Schoorl meeting 2019

Nederlandse **V**ereniging voor **T**heoretische **B**iologie
23-24 May, 2019

Nederlandse Vereniging voor Theoretische Biologie

NWO
Netherlands Organisation for Scientific Research

Dear participants,

We once again welcome everyone to the Annual NVTB meeting. It is always a bit exciting to wait and see how many people will show up, but we have landed on 42 participants this year. We have 2 invited speakers, and a total of 17 presentations submitted by our current or future members. We are looking forward to learn from you all!

The invited speaker on Thursday (May 23rd) is José Borghans, who has a background in theoretical immunology, and currently runs an interdisciplinary research group on leukocyte dynamics. Her talk will be on the T-cell dynamics in health and disease. On Friday, Marjon de Vos will start our day discussing the interplay between ecology and evolution, adaptive landscapes, and adaptive constraints in microbial communities.

The meeting is once again subsidised by NWO. This allows us to keep the meeting affordable, which is of course especially compelling for the many students and early-career scientists that join us each year. For this, we are of course very grateful to NWO. Like in former years, all these young speakers are once again eligible for the NVTB-presentation award of € 100,-! All students (bachelor, masters, and PhD candidates) can win this price, so give it your best shot!

We wish you a pleasant stay, and an interesting meeting!

The board of the NVTB,

Kirsten ten Tusscher (Chair)
Jeroen Meijer (Treasurer)
Bram van Dijk (Secretary)

Practical information:

Address:

Dopersduin
Oorsprongweg 3
1871 HA Schoorl
phone: (072) 509 12 74
website: www.dopersduin.nl.

Nights and Meals:

In "Dopersduin" the overnight accommodation consists of simple 4 person bedrooms with bunk-beds, as well as double and single bedrooms with shower and toilet. All prices include overnight stay and meals. The four-bedded rooms do not included bed linnen, which you can rent for € 8.50, but you can also bring your own sleeping bag and pillow case.

Finances:

Thanks to a subsidy of the NWO–ALW, we are able to keep the costs for participants low. You will receive an invoice by email 1 week before the meeting. Please transfer the required fee a few days before the meeting so we can confirm your payment at registration.

Membership fee	€ 12,-
Single day attendance	€ 50,- *(non-members € 65,-)*
Single day students*	€ 30,- *(non-members € 45,-)*
Two days with four-bedded room *(No bed linnen included, bring a sleeping bag or hire bed linnen for € 8,50)*	€ 55,- *(non-members € 70,-)*
Four-bedded room students* *(No bed linnen included, bring a sleeping bag or hire bed linnen for € 8,50)*	€ 35,- *(non-members € 50,-)*
Double room	€ 80,- *(non-members € 95,-)*
Single room	€ 100,- *(non-members € 115,-)*

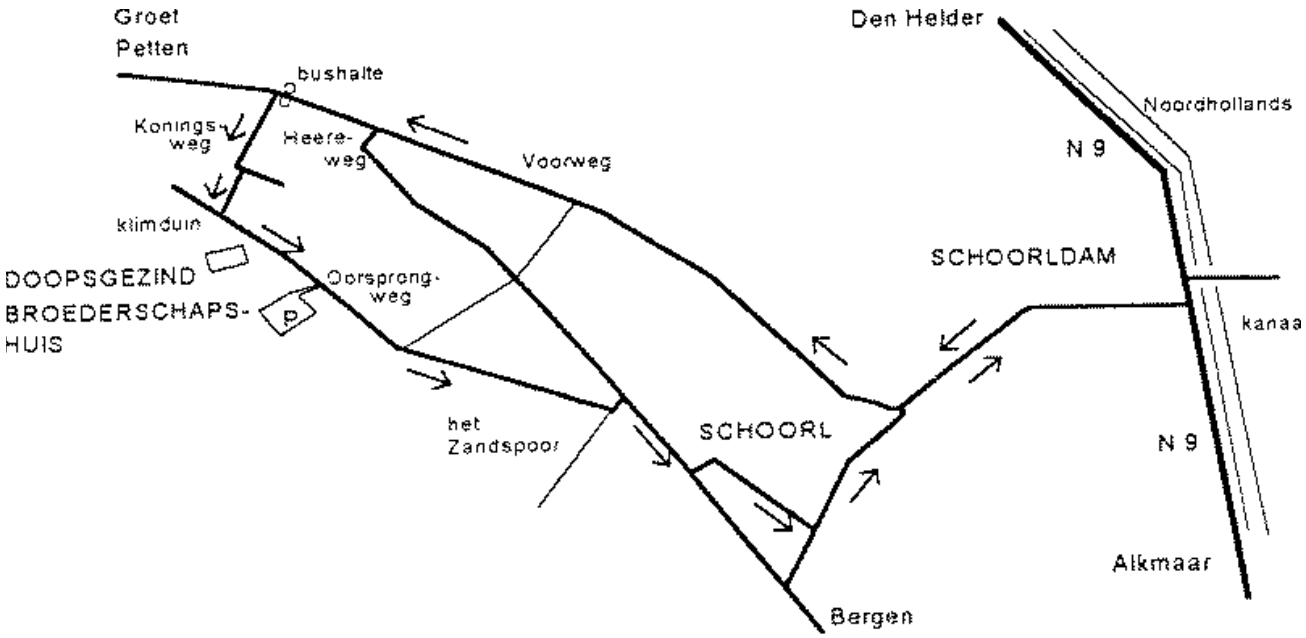
*Bachelor and master students.

