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Mathematical Foundations of Biological Organisation

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Abstract. The workshop aimed to explore the use of new mathematical and computational approaches to investigate the fundamental principles governing the organization and dynamics of biological systems. This necessitated conversations among mathematical biologists working at different scales, from molecular to organismal levels. The meeting aimed to encourage interdisciplinary collaborations and showcase recent advances in diverse areas.

Mathematics Subject Classification (2020): 92-XX.

Introduction by the Organizers

The workshop on *Mathematical Foundations of Biological Organization* aimed to explore the use of new mathematical and computational approaches to investigate the fundamental principles governing the organization and dynamics of biological systems. Although mathematical biology as a distinct field dates back to Alan Turing and Waddington in the 1950s, and its importance has increased over the years, our understanding of biological intricacies remains limited. This necessitates conversations among mathematical biologists working at different scales, from molecular to organismal levels. The workshop aimed to encourage interdisciplinary collaborations and showcase recent advances in diverse areas such as single protein structure, subcellular structures, single-cell behaviors, and complex community-level interactions among organisms. The wide range of topics facilitated extensive and in-depth discussions both during and after the talks.

The workshop commenced with Jean-Pierre Eckmann emphasizing the significance of employing mathematics in biology not only for describing observed phenomena but also for making predictions. Subsequently, 18 different talks revisited

this theme, aiming to align their creative mathematical thinking with pressing biological problems. Some of the presented talks called for a reevaluation of conventional frameworks, including the linear representation of DNA, intra-cellular vesicular trafficking dynamics, and the computational capabilities of single cells.

In addition, researchers with specific areas of interest were provided the opportunity to conduct satellite sessions to facilitate more in-depth discussions. One of these sessions focused on neuroscience and served as a platform to debate the value of investing significant resources in exploring the specific connectome and topology of neuronal networks in organisms. This discussion challenged a fundamental and historically accepted approach to understanding brain functions, prompting many researchers to contemplate a reevaluation. Such discussions were in line with the workshop's objective and proved to be stimulating for both senior scientists and young researchers and students alike.

The week-long meeting, held in the heart of the Schwarzwald, provided a refreshing atmosphere for all participants. In terms of organization, one notable feature was the deliberate randomization of seating arrangements during lunch and dinner. It was during these informal and often off-topic conversations that many enjoyable and memorable discussions took place, which undoubtedly served as crucial and decisive moments for future scientific collaborations.

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Workshop: Mathematical Foundations of Biological Organisation

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Abstracts

Emergence of intracellular compartments in eukaryotic cells

Mukund Thattai

Of the three domains of life (bacteria, archea, and eukaryotes), only eukaryotes have a fully developed system of intracellular membrane-bounded compartments (such as the ER, Golgi apparatus, etc.). Each compartment type has a distinct chemical identity, and exchanges cargo with other compartments through small membrane-bound carriers known as transport vesicles. The system may be represented as a graph (nodes are compartments, directed edges are vesicle fluxes) with additional structure capturing chemical identity and exchange rates. The steady states of such a system emerge dynamically: exchange fluxes must balance, and this condition defines compartment and vesicle identities. However, the identity transfers determine which exchange fluxes are possible, by regulating the process of vesicle budding and fusion. The steady state of the system must therefore be determined self-consistently. We have explored the entire space of vesicle transport graphs which admit a self-consistent description in terms of molecular interaction. Such graphs are rare (e.g. 1000 out of 25,000,000 directed graphs up to 3 nodes and 12 edges are consistent). We can state some consistency conditions in simple terms (see figure). By making mutations at the molecular level, we can also explore evolutionary trajectories by which one kind of graph can evolve into another.

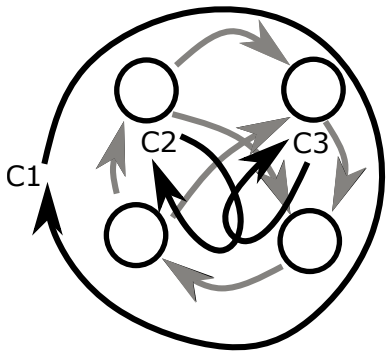

Figure 1. A transport graph with 4 compartments and 6 edges. Each edge belongs to a distinct subset of directed cycles. By placing distinct chemicals on distinct cycles, each vesicle edge can be given a distinct chemical identity. For this to hold, it is necessary and sufficient that the graph has no 2-cuts.

Collective problem solving in ants and humans

Ofer Feinerman

To try and understand how smarter a group of ants is compared to individuals, we presented them with geometrical puzzles that can be produced at different scales. The puzzles include a piece of 'food' that the ants transfer to the nest through an environment that includes obstacles. Constructing such a puzzle on a small scale can be presented to an individual ant. On a larger scale, the same puzzle is presented to a group of ants that cooperatively transport it. We now explore how the performance of puzzle solving scales with group size. We try to trace the improvement with ant number to group effects and to individual ant contributions to the group. Even larger versions of the puzzle were presented to groups of up to 26 cooperatively transporting humans.

