Keynote abstracts

Which memory T cells mount subsequent immune responses?
De Boer, R.J.

During a primary immune response, hundreds of naive T cells undergo clonal expansion. While some proliferate extensively and dominate the response, others cease division early, forming only small progeny families [1,2]. Using a division-tracing experimental system, we found that secondary immune responses primarily originate from these small families, whereas large families contribute minimally [3]. To explain this paradox, we developed mathematical models that provide quantitative and mechanistic insights. Our analysis reveals that rare stochastic "dropout" events —where individual cells exit expansion early— are key drivers of robust secondary responses. These "dropouts" differ from the vast majority of "conventional" memory cells formed during and after an immune response.

1. Gerlach C, Rohr JC, Perié L, van Rooij N, van Heijst JW, Velds A, Urbanus J, Naik SH, Jacobs H, Beltman JB, de Boer RJ, Schumacher TN. Heterogeneous differentiation patterns of individual CD8+ T cells. Science. 2013 340(6132):635-9.
2. Buchholz VR, Flossdorf M, Hensel I, Kretschmer L, Weissbrich B, Gräf P, Verschoor A, Schiemann M, Höfer T, Busch DH. Disparate individual fates compose robust CD8+ T cell immunity. Science 2013 340(6132):630-5.
3. Bresser K, Kok L, Swain AC, King LA, Jacobs L, Weber TS, Perié L, Duffy KR, de Boer RJ, Scheeren FA, Schumacher TN. Replicative history marks transcriptional and functional disparity in the CD8+ T cell memory pool. Nat Immunol. 2022 23(5):791-801.

Evolutionary dynamics of parental sex roles
Long, X; Weissing F.J.

In many animal species, parents invest considerable effort in caring for their offspring. However, the way parental care is divided between males and females varies greatly across species. Despite extensive theoretical work on parental sex roles, their underlying causes remain a topic of ongoing debate. In this talk, I will present new insights into the evolution of parental sex roles, gained through a variety of theoretical modeling approaches. For example, our individual-based evolutionary simulations reveal an intrinsic evolutionary tendency for asymmetry in parental care to emerge between the sexes, even in the absence of sex differences. Additionally, I have found that parental care patterns are ‘evolutionarily labile’: an evolved care pattern that appears to be stable can switch to a completely new one in a brief period of time. This finding helps explain the puzzling fact that new parental care patterns frequently and unexpectedly pop up in phylogenetic trees. Furthermore, I will show the complex interplay between sexual selection and parental care, as well as the intricate relationships between sex ratios and care patterns.

The economy of single-celled organisms
Planqué, R.

Single-celled organisms like bacteria are remarkably good at adapting to their environment. One of the ways they do this is by adjusting how much of certain enzymes they produce. These enzymes help drive the chemical reactions that bacteria rely on to grow and reproduce. When food sources or nutrients change, bacteria can shift their enzyme production to keep these reactions running efficiently, helping them grow as fast as possible.

What makes this even more impressive is the sheer complexity of the internal machinery that supports growth. A cell's biosynthetic network involves hundreds of reactions, all tightly interconnected, and all competing for limited resources. It might seem impossible to figure out how a cell could regulate such a tangled web. But surprisingly, this complexity still contains enough structure to allow for a rational solution: there is a best way to allocate enzymes to different reactions, depending on nutrient conditions. In this talk, I will present a mathematical model that captures this idea. It shows how cells might use simple adaptive rules—like those implemented through gene regulation—to navigate this complexity and find near-optimal strategies for growth. Despite the tangled network, order and efficiency emerge from surprisingly basic principles.

Long talk abstracts

The Mathematics of Molecular Thievery: Therapeutic Interfering Particles for Treating HIV-1 Infection
Dodd G.K.; de Boer R.J.