To get to Schoorl / Dopersduin by public transport:

• At the trainstation in Alkmaar, you can cross the railway tracks at the end of the platform (in the direction to Den Helder) to arrive at the busstation directly. From Alkmaar take **bus 151** (Connexxion) to Petten (9u53m recommended to be in time for registration) and exit at the stop KONINGSWEG (that takes a little over 15 minutes). The bus departs every 30 minutes.
• In Schoorl: cross the road and follow the Koningsweg to the dune. Once you arrive at the dune, go left into the Oorsprongweg, and after 100 meters **Dopersduin** is on your right (see image below). The walk takes about 5 minutes.

To get to Dopersduin by car:

Take the N9 (*Alkmaar–Den Helder*) and exit at *Schoorldam* to Schoorl. After about 750 meter keep right at the crosspoint in the direction *Groet/Petten*. This road is called Voorweg and later Heereweg. After about 1 kilometer go straight at the crossing to *Centrum*. After 200 meter turn right onto the Koningsweg (there is a sign Dopersduin there). At the end, turn left onto the Oorsprongweg (this is a one-way road, so be sure to come from this direction). After about 100 meters, Dopersduin is on your right. The driveway leads to the parking lot.



Programme NVTB Meeting 23-24 May 2019

Day 1: Thursday May 23rd

10:15 - 10.45	**Registration (Tea / Coffee)**
10:45 - 10.55	Kirsten ten Tusscher, *Opening statements*

10:55 - 11.45 José Borghans, *T-cell dynamics in health and disease*

11.45 - 12.10	Enrico Sandro Colizzi, *High rates of duplications and deletions prevent genome deterioration. Understanding yeast ribosomal DNA evolution.*
12.10 - 12.25^{short}	Leonie van Steijn, *Topotaxis: cell movement guided by environmental crowding*
12:30 - 13:30	**Lunch**
13:30 - 13:55	Margriet Palm, *Data driven modeling uncovers antagonistic feedback loops in T cell expansion*
13:55 - 14:20	Meike Wortel, *Evolution in serial transfer cultures: Selection pressures and conditions for coexistence*
14:20 - 14:45	Laura van Schijndel, *Quantifying natural selection at different spatial scales*
14:45 - 15.10	**Tea / Coffee**
15:10 - 15.35	Kevin Kort, *Ecological and metabolic dynamics of a multi-species microbiome*
15.35 - 16.00	Alejandro Javier Alarcón González, *Inferring dynamics from data in rotavirus epidemiology*
16.00 - 16.15^{short}	Dario Bijker, *Agent Based Modelling for the quantification of Tumor Control Mechanisms employed by Cytotoxic T Lymphocytes in vivo*
16.15 - 16.35	Richard Beck, *Stochastic Simulations of Multiple Hitting Cytotoxic T Lymphocytes*
16:40 - 17.00	**Registration continued**
17:00 - 17:50	**Yearly (general) meeting**
18:00 - 19.00	**Dinner**
19:15 - ...	**Tradition of getting lost in the dunes of Schoorl**

Programme NVTB Meeting 23-24 May 2019

Day 2: Friday May 24th

08:30 - 9:30	**Breakfast**

9:30 - 10.20	Marjon de Vos, *Ecology dictates evolution? Evolution of antibiotic resistance in microbial communities*

10:20 - 10.45	Jacob Rutten, *Taming the meristem: how organ level control emerges in dividing root cells*
10:45 - 11.00^{short}	Demi Bolleman *Spatial T cell organization affecting the T cell activation process*
11:00 - 11.25	**Tea / Coffee**
11:25 - 11.50	Yiteng Dang, *Collective dynamics and self-organisation in a population of communicating cells*
11:50 - 12.15	Jeroen Meijer, *Evolutionary contingency drives microbial metabolism, community structure, and its predictability*
12:15 - 12:30^{short}	Sam von der Dunk *Symmetry Breaking in a Spatial Model of RNA-Like Replicators*
12:30 - 13.30	**Lunch**
13:30 - 13.55	Bas Jacobs, *Small GTPase patterning: How to stabilise cluster coexistence*
13.55 - 14.20	Kris Veeken, *Speciation-like behaviour in self-replicating molecules*
14:20 - 14.50	**Tea / Coffee**
14:50 - 15:15	Johan L. van Leeuwen, *How fish larvae swim: lessons from bending moment patterns*
15:15 - 15.40	*Presentation price & closing words*

Abstracts (day 1)

T-cell dynamics in health and disease

Jos'e Borghans
Laboratory of Translational Immunology, UMC Utrecht

T-lymphocytes are best-known for their role in pathogen clearance. The immunological memory they provide forms the basis of one of the greatest medical achievements: prevention of infection through vaccination. Unfortunately, T cells are also causally related to many chronic inflammatory diseases. Despite the enormous immunological progress that has been made over the last decades, our knowledge about T cells remains highly descriptive, and quantitative insights are still limited. This presentation will focus on different studies on the quantification of T-cell dynamics in healthy people and laboratory animals. It shows how the quantification of T-cell dynamics has revealed a fundamental difference in the maintenance of naive T cells between mice and humans. It also addresses the dynamics of T cells in patients after stem-cell transplantation, and shows that it is questionable whether the human immune system is capable of inducing a successful homeostatic response to low lymphocyte numbers. Finally, it focusses on recent insights into memory T-cell dynamics. We show that cellular longevity is not a key characteristic of memory T cells. Importantly, insights into immunological memory in humans are almost exclusively based on studies of cells from the blood. It has recently been suggested that the bone memory provides a niche for long-lived memory T cells that hardly recirculate through the blood and therefore go unnoticed in most immunological studies. Our recent results suggest that that even memory T cells in the bone marrow are maintained dynamically, and show how contradicting conclusions in the literature are related to the specific techniques used.

