of ideas solicited from participants applied to other biomedical packages. Several bugs reported during the workshop were fixed by CompuCell3D and SBW developers and new features which seemed to be important were also added to the packages.

Overall, by avoiding rigid workshop structure we were able to engage all participants in scientific projects and open discussions. All participants were enthusiastic and it was obvious that the level of interest in quantitative tissue modeling is significant. Given that the registration for the workshop was open for only few weeks we were surprised to see that all the slots were filled and we had to reject several applications.

This clearly shows the importance of cell-based modeling of tissues. Consequently, it is critical that adequate training programs exist for young scientist to embrace state-of-the art tools which will impact how future research is done. QuantTissue Consortium has already made significant investments in outreach and training and the we hope that this workshop fulfilled part of the QuantTissue mission.

We have asked all participants to acknowledge QuantTissue and European Science Foundation in any publication that will originate from the research done during the workshop.

Overall we were very happy with the workshop outcomes and we hope that ESF and QuantTissue share our enthusiasm.

Program '*Modeling of Multicellular Development and Cancer European CompuCell3DSBW Hands-on Workshop*'

Monday 8 October 2012

09:00 – 10:00	Arrival and office assignment
10:00 – 10:15	Welcome by the manager of the Lorentz Center
10:15 – 10:45	Introduction to Workshop Aims and Goals by the scientific organizers
10:45 – 11:00	Introduction to Model Development Workflow by **James Glazier**
11:00 – 11:30	Coffee and tea break
11:30 – 12:15	**Marten Postma** Gastrulation mechanisms in Nematostella vectensis
12:15 – 13:00	10 minute talks by participants, describing the problem they would like to model
13:00 – 14:00	Lunch
14:00 – 15:30	10 minute talks by participants, describing the problem they would like to model
15:30 – 16:00	Coffee and tea break
16:00 – 17:00	10 minute talks by participants, describing the problem they would like to model
17:00 – 19:00	Wine & Cheese party

Tuesday 9 October 2012

09:00 – 9:45	**Carl-Philipp Heisenberg** Cell and tissue mechanics in zebrafish gastrulation
09:45 – 10:15	Preliminary "match-making" of participants and instructors to assemble small teams of participants and instructors with shared research interests and complementary skills. Instructors will move from team to team as needed throughout the Workshop.
10:15 – 10:45	Coffee and tea break
10:45 – 12:30	Optional hands-on introduction to Systems Biology Workbench with exercises, for those who are interested **|** Initial qualitative model design discussions between teams and instructors for remaining participants.
12:30 – 14:00	Lunch
14:00 – 17:00	Optional hands-on introduction to CompuCell3D with exercises, for those who are interested **|** Continuing qualitative model design discussions between teams and instructors for remaining participants.

Wednesday 10 October 2012

09:00 – 9:45	**Julio Belmonte** A Multi-cell, Multi-scale Model of Vertebrate Segmentation and Somite Formation
09:45 – 10:15	Brief overview of rest of week, wrap-up of introduction, opportunity to reorganize teams.
10:15 – 16:30	Teams work on finalizing their initial qualitative models and translating them into quantiative models. Depending on participant needs and interests, instructors will offer brief introductions to advanced topics, e.g. extending CompuCell3D, CompuCell3D batch scripting, connecting Systems Biology Workbench models to CompuCell3D models, etc..
12:30 – 14:00	Lunch
16:30	Departure bus to boat
17:00 – 22:00	Boat Trip and Dinner (aka Booze Cruise)

Thursday 11 October 2012

09:00 – 15:30	Teams translate their quantitative models into simulations and refine their models and simulations. Depending on participant needs and interests, instructors will offer brief introductions to advanced topics, open to any interested participants.
12:30 – 14:00	Lunch
15:30 – 17:30	Feedback session. Participant teams briefly present their first results to the rest of the group, receive feedback from other participants. Opportunity to reorganize teams.

Friday 12 October 2012

09:00 – 12:30	Teams refine their models and simulations. Depending on participant needs and interests, instructors will offer brief introductions to advanced topics, open to any interested participants.
12:30 – 14:00	Lunch
14:00 – 17:30	Teams run and collect initial results from their models and simulations. Depending on participant needs and interests, instructors will offer brief introductions to advanced topics, open to any interested participants.
18:30 – 21:00	Conference Dinner - Leiden City Center @ Malle Jan

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Saturday 13 October 2012

09:00 – 13:00	Teams run and collect results from their models and simulations
13:00 – 14:00	Lunch
14:00 – 16:30	Wrap up: Participant teams present “final” results and future plans
16:30 – 17:00	Concluding remarks by organizers

----------End of workshop----------