The current standard treatment for HIV-1 infection is antiretroviral therapy, which effectively suppresses viral replication but requires a lifelong drug regimen. An alternative treatment approach is a single injection of a modified version of the HIV-1 virus, termed a therapeutic interfering particle (TIP), that lacks replication machinery and suppresses the wild-type virus by competing for viral proteins. Using a novel ordinary differential equation model of TIP dynamics, we confirm results from previous models that TIPs can reduce viral load for a wide range of biologically reasonable parameter values. By deriving the basic reproduction number R0 of a TIP, we predict that concurrent antiretroviral therapy should make it more difficult for a TIP to persist in a host. Adding a simple immune response to our model reveals that a moderate immune response against virally infected cells drastically decreases the range of parameter values for which therapy is effective. Together, these results show that the success of TIPs depend strongly on the properties of the wild-type virus and the immune response, which makes it hard to predict therapeutic success.

Start, pause or stop: modeling cellular decisions controlling proliferation in C. elegans
Planterose Jiménez B.; Landzaat N.; Ramalho J.J.; van den Heuvel, S.; ten Tusscher, K.; Tsingos, E.

During multicellular development, an entire organism arises from a zygote through successive cell divisions. As development advances, resulting cells become increasingly specialized, ultimately undergoing irreversible cell cycle exit and acquiring terminal fates. Some cells, however, exit the cell cycle reversibly, entering a dormant state known as quiescence, which allows future re-entry into proliferation upon stimulation. Tight coordination of proliferation (P), quiescence (Q), and terminal differentiation (D) is essential for the proper formation of tissues and organs, and disruptions in this balance can lead to disease.
To investigate the hierarchy of cellular decisions controlling proliferation, we focus on the postembryonic M lineage of C. elegans, an ideal system since it undergoes multiple transitions between cell cycle entry, quiescence, and terminal arrest: initially, a single quiescent progenitor re-starts proliferation in response to insulin signaling, producing 16 differentiated and 2 quiescent cells; the latter resume proliferation at later stages, each generating 8 differentiated cells. We developed a series of ordinary differential equation models of increasing complexity to recapitulate how cellular decisions emerge from the molecular interactions and gene regulatory networks in this lineage, including signal transduction, cell cycle and its regulation. Our final model reproduces transient periods of oscillations in cell cycle components (P), converging to one of two distinct steady-states—either permissive (Q) or non-permissive to future oscillations (D)—depending on the dynamics of differentiation factors during the proliferative window. We currently explore alternative models that align with observations and how to experimentally distinguish between them. Overall, our study sheds light on the principles of proliferation control and gene regulatory motifs in this lineage, offering insights that may be informative across developmental systems.

Multiscale modeling of antimicrobial resistance evolution in microbial communities
Demirbas, B.; Wortel, M.
Predicting evolutionary trajectories of antimicrobial resistance (AMR) is crucial in tackling challenges posed by resistant microbes. AMR incurs both costs and benefits to organisms, which depend on extracellular conditions, such as interspecies interactions in microbial communities. How interactions in communities consisting of many species affect the predictability of AMR evolution has so far been understudied, especially in fungi. To address this question, we developed a multiscale model integrating cell growth, metabolism, and resistance mechanisms in Candida species exposed to the

antifungal drug fluconazole. Our resource allocation model captures the kinetics of key metabolic pathways, and is parameterized using experimental and literature data. We propose that alterations in fungal metabolism are central in the development of different modes of antifungal resistance. Indeed, our results show that the optimal resistance strategy depends on the metabolic mode, i.e. respiration or fermentation. We extend this model to include multiple species and run computational simulations where we track AMR evolution in diverse microbial communities. In this way we generate testable hypotheses on how community interactions such as nutrient competition and cross-feeding influence the evolution of fluconazole resistance. Our findings have potential applications in designing robust antifungal strategies and improving our understanding of AMR emergence in natural and clinical settings.

Factors determining invasion in a gut microbiome community
Wortel, M. T., van Leeuwen, P., Gadaleta, P., Brul, S., Seppen, J.