High rates of duplications and deletions prevent genome deterioration. Understanding yeast ribosomal DNA evolution.

Enrico Sandro Colizzi
Origins Center

The ribosomal RNA genes (rDNA) form clusters of hundreds of copies in eukaryotic genomes. Since ribosomes are highly abundant and must be synthesised throughout a cell's life, the rDNA experiences frequent scheduling conflicts between transcription and DNA replication complexes. Unresolved conflicts can cause DNA breaks which often lead to rDNA copy number variation. Strikingly, it was recently found that yeast can upregulate these mutations depending on

the availability of nutrients. These mutational dynamics, however, do not alter growth rates in yeast and are thus selectively near-neutral. We investigate these puzzling mutational dynamics observed in yeast with a cell-based computational model in which mutations occur more frequently with larger transcriptional load. We show that these transcription-associated mutations are beneficial when biased towards duplications and deletions even though they increase the overall mutation rates. Genome stability is in fact compromised when duplications and deletions are as frequent as point mutations even when their overall rate is small, due to a deleterious evolutionary ratchet. Taken together, our results show that the mutational dynamics observed in yeast rDNA are beneficial for the long term stability of the genome, and pave the way for a theory of evolution where genetic operators are themselves cause and outcome of the evolutionary dynamics.

Topotaxis: cell movement guided by environmental crowding

Leonie van Steijn
Mathematical Institute, Leiden University

Cells use many environmental inputs to direct their movements. Among well-known examples are chemotaxis, where cells move along a gradient of a chemical compound, and durotaxis, cell motion from soft to stiff environments. However, in vivo cells move in crowded environments containing obstacles, other cells, etc, restricting their movements. Experiments on ameboid cells, where cells are imaged and tracked on a substrate with micropillars, have revealed a new form of taxis, topotaxis: the motion of cells towards less crowded areas. A simple particle-based computational model reproduced the effect of topotaxis, although the effect was smaller than found experimentally. In this study, we use a more realistic model, the Cellular Potts model, too see whether it is able to reproduce the effect of topotaxis and to see if the effect is closer to the one found experimentally. By using the Cellular Potts model, we can study the effects of the cell shape, the cells ability to squeeze through narrow spaces and its adhesion to the obstacles. By using the Act-extension by Niculescu et al. we can also study the effect of subcellular reorganization in navigating around obstacles.

Data driven modeling uncovers antagonistic feedback loops in T cell expansion

Margriet Palm
Division of Drug Discovery & Safety, LACDR, Leiden University

When T cells are activated after infection, the population of activated T cells typically expands quickly, followed by regression. While multiple regulatory

ligand-receptor pairs for T cell dynamics are known, it remains unclear to what extent the population dynamics are controlled by external signals and to what extent signaling between T cells suffices for population control. We created an in vitro set up in which CD8+ T cells are activated by peptides presented by other T cells. Perturbation experiments showed that the pro-survival pathways driven by CD28 and IL-2R signaling play a key role in the growth and regression of the T cell population. To unravel the contribution of these signaling networks to population dynamics, we built multi-compartment ODE models to identify the minimal signaling that could quantitatively explain the population dynamics observed in the in vitro model. In these models we limited the degrees of freedom by incorporating experimentally observed levels of ligands and receptors. We found that the immune checkpoint CTLA-4, which inhibits CD28 signaling, together with CD28 and IL-2R signaling was required to explain the dynamics. Furthermore, the data are most consistent with a model in which CTLA-4 expression is regulated by IL-2R signaling. In conclusion, our work suggests that the typical pattern of T cell activation followed by regression is controlled by a set of antagonistic feedback loops.

Evolution in serial transfer cultures: Selection pressures and conditions for coexistence

Meike Wortel
Origins Center / University of Amsterdam

Studying evolution in the laboratory has led to insights into evolutionary questions, such as repeatability and contingency. For practical purposes, such experiments are often performed with microbes grown in liquid cultures which are propagated after a stationary phase is reached. Although practical, conceptually this environment is complicatedwith a lag-phase, exponential growth phase, nutrient-limited growth phase and stationary phaseand the consequences for evolutionary adaptation are not yet fully understood. As the microbes evolve, they also change the dynamics of these different growth phases, allowing for an eco-evolutionary feedback and enabling the possibility of frequency dependent coexistence. We derived the selection coefficient for the exponential and nutrient-limited growth phase in a liquid culture in terms of maximal growth rate and substrate affinity, with which we can analytically verify previous simulation results. We predict how the optimal strategy and, using experimental data of a growth-rate/affinity trade-off, how coexistence depends on the external conditions, such as initial resource concentration. This coexistence consists of a high growth-rate (r-strategy) strain with a high affinity (K-strategy) strain grown on a single resource. Coexistence of these strategies has been shown before, but with our analysis we can investigate when this coexistence is evo-

lutionarily stable, i.e. whether this coexistence will disappear when we let the traits evolve. These results can predict experimental conditions for evolutionarily stable coexistence and evolution towards coexistence. We outline how this method can be tested in an experimental setting with microbes or digital organisms.

Quantifying natural selection at different spatial scales

Laura van Schijndel
Theoretical Biology and Bioinformatics, Utrecht University

Natural selection is the result of many biological interactions, such as predation, cooperation and competition. These processes happen at different spatial scales, and their contributions to natural selection may differ in strength and direction. As a result, the selection acting on local environments may differ markedly from that experienced by the population as a whole. We ask: can we define and measure the selection pressure at each length scale? Opposing selection pressures at different scales are the core of the altruism problem, for which group selection offers a solution. Within the group selection literature, two main methods have been proposed to quantify the relative contributions of group-level selection and individual-level selection: the Price method and the contextual method. We aim to combine generalised versions of both methods, in order to quantify the strength and direction of selection at different length scales. In earlier work, our group has generalised the Price method to structured populations where an individual's neighbours influence its fitness but no discrete groups exist. In this talk, I will explain this generalisation, and show how to generalise the contextual method in an analogous way. Moreover, I will show how both approaches can be combined fruitfully, and the potential biological value of the resulting mathematical decomposition. This combination of approaches has not been described previously, and yields a clearer insight in the differences and similarities between the two approaches. More work needs to be done before the various terms of the decomposition can be connected to biological situations.

Ecological and metabolic dynamics of a multi-species microbiome

Kevin Kort
TRÊS - Rijksuniversiteit Groningen

The human gastrointestinal tract hosts a complex and species-rich microbial ecosystem, the gut microbiome. Changes in microbiome composition (dysbiosis) have been associated with inflammatory bowel diseases, such as Crohns disease and ulcerative colitis, and metabolic syndromes, such as diabetes and

obesity. However, the way dysbiosis arises, is largely unknown, some plausible causes are; changes in the host diet, new (pathogenic) species invading the microbiome, or simply by ecological succession. In order to predict how and when dysbiosis arises, a detailed model of bacterial growth and their ecological interactions is needed. To this end, we developed an in silico method that allows for simulation of large microbial ecosystems. Our method uses genome-scale metabolic maps in combination with flux balance analysis to simulate the metabolism and growth of species inhabiting the microbiome. The model uses nutrient availability and the metabolic maps to calculate the growth rate of each species. Growth rates can be influenced by the presence of other species, which might consume or produce important nutrients. This metabolite-specific competition and cross-feeding can lead to the emergence of complex ecological interactions as two or more species might be competing for multiple metabolites, whilst also cross-feeding other metabolites. With this model we hope to gain better insights into the ecological effects that are at play during community assembly and succession. During this presentation, I will introduce the model we developed and discuss some of our preliminary results and our future directions.
Keywords: microbiome, dysbiosis, flux balance analysis, dynamic multi-species metabolic modelling, community assembly and succession.

Inferring dynamics from data in rotavirus epidemiology.

Alejandro Javier Alarcón González
Unit for Infectious Disease Modelling at RIVM/Mathematics Institute at Utrecht University.

I present my thesis project for the Master of Mathematics with specialization in Complex Systems at the University of Utrecht. The motivation for this is research are statistics of infections levels of Rotavirus in the Netherlands, which suggest that a period-doubling bifurcation in the infection dynamics may have taken place within recent years. In my thesis project I look into mathematical methods for inferring dynamics from data. These include: attractor reconstruction through delay-embeddings, measures in probability spaces, computation of Wasserstein distances and diffusion maps. Using these methods, I try to quantify the degree or likelihood of a bifurcation in the infection dynamics of Rotavirus. By reconstructing an attractor from observations, we proceed with a methodical approach to obtain system-level topological information from a single observable, which can provide with a first insight into the infection dynamics. By transforming a time series into a probability measure, we encode the long term behaviour of observations. Furthermore, if we regard such measures as elements within a phase space for which a distance is provided, then we can assess the dynamical similarity in between time series corresponding to any two

measures by computing the distance in the phase space. These distances are called Wasserstein distances, and we expect them to detect bifurcations in the dynamics. Throughout the project we perform the same analysis on synthetic time series obtained from a transmission model for which a period-doubling bifurcation is known, in order to shape our expectations

Agent Based Modelling for the quantification of Tumor Control Mechanisms employed by Cytotoxic T Lymphocytes in vivo.

Dario Bijker
Leiden Academic Centre for Drug Research, Division of Drug Discovery & Safety

While cancer immunotherapy has proven very efficient in recent years, there is a clear need for more fundamental understanding of the mechanisms involved. Cytotoxic T Lymphocytes (CTLs) have long been considered to control tumor growth mainly through a highly efficient contact-dependent apoptosis induction mechanism. However, CTls are also known to produce cytokines, with excretion of IFN? receiving particular interest recently. A systemic evaluation of the mechanisms employed by CTLs in tumor control would evidently be highly insightful. Matsushita et al. (1) showed that B10F10 tumor control by adoptively transferred CTLs in C57BL/6 mice is mostly dependent on antiproliferative effects of IFN? excretion. Our current research aims to quantify the importance of contact-dependent apoptosis versus IFN? mediated tumor growth suppression in this model. Earlier research at our department used Ordinary Differential Equation (ODE) modelling to quantify the mechanisms of tumour control employed by CTLs in the empirical data from Matsushita et al. The ODE model indeed indicated that tumor control is mostly dependent on indirect (IFN?) rather than direct (contact-dependent apoptosis) CTL tumor control mechanism. The results of this study remain partially inconclusive, and oversimplification of cell density heterogeneity, both spatially and over time, may have influenced the representability of this model. For these reasons, the current research expands upon earlier findings through an Agent Based Modelling (ABM) approach. ABM modelling is suited in this context as it can readily recreate representative emergent behaviours, as well as spatial heterogeneity. An earlier ABM model developed within our research department was here used as a starting point (2). Presently, a control-case ABM matching tumor growth in untreated mice is reaching its final development stages. This model will subsequently be expanded to include CTL transfer, eventually allowing for a quantitative analysis of the mechanisms underlying the empirical data from Matsushita et al. (1) Matsushita, H. et al. Cytotoxic T Lymphocytes Block Tumor Growth Both by Lytic Activity and IFN -Dependent Cell-Cycle Arrest. Cancer Immunol. Res. 3, 2636 (2015). (2) Beck, R. J., Slagter, M. &