The gut microbiome plays a crucial role in host homeostasis, with implications for nutrition, immune development, metabolism, and protection against pathogens. Protection against pathogens can be the result of a microbiome that is resistant against invasions. But what properties make a microbial community resistant to invasions and does that depend on the properties of the invaders? The large communities and wealth of interactions between species in the gut microbiome make this a challenging question. We studied 10 prevalent species from the human gut microbiome and characterized their properties and interactions in vitro. With a mathematical model based on the generalized Lotka-Volterra framework we predict the abundances in multispecies communities. Next, we study the effect of adding a species to a stable community in silico and discriminate between invasion, disruption, integration and no effect. We show which properties of the invading species and the native community affect these invasion types. Moreover, we show that we can replicate some of these predictions in vitro. These insights can aid both for creating a stable gut microbiome community as well as disrupting an unhealthy community, for example when dominated by a pathogen.

Bocci F.; Zhou P.; Barcenas M.; Li T.; Nie Q.
Navigating the attractor landscape of single cells

Modern single cell sequencing technologies enable us to probe cellular processes at unprecedented resolution, while introducing new theoretical challenges. A major difficulty lies in constructing dynamical models of cell behavior, as these technologies capture only a single snapshot of a cell's state, thereby preventing the observation of temporal dynamics. In this talk, I will discuss how we utilized single cell transcriptomics – a technique that measures RNA expression in individual cells – to develop a mathematical framework of gene expression and construct the attractor landscape regulating cell fate decisions. By applying this model under both equilibrium and non-equilibrium conditions, we analyzed the stability, transition paths, and cell type-specific regulatory networks that govern cell fate. Building on this framework, we introduce a transition tensor that harmonizes small stochastic fluctuations in gene expression locally (within individual attractors) with global changes in cell fate (transitions between attractors) to dissect cellular dynamics across multiple scales. Finally, I will discuss how we incorporated spatial information into our mathematical framework to project cell fate transitions in space.

Approximation of a compound-exchanging cell by a dirac point
Yang X.; Hille, S.; Peng, Q.

Communication between single cells or higher organisms by means of diffusive compounds is an important phenomenon in biological systems. A straightforward model is by a diffusion equation with suitable flux boundary conditions at the cell boundaries. Such a model will become computationally

inefficient and analytically complex when there are many cells, even more so when they are moving. We propose to consider also a point source model. Each cell is virtually reduced to a point and appears in the diffusion equation for the compound on the full spatial domain as a singular reaction term in the form of a Dirac delta measure located at the cell's centre. The amplitude of the Dirac delta measure is a nonlocal term of the compound's concentration near the virtual cell boundary so as to preserve the essential biological features. To investigate the positivity of the solution and the structure of steady states, we employ the Laplace transform. In addition, the theory of elliptic curve is also involved.

Short talk abstracts

Tell your friends: Secondary signalling by immune cells during chemotaxis
Versluis D. M.; Insall R.

Many immune cells generate their own gradients to find their way towards infections or other immune cells. These self-generated gradients allow for efficient movement across long distances, but can only be followed by a limited number of cells before the gradient is destroyed. Our models suggest immune cells compensate for this by producing secondary signals while creating a gradient. Such a secondary signal allows more cells to follow the original signal. The dynamics of secondary signals are largely unexplored, so we have set out to create an overview of how immune cells may use secondary signals to enhance chemotaxis.

We use an agent-based modelling approach to simulate the interactions between immune cells in a dynamic environment of multiple diffusing attractants. Each agent represents a single cell, which all start at one side of a simulated ‘bridge’ filled with a primary attractant. Each cell destroys the primary attractant and produces the secondary attractant. The cell then uses saturable receptors to sense higher concentrations of attractants to move towards. Cells that cross the bridge are considered to have successfully migrated.

We focus on cases where the secondary attractant does not diffuse faster than the primary attractant, but does differ in other ways, such as by being consumed slowly. This leads to trade-offs where increased production of a secondary attractant increases the number of cells that migrate, but decreases their speed. The trade-off may be mitigated in several ways, such as by producing a saturating amount of secondary attractant when the primary attractant is present. Finally, we will examine a case study of neutrophil swarming. In neutrophils the secondary attractant is also further relayed, leading to complex swarming dynamics. We show how conversion of a secondary attractant to an inhibitor can explain the limited swarming observed in vitro, and how our approach may be used to model other similar systems.