Beltman, J. B. Contact-dependent killing by cytotoxic T lymphocytes is insufficient for EL4 tumour regression in vivo. Cancer Research 9.13. (2019). doi: 10.1158/0008-5472.CAN-18-3147

Stochastic Simulations of Multiple Hitting Cytotoxic T Lymphocytes

Richard Beck
Department of Drug Discovery and Safety, Leiden Academic Centre for Drug Research

The killing behaviour of Cytotoxic T Lymphocytes (CTLs) remains insufficiently characterised. An established model of CTL killing treats CTL cytotoxicity as a poisson process [1], based on the assumption that CTLs serially kill antigen-presenting targets via delivery of lethal hits, each lethal hit corresponding to a single injection of cytotoxic proteins into the target cell cytoplasm. Contradicting those results, a recent in vitro study of individual CTLs killing targets over a 12-hour period found significantly greater heterogeneity in CTL killing performance than predicted by the poisson killing model [2]. The observed killing process was non-stationary, with the best performing CTLs exhibiting a marked increase in killing during the final hours of the experiments, along with a burst killing kinetic. No mechanism to explain the heterogeneous killing kinetics could be found. Here we used stochastic simulations to assess whether target cells might require multiple hits from CTLs before undergoing apoptosis. We employed minimal stochastic simulations to characterise how a requirement for multiple hits might influence the kinetics of the CTL killing process. Our simulations reproduced the late onset, burst killing dynamics observed in vitro. Data-fitting models were obtained with parameter sets compatible with recent observations of multiple hitting in vivo, wherein target cells usually died after 1-5 contacts from CTLs [3]. Our models also predict that the number of available targets may influence the realised CTL killing rate. [1] Perelson, Allan S., and Catherine A. Macken. Mathematical biosciences 70.2 (1984): 161-194. [2] Vasconcelos, Zilton, et al Cell reports 11.9 (2015): 1474-1485. [3] Halle, Stephan, et al. Immunity 44.2 (2016): 233-245.

Abstracts (day 2)

Eco-evolutionary interactions in bacterial communities
Marjon de Vos
Groningen University

Communities of bacteria can be viewed as small ecosystems. By measuring the pair-wise interactions we obtained a unique insight in the ecological interactions of communities responsible for urinary tract infections. Based on these measured data we can elucidate these network properties of these ecosystems, as well as the ecological stability of these communities. Additionally, we discovered that many of these bacterial interactions affect the immediate tolerance to antibiotics, as well as the ability to evolve antibiotic resistance. This shows that environmental circumstances have an effect on both the ecology and the evolution of bacterial consortia.

Taming the meristem: how organ level control emerges in dividing root cells
Jacob Rutten
Theoretical biology Utrecht University

Plants dynamically alter the speed at which their roots grow, allowing them to prioritize much needed resources, or invest in other organs, for faster growth. Plant development is characterized by self renewing growth domains, where cell division is followed by differentiation in both space and time. New cells formed through stem cell division eventually push older cells out of the dividing zone, after which these older cells stretch and differentiate. Each root end contains such a division domain. The larger this domain, the more cells divide. The size of the growth domain is therefore an indication of how much the root commits to growth, a decision it bases on both local and global signals. A variety of these signals is integrated at the root tip. The most well studied amongst them is Auxin, which is transported down to the tip in the inner tissues, and upwards in the outer tissues, only to go back inwards after the division zone is passed, in a motif called the reverse fountain. Here we show how the positive feedback loop between the the rapidly transported auxin and the very slow transcription factor Plethora, which determines if a cell is allowed to divide or not, drives an initial increase in the number of dividing cells. Despite the positive feedback loop only getting stronger, the meristem eventually stabilizes due to: diminishing returns on production, a focus of auxin into a limited domain due to active transport, and a dilution inherent to growth. Antagonistic transcription factors

called ARRs can dynamically determine what this stabilizing size should be. They exert this control from outside the division zone through their inhibitory effects of auxin, as well as direct effects on the Plethora transcription. Because auxin is so rapidly transported across the root, its degradation outside the division zone affects the root tips auxin levels, allowing the ARRs to indirectly affect the auxin levels in the root tip. Through manipulation of the strength of any of the involved interactions, the root can integrate a number of distinct signals into a coherent organ level response.

Spatial T cell organization affecting the T cell activation process

Demi Bolleman
Drug discovery & safety at Leiden university

Cancer immunotherapy utilizes the mechanism of T cells, which kill tumor cells to halt tumors from growing. In this project we focus on a better understanding of the mechanism underlying the immune response, which could benefit treatment. Key factors in T cell activation have pro-activating and/or regulatory functions. T cell receptor signaling, via the receptor CD28 and its ligands CD80 and CD86, expands the activated T cell population. Activated T cells produce diffusible IL-2 which promotes T cell survival. Infinite expansion due to CD28 signaling is prevented by the immune checkpoint CTLA-4, which binds CD80 and CD86 with a higher affinity than CD28. Mentioned ligand-receptor pairs are membrane-anchored, hence T cell signaling is contact-dependent. This indicates T cell activation is affected by the spatial organization of T cells. Using an in vitro set up with CD8+ T cells only and glycoprotein-33 to mimic the effect of antigen presenting cells shows that T cell activation results in the formation of dense clusters which collapse after two days. Exogenous activation of IL-2 or CD28 signaling, or blockage of CTLA-4 postpones cluster formation, increases cluster size and increases the time to cluster collapse. To understand how the aforementioned signaling pathways regulate T cell activation in this spatial context, we build a cellular Potts model in which we include IL-2, CD28 and CTLA-4 signaling. By closely mimicking the in vitro set up and analyzing the simulation and in vitro results with the same image analysis pipeline, we aim to find the minimal signaling that explains the in vitro data.