The use of evolutionary topology optimization algorithms to elucidate links between form and function in vertebrate morphology.
van der Ree, M.J.; Löffler, M.; Schulp, A.S.; Bijlert, P.A.

Previous work has used deductive Finite Element Analysis (FEA) methods to test hypotheses about functional morphology by generating virtual morphology from stress and strain distributions using shape optimization algorithms. This approach is based on the assumption that ‘form follows function’; morphology is thought to be fully explained by the mechanical demands placed upon it. Virtual morphology generated through shape optimization is compared to the true morphology in order to verify- or falsify model hypotheses about the magnitude-, orientation-, and placement of external loads such as bite forces. We argue that existing deductive FEA techniques, particularly the Finite Element Structure Synthesis (FESS) method developed by Preuschoft and Witzel, have important limitations which reduce their usefulness as research tools in paleontology. Limitations include an inability to take phylogenetic biases into account, failure to converge to truly optimal solutions, and an exclusive focus on mechanical stress which ignores other potential drivers of morphological evolution. To address these issues, we propose an evolutionary methodology for deductive finite element analysis. We present a custom-built evolutionary algorithm which can be used in deductive analysis of skull shape and compare its performance with that of FESS using a case study on the cranium of Tyrannosaurus rex. The algorithm presented represents only a first step in the development of a novel research tool, and several avenues of future development remain open. Despite this, performance already outstrips

existing approaches in several key areas, such as optimality of generated shapes, and similarity to true morphology.

Modelling the development of microvilli and brush border patterns
van Osch, H.; Woeltjes, J.M.; Boxem, M.; Tsingos, E.

Microvilli are apical cell protrusions through which cells can increase their surface area, an example of this are the microvilli in the intestine. One cell can have many microvilli on its surface; this array of multiple microvilli is named the brush border. Despite the importance of this structure for our gut health, very little is known about how it forms. The goal of our research is to finetune a computational model, to better understand how microvilli form and how they assemble into brush border patterns.

We developed a cellular automata model, which simulates the actions of individual microvilli in a 2D hexagonal grid. By quantifying the results from these simulations and comparing them to in vivo experimental data, we aim to determine the relevance of certain processes such as microvillus-microvillus cross-stabilisation, inhibition of microvilli growth due to membrane curvature, microvilli movement and more.

Ultimately, with this model, we aim to identify the mechanistic processes that are essential for microvillus formation and brush border assembly. This could be used to further elucidate the functions of the molecular players that are involved in microvillus development.

The link between model characteristics and outcomes in spatial savanna models
Sterl, X.; van der Kaaden, A.; Weinans, E.; Doelman, A.; Rietkerk, R.

Spatially explicit ecosystems are a useful tool to study spatial effects in changing savanna ecosystems. However, it is unclear which ecosystem characteristics and included mechanisms in these models lead to certain spatiotemporal dynamics, or whether these dynamics are typical of certain model types. In this study, we gathered available savanna models and linked ecosystem characteristics and mechanisms, and model characteristics to observed spatiotemporal dynamics. We grouped the available models based on their model type and included ecosystem characteristics. We also determined the spatiotemporal dynamics generated by these models. Using statistical analyses, we aim to understand whether certain model types or ecosystem characteristics are related to certain spatiotemporal dynamics.

Computational modeling of nutrient absorption by complex-shaped marine organisms in a diffusive environment
Knijff N., Busch K., Kaandorp J.

In this Master's thesis, a computational model was developed to simulate nutrient absorption by complex-shaped marine organisms like corals and sponges. The model simulates diffusion and surface absorption of nutrients in a voxelized 3D environment (cubic cells) and highlights the influence of geometry on nutrient absorption. The simulation proceeds in four stages:

1. Initialization – a 3D grid is set with nutrient sources on five boundary planes, and a reflective ground plane representing the ocean substrate.
2. Voxelization – A triangulated mesh of organisms is converted to a voxel representation to allow the object to interact with the voxelized diffusive environment.
3. Diffusion – Time-independent diffusion is computed using a Successive Over-Relaxation scheme to solve the Laplace equation, to find a steady-state solution.