Collective dynamics and self-organisation in a population of communicating cells

Yiteng Dang
Department of Bionanoscience, TU Delft

The mystery of how patterns arise in living systems has captivated scientists for centuries. In a classic work, Alan Turing proposed a simple mechanism for pattern formation in models with reacting and diffusing chemicals, which are still widely used today. While this approach provides insight into continuous fields of tightly packed cells, it cannot treat small populations of discrete cells. Here we develop a cell-based hybrid model, consisting of a cellular automaton coupled to reaction-diffusion equations, that describes how a finite number of communicating cells coordinate their gene expression in space and time. I will give an overview of various results we obtained regarding the phenomenology and analysis of this model. First, we found that molecular tuning of effective parameters allow the cells to modulate between responding individually and responding collectively, and constructed statistical quantities to quantify the collectiveness of the response. Secondly, we constructed a macroscopic description for how the average gene expression and spatial order of the population evolve dynamically without resorting to individual simulations. Thirdly, we extended the framework to more complicated types of signalling and observed that under certain conditions, the cells were able to self-organise into dynamic spatial patterns such travelling waves and spiral waves. We then analysed the conditions under which self-organization occurs and found that these can be summarized by a number of conditions and mathematical constraints. By combining simulations with analytical theory, our work draws a bridge between the microscopic rules at the cellular and sub-cellular level with the macroscopic response at the population level.

Evolutionary contingency drives microbial metabolism, community structure, and its predictability

Jeroen Meijer
Theoretische biologie, Universiteit Utrecht

Metabolic dependencies are widespread in natural microbial communities and an important driver of ecosystem structure and diversity. Metabolically autonomous microbes are also common, which raises the question what determines whether microbes evolve metabolic division of labour or maintain self-sufficiency. Here, using a parallel evolution experiment in which we evolve a communities of digital microbes in a constant, one-niche environment, we show that the evolution of cross-feeding is an evolutionary contingency. Initially identical microbial communities follow different evolutionary trajectories, with half of the communities diversifying in cross-feeding lineages and the other half evolving a self-sufficient lifestyle, producing and recycling all essential building blocks. Which type of community evolves depends on prior metabolic adaptations. This suggests that the evolution and assembly of microbial communities might not

reflect global optimization of resource utilization, and cannot be predicted from the biochemical constraints or first principles, but instead is contingent on biological, evolved properties of the cell.

Symmetry Breaking in a Spatial Model of RNA-Like Replicators
Sam von der Dunk
Theoretical Biology & Bioinformatics, UU

Molecules that replicate in trans are vulnerable to evolutionary extinction because they decrease the catalysis of replication to become more available as a template for replication. This problem can be alleviated with higher-level selection that clusters molecules of the same phenotype, favouring those groups that contain more catalysis. Here, we study a simple replicator model with implicit higher-level selection through space. We ask whether the functionality of such system can be enhanced when molecules reproduce through complementary replication, representing RNA-like replicators. For high diffusion, symmetry breaking between complementary strands occurs: one strand becomes a specialised catalyst and the other a specialised template. In ensemble, such replicators can modulate their catalytic activity depending on their environment, thereby mitigating the conflict between levels of selection. In addition, these replicators are more evolvable, facilitating survival in extreme conditions (i.e., for higher diffusion rates). Our model highlights that evolution with implicit higher-level selectioni.e., as a result of local interactions and spatial patterningis very flexible. For different diffusion rates, different solutions to the selective conflict arise. Our results support an RNA World by showing that complementary replicators may have various ways to evolve more complexity.

Small GTPase patterning: How to stabilise cluster coexistence
Bas Jacobs
Biometris, Wageningen University

Small GTPases are highly conserved proteins capable of establishing membrane patterns. These patterns are used for localising proteins and other molecular players to specific membrane domains in a wide range of biological processes. Some of these processes require the formation of a single cluster of active GTPase (polarisation), whereas others need multiple coexisting clusters. Mathematical models have been an important tool in understanding the mechanisms behind patterning of small GTPases in yeast and animal cells. However, these classical models consistently yield only a single cluster, and therefore cannot explain the patterns of coexisting clusters found in certain types of plant cells. We found

two different modifications to these models that can each stabilise coexistence of multiple GTPase clusters: GTPase turnover and negative feedback. We also studied simplified ODE representations of a polarisation model and two of its coexistence variants. Using this approach, we uncovered the mechanisms that underly the different patterning outcomes, providing a better understanding of how cells can tune a single system to generate a wide variety of relevant patterns.

Speciation-like behaviour in self-replicating molecules

Kris Veeken
TRÊS, GELIFES

Self-replicating molecules offer some promising insights into the origin of life, as their ability to reproduce satisfies one of life's fundamental requirements. Furthermore, studying how such molecules form ordered systems and structures from relatively simple beginnings point to possibilities of one day answering the question of how complex modern life came to be. The self-replicator system we will be looking at here (quickly shown in an animation: `https://www.youtube.com/watch?v=w2lqZL153JE`) has another peculiar property. Briefly, the dynamics in this system start from a building block (monomer), which can cyclize and form different multimeric structures. One of those structures, a 6-membered-ring (hexamer), is able to stack and assemble into fibers, which then catalyze the production of new fibers. The interesting part is, that when two different building blocks are mixed, two distinct sets of fibers are formed, one descendant from the other. These sets of fibers can be seen as competing for the different building blocks (resources), comparable to how organisms competing for resources can end up as a new species. Further investigation into this system, then, may improve our fundamental understanding of the process of speciation. Therefore, this project aims to use mathematical models in examining these self-replicators, and to better understand the speciation-like behaviour they exhibit.