4. Absorption – nutrient absorption is simulated by extracting nutrient concentrations locally near the object's surface and reducing them according to an absorption rate α.

This analysis was performed on 12 sponges, scanned with a visible light technique and 3 CT-scanned archaeocyaths, each represented as triangulated surface meshes. Absorption profiles—histograms with nutrient absorption frequencies—reveal that geometry significantly influences absorption. Symmetric shapes tend to produce Gaussian-like profiles, while complex detailed forms such as archaeocyaths exhibit power-law decays, and an overall higher difficulty absorbing. nutrients Vertices near the bottom plane absorb less due to low local concentrations, especially in massive shapes. These findings suggest that geometrical complexity impacts absorption efficiency, with flatter or concave regions exhibiting lower access, which applies to complex branching forms as well. Future extensions may incorporate advection–diffusion and light propagation to simulate more realistic marine conditions.

A coupled computational model of gastrulation in the sea anemone Nematostella vectensis
Tan, N.; Kaandorp, J.

Gastrulation in the sea anemone Nematostella vectensis is an essential process forming a bi-layered blastula driven mainly by invagination and zippering of the pre-endodermal germ layer. Computational models have been developed that accurately capture the gastrulating movement of the embryo and have been able to contribute to hypotheses on occurring morphological phenomenon and on the framework that drives gastrulation. Studies on the underlying genetic regulatory mechanisms have showed some conserved gene clusters play a role in successful gastrulation and hypotheses on genetic regulatory networks have been made.
We now aim to create a multi-scale model that couples a pre-existing cell model with a genetic model, which simulates the reaction-diffusion and interactions of gene products, thereby offering more insight into how the interaction of morphological changes and genetic signaling could influence the embryo's development.

Polymer Self-Consistent Theory for Understanding DNA Spatial Organization
Yan. Y.; Zwanikken J.

The understanding of chromosomal spatial organization is important for predicting gene regulation. In this research, we utilized the self-consistent field theory of polymers to model the statistical field of the spatial distribution of DNA. Leveraging experimental Hi-C contact maps available from literature, we aim to quantitatively predict the polymer chain's pair-correlation functions. The goal is to quantitatively predict this pair-correlation, directly comparable to Hi-C contact maps, enabling deeper insights into the thermodynamics underlying the chromosomal spatial organization.

Modeling multivalent binding to understand super-selectivity
Mijatović, T.; Zwanikken, J.W.

By binding to multiple receptors simultaneously, viruses can very precisely select the cells they infect. Such high selectivity would also be useful in targeted drug delivery, to minimize side effects. To achieve this, we need a thorough understanding of how multivalent binding leads to high selectivity. In this talk I will introduce our modeling approach based on differential equations and our initial results that will help to improve this understanding.
Mechanotransduction in Lateral Root Initiation via the interplay of growth and auxin flows - Vertex modelling of plant biomechanics and morphogenesis

Ecological effects on diversity and repeatability during antibiotic resistance evolution

Gadaleta, P.; Wortel, M.T.

The trajectory and outcome of evolution can be represented by a fitness landscape, which defines the relationship between genotype and fitness. While most studies focus on static or externally driven fluctuating landscapes, little attention has been given to dynamic landscapes shaped by interactions within the population. Understanding these dynamics is crucial, as ecological interactions can fundamentally alter evolutionary trajectories, affecting diversity, repeatability, and adaptability in ways traditional models fail to capture. To address this gap, we introduce a fitness model incorporating ecological interactions through environmental feedback. We simulate E. coli evolution under Cefotaxime, a β-lactam antibiotic, through a serial transfer experiment. Experimental data show that resistance mutations improve survival but reduce growth without the antibiotic. Additionally, resistant bacteria degrade the antibiotic faster, benefiting sensitive but faster-growing strains. We developed an algorithm that simulates this experimental setting, incorporating genetic drift, selection, and environmental changes driven externally or by the genotypes within the population. We analyze how these factors shape evolutionary outcomes, repeatability, and population diversity. Finally, we compare our results with a deterministic model to evaluate the predictive power of our approach in fluctuating environments.