How fish larvae swim: lessons from bending moment patterns. Cees J. Voesenek[1], Gen Li[2], Florian T. Muijres[1] and Johan L. van Leeuwen[1] [1]Experimental Zoology Group, Department of Animal

Johan L. van Leeuwen
Experimental Zoology Group, WUR

Most species of fish swim with body undulations, also in their larval stages. These undulations result from fluid-structure interaction between the internal tissues of the fish and the surrounding water. Although the governing physics

are complex, just-hatched larvae can already swim effectively, despite their presumably limited neural capacity for muscle control and lack of swimming experience. To examine how these larvae swim, we calculated spatiotemporal distributions of the net bending moment along the body of free-swimming zebrafish larvae from 312 dpf. These distributions were computed from a large data set of video-tracked 3D motion, applying 3D computational fluid dynamics, and a large-amplitude deformation model of the body. We show that bending moment patterns of each half-beat are similar throughout larval development, and across their typical swimming repertoire. The pattern changes mainly in amplitude and duration, depending on the combination of swimming speed and acceleration: combinations with high amplitudes and/or short durations support swimming at high speeds, or with strong accelerations. Although the patterns are similar, the envelope of possible amplitudes increases considerably in the first days of development, allowing older larvae to swim at higher speeds and accelerations. The similarity of the bending moment patterns suggests that muscle activation patterns are also comparable. This may imply that fish larvae actuate their swimming relatively simply, despite the complex physics.

NVTB jaarvergadering 2019

The agenda of the annual meeting on Thursday 23rd of May 2019, to commence at 17:00, is as follows:

- Opening
- Minutes meeting 2018 (page 21)
- Annual report secretary (page 22)
- Annual report treasurer (page 23)
- Voting for the new secretary of the NVTB
  (candidate: Timo van Eldijk)
- Report treasury committee 2018 *Approved by Jaap Rutten (present) Approved by Leonie van Steijn (present)*
- New treasury committee 2020
- Budget 2019
- Applications for symposia grants for 2019
- Evaluation of the "Kerkzaal"
- Evaluation of the meeting schedule 2019
- Room organisation Schoorl
- Moving to another bank
- Ideas for invited speakers 2020
- Date NVTB meeting 2020
- Survey
- Concluding remarks

Minutes NVTB meeting 2018

April 5th Thursday, 16:15

Chaired by Jaap Kaandorp, Present: Reinder Bosman, Jeroen Creemers, Lotte de Vries, Hilje Doekes, Karim Hajji, Lia Hemerik, Rutger Hermsen, Gerard Jagers op Akkerhuis, Remie Janssen, Jaap Kaandorp, Kevin Kort, Helen Kruize, Sander van Doorn, Emiliano Mendez Salinas, Glenn Mulder, Theo Pannetier, Marina Papadopoulou, Jacob Rutten, Sjors Stouten, Shabaz Sultan, Kirsten ten Tusscher, Bram van Dijk, Fransje van Weerden, Levien van Zon, Inge Wortel

Reports 2017 Upon discussing the treasurer report we found that we are not transparent enough on the 500 euros people can ask for symposia. We think that the emails from the secretary (from `bramvandijk88@gmail.com`) might often end up in peoples spam box, so we decided to do the announcements via `mail@theoreticalbiology.nl` The financial report has been approved by Jaap Rutten, who will also check it next year. Leonie van Steijn will also check the report next year.

New board members: Vote for new chair Kirsten ten Tusscher passed with 0 objections Vote for new treasurer Jeroen Meijer - We need to tell him we scrap people after 5 years.

Budget 2018 Were looking good. With that in mind, we decided to make the symposium money deadline more lenient, and just make it a first-come-first-get deal up to 1500 euros. Requests for this can be sent to `mail@theoreticalbiology.nl`

Meeting schedule 2018 Meeting schedule should be between 2018 and 2017 in terms of number of speakers.
Keynote suggestions 2019:

- Marjon de Vos
- Bob Planquee
- Max Rietkerk
- Vincent Buskens

Date 2019: Either 16-17 may or 23-24 may. Reservations to be made later this year.

Survey:

- Gerard wants more other types of talks. He will look into people
- Sander talks about NLSEB and how to organise all these different fields in evolutionary biology and make a clearer structure. Maybe work together with different societies to organise overarching meetings.
- Lia suggests that for the year of theoretical biology we organise a symposium with all the founders of theoretical biology in the Netherlands AND some of the next generations (e.g. Kirsten, Jaap, etc.) The history and future of theoretical biology.
- Someone suggests to move to triodos instead of ING. (its greener and cheaper)

Annual report secretary 2018

Last year, the meeting of the NVTB took place on April 5 and 6th, 2018. In total, 35 people attended and 14 presentations were given. Two of these presentations were the invited speakers: Bert Theunissen and Sander van Doorn. In total, we got 11 new members in 2018, and lost only 1 member. 5 other members have been expulsed due to inactivity. This means that the NVTB has 205 members as per 01-01-2018.

I have been the secretary of the NVTB for 4 years. I will now resign, but luckily Timo van Eldijk has offered to take my place. Votes will pass on this appointment at the general meeting. It is possible that I will remain as a web manager during the transition to next years meeting. If you or any of your colleagues ever feels the need to organise an event and needs an online platform to do so, you can use our website and our Google Group to spread the word. If you find any other issues with the website, please report them to me via the contact form on the website[1].