Trade-off in Life History Traits in Soil-Borne Fungal Phytopathogens
van der Most J.; Doekes H.M.; van Schijndel L.L.M.

The high diversity of pathogen virulence (i.e. damage inflicted on a host) remains a fundamental question in evolutionary biology, with direct implications for public health, wildlife conservation, and agriculture. Trade-off theory gives an explanation of why pathogens rarely evolve toward avirulence. Specifically, higher transmission rates often require increased host exploitation, leading to greater virulence. In addition, spatially explicit models show that, when infections are localised, selection favours reduced virulence to prevent local host population collapse
However, most spatial models used to study virulence evolution employ an individual-based approach that models only host states. While this may suffice for pathogens dispersing in small units (e.g., viral particles, bacterial cells, spores), it fails to capture the complex host–pathogen interactions of soil-borne fungal plant pathogens. Soil-borne fungi present an interesting and understudied case due to their mycelia network growing through the soil, connecting multiple host plants and enabling secondary infections without spore dispersal. The connectivity of the mycelial colony may alter evolutionary pressures on both transmission and virulence.
To investigate these dynamics, this thesis develops a two-level individual-based model that couples fungus colony growth, modelled with cellular automata, with host infection dynamics on a secondary grid. By scaling from colony expansion to epidemiological spread, these models examine how mycelial networks influence the virulence–transmission trade-off. Preliminary results suggest that a non-linear relationship between nutrient depletion (virulence) by the pathogen and host-experienced nutrient loss is necessary for a trade-off to emerge. In addition, the models indicate the importance of biomass recycling and the breakdown of redundant mycelial regions for maintaining network viability in large colonies.

Mechanotransduction in Lateral Root Initiation via the interplay of growth and auxin flows - Vertex modelling of plant biomechanics and morphogenesis
D. Ramos, J.R.; Reyes-Hernández, B.J; Alim, K.; Maizel A.

Plant development relies on the precise coordination of cell growth, which is influenced by the mechanical constraints imposed by rigid cell walls. The hormone auxin plays a crucial role in regulating this growth by altering the mechanical properties of cell walls. During the post-embryonic formation of lateral roots, pericycle cells deep within the main root are triggered by auxin to resume

growth and divide to form a new root. This growth involves a complex interplay between auxin, growth, and the resolution of mechanical conflicts, that is still not well understood.
We propose a model that integrates tissue mechanics and auxin transport, revealing a connection between the growth-induced relaxation of mechanical stress in the pericycle and auxin signalling in the endodermis.
We show that the growth of pericycle cells is initially limited by the endodermis. However, the resulting modest growth is sufficient to redirect auxin to the overlying endodermis, which then actively accommodates the growth, allowing for the subsequent development of the lateral root. Our model uncovers the mechanical parameters that underlie endodermal accommodation and how the structure and shape of the endodermis influence the formation of the new root.
These findings emphasize the vital role of the endodermis in shaping root development through mechanotransduction and auxin signalling.
Quantitative analysis of plant biomechanics is paramount to empirically test theoretical models and we discuss how some of the methods developed throughout this work could help infer patterns of strain and stress in plant tissue in 2D and in 3D.

Understanding how Arabidopsis responds to heat and drought
van Loo, T.H.P.; Garcia-Gomez, M.L. Monica; ten Tusscher, K.H.W.J.

Plants respond to temperature and water availability changes by modifying their growth and development. These modifications result from coordinated responses in different organs through complex gene regulatory networks, hormonal regulators enabling long-range shoot to root communication, and physiological responses. Some of these processes such as phosphorylation or the circadian clock are know to contribute to temperature and drought responses, but the mechanisms are far from being understood completely. Here we aim to understand this regulation using a mechanistic modelling approach to integrate prior evidence and experimental data into ordinary differential equation modelling. Using these models, we aim to explain how single and combined temperature and water conditions affect plant growth, development, and ultimately resilience.