Finally, I wish to thank Jaap Kaandorp, Nienke Hartemink, Lotte de Vries, Kirsten ten Tusscher and Jeroen Meijer for helping me in the organisation of Schoorl, and Bob Planque and Boris Schmid for managing the website and Google groups mailing list respectively. It has been a pleasure to work with you in organising these events, which can only be described as “schoolreisjes voor volwassenen”, and I hope to see you around in the years to come!

[1] http://theoreticalbiology.nl/contact.php

Report on the financial year 2018

2018

In 2018 our society achieved a positive result of €842.60. This is due to the following factors: we scrapped Ramiro Magno's symposium from our financial records (€500) as discussed during the annual meeting in 2018, and we budgeted more for funding of symposia than we spent (€1,500 budgeted, €1,000 awarded), and the costs for this year's hosting of the website (€96.27) were transfered to the next financial year (2019). We received and granted several requests for funding symposia in 2018, but most people did not follow up on their (successful) applications.

Schoorl 2018

The costs for the Schoorl meeting (€3,722.50) were partly covered by the participants (€1,749.08), and partly by the NWO subsidy €1,160). We had a net negative result (€813.42) for Schoorl due to low attendance (27 participants).

Other costs and benefits

Costs for the bank account and transfers were €121.62. We received €5.63 interest on the savings account.

2019

Schoorl 2019

Whether Schoorl will give a net positive or net negative result depends mostly on the number of participants. Assuming the same low number of participants as last year (27), we expect a net negative result (€1,581,72). This estimate is a worst case scenario as the Dopersduin fee will also be reduced for low attendance, and we currently expect 39 attendants for the 2019 Schoorl meeting. The net result over the whole financial year will also depend on whether any money is requested for symposia, but a net positive result is expected.

Symposia 2019

We have again budgeted a total of €1500 for symposia.

Balans 1-1-2019

Activa (€)		Passiva (€)	
tegoed contributie 2010	10.00	vermogen 1-1-2018	17.008.98
tegoed contributie 2011	50.00		
tegoed contributie 2012	84.00	positief resultaat 2018	842.6
tegoed contributie 2013	120.00	vermogen 31-12-2018	17.851.04
tegoed contributie 2014	192.00		
tegoed contributie 2015	336.00		
tegoed contributie 2016	480.00		
tegoed contributie 2017	948.00	Vooruit betaalde contributie 2019	12.00
tegoed contributie 2018	1980.00		
voorschot Schoorl voor 2019	1232.95		
spaarrekening	6791.25		
in kas	5639.34		
Totaal	17.863.54	totaal	17.863.04

Balans 1-1-2018

Activa (€)		Passiva (€)	
tegoed contributie 2010	10.00	vermogen 1-1-2017	14.372.98
tegoed contributie 2011	50.00		
tegoed contributie 2012	84.00	positief resultaat 2017	2.635.46
tegoed contributie 2013	136.00	vermogen 31-12-2017	17.008.44
tegoed contributie 2014	240.00		
tegoed contributie 2015	384.00		
tegoed contributie 2016	516.00		
tegoed contributie 2017	1.056.00	Vooruit betaalde contributie 2018	60.00
voorschot Schoorl voor 2018	2.821.40		
spaarrekening	5.633.71	reservering Ramiro Magno	500.00
in kas	6.637.84		
Totaal	17.568.95	totaal	17.568.44

Resultatenrekening 2018

Kosten (€)		Opbrengsten (€)	
Schoorl 2018	3,722.50	bijdrage NWO Schoorl 2018	1,160.00
Kosten website 2018*	0	Bijdragen leden Schoorl 2018**	1,749.08
Posterprijs 2018	100.00		
Bijdrage dag van de Mathematische biologie	1,000.00		
Kosten ING (betaald in 2018)	121.62	Rente over 2018 (in 2018 gestort)	5.63
		Verwachte contributie 2018	2,460.00
onbetaald 2013 agv opzegging 2018	4.00	Giften	0.01
onbetaald 2014 agv opzegging 2018	12.00	Reservering Ramiro Magno geschrapt	500.00
onbetaald 2015 agv opzegging 2018	12.00		
onbetaald 2016 agv opzegging 2018	12.00		
onbetaald 2017 agv opzegging 2018	24.00		
onbetaald 2018 agv opzegging 2018	24.00		
Totaal	5,032.12	Totaal	5,874.72
		Positief resultaat 2018	842.60

* €96.27 voorgeschoten door penningmeester, terugbetaald in 2019
** bijdrage leden Schoorl is na aftrek van kosten voor wijn voor sprekers en kosten naamstickers

Begroting 2019

Kosten (€)		Opbrengsten (€)	
Uitgaven Schoorl 2019	4.931.80	bijdrage NWO Schoorl 2018	1160.00
Posterprijs 2019	100.00	bijdrage leden aan Schoorl 2018	1749.08
symposia	1.500.00	contributie 2018	2.460.00
geroyeerde leden	200.00	rente	5.00
kosten ING (incl. internetbankieren)	125.00		
kosten website	100.00		
Totaal	6.9550.80	Totaal	5.3740.08
		Verwacht resultaat 2019	-1581.72

Begroting 2018

Kosten (€)		Opbrengsten (€)	
Uitgaven Schoorl 2018	4.500.00	bijdrage NWO Schoorl 2017	2.000.00
Posterprijs 2018	100.00	bijdrage leden aan Schoorl 2017	2.500.00
symposia	1.500.00	contributie 2017	2.200.00
geroyeerde leden	200.00	rente	10.00
kosten ING (incl. internetbankieren)	120.00		
kosten website	100.00		
Totaal	6.520.00	Totaal	6.710.00
		Verwacht resultaat 2018	190.00

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