Nonequilibrium dynamics in living and artificial systems

Yuhai Tu

Complex systems from biochemical networks to artificial neural networks operate far out of equilibrium where detailed balance and fluctuation-dissipation theorem are broken, and thus can only be described by their underlying non-equilibrium stochastic dynamics.

In this talk, we describe some of our recent work in applying concepts and methods in non-equilibrium physics to understand biochemical networks in living systems and artificial neural networks in machine learning. The talk consists of two parts.

Part I: The cost-performance tradeoff in biochemical systems. By using synchronization of molecular clock as an example, we address two related questions: What is the molecular mechanism to control noise to achieve the desired biological function (synchronization)? What is the energy cost for implementing these molecular mechanisms? We then applied the theoretical framework to study the molecular mechanisms for synchronization of the KaiC hexamers in Cyanobacteria, which is critical for maintaining its circadian rhythm [1].

Part II: The inverse Einstein relation in deep learning. In deep neural networks (DNN), weight parameters are updated by following stochastic gradient descent (SGD). By using PCA analysis, we find that the fluctuations of weights depend inversely on the flatness of the loss landscape, which is opposite to the fluctuation-dissipation relation (or Einstein relation for Brownian motion) in equilibrium systems. This inverse Einstein relation is caused by a landscape dependent noise in SGD, which drives the system towards flatter minima that are known to have better generalization [2].

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Towards a theory of catalysis

Olivier Rivoire

Is living matter fundamentally different from non-living matter? We study this question in the context of enzymes, the essential catalysts of biological processes whose efficiency remains unmatched despite considerable efforts to make comparable artificial catalysts. I have presented our approach to this problem, which consists in developing simple theoretical models designed to recapitulate the fundamental trade-offs to which catalysis is subject. Analysis of these trade-offs led us to hypothesize a physical principle that could explain the superiority of enzymes.

Nuclear positioning and size scaling – using modelling for hypothesis testing

Angelika Manhart

(joint work with Mary Baylies, Vivienne Leech, Alan Lindsay, Alex Mogilner and Stefanie Windner)

How a cell organizes its organelles is fundamental to its function. I will focus on the nucleus, a cell's central organ, and its properties, such as number, size, and position. Starting with single-nucleated cells, I will discuss how to use differential-equation models to test in vivo data against six different hypotheses for nuclear growth dynamics. Next, I will discuss nuclear positioning and size scaling in multi-nucleated muscle cells. Mispositioned nuclei are associated with muscle disease. Using coarse, deterministic, as well as detailed, stochastic models, we use data from drosophila larval muscles to identify the most plausible model. This model assumes repulsive forces created by microtubules between nuclei and the cell sides and correctly reproduces and predicts bifurcating nuclear positioning patterns and nuclear shapes.

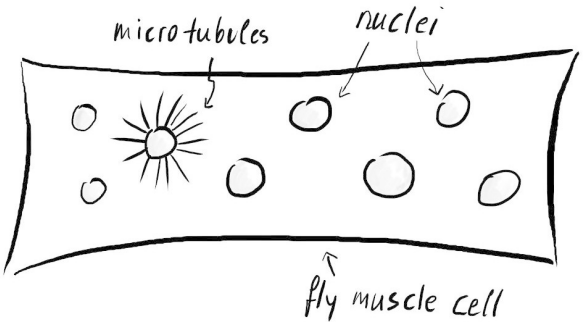

Figure 1

Finally, we show that nuclear size scaling is driven by nuclear positioning, evidenced in the data and predicted by a partial-differential-equations size sensing model. This creates a plausible link between mispositioned nuclei and muscle disease.

Dimensional reduction in evolution and adaptation

Kunihiko Kaneko

A macroscopic theory for adaptive changes of cells is presented, based on consistency between cellular growth and molecular replication, as well as robustness of fitted phenotypes against perturbations. Adaptive changes in high dimensional phenotypes are shown to be restricted within a low-dimensional slow manifold, from which a macroscopic law for cellular states is derived, as is also confirmed by adaptation experiments of bacteria under stress. The theory is then extended to evolution, leading to proportionality between phenotypic responses against genetic evolution and phenotypic variances by perturbations, which also explains the evolutionary fluctuation-response relationship previously proposed. Generality of the results is demonstrated for catalytic-reaction network, gene regulation networks, protein dynamics, as well as evolving spin-glass models, whereas possible statistical-physics theory will be discussed.

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Geometry and genetics

Eric D. Siggia

The application of quantitative methods to biological problems faces the choice of how much detail to include and the generality of the conclusions. Both routine data analysis and airy pronouncements that have almost nothing to say about almost everything are to be avoided. The middle ground entails some use phenomenology, a well-regarded approach in physics. A sampling of examples will be presented from my work in the area of developmental biology, to give a flavor of what is possible. The phenomenon of canalization is a license to develop models that are quantitative and dynamic yet do not begin from an enumeration of the relevant genes. Modern mathematics (i.e., post 1960) has many similarities to experimental embryology and allows the enumeration of categories of dynamical behaviors. Applications to stem cell differentiation will be given as illustrations. Theory can also use computational evolution, in analogy to a screen, to suggest dynamical systems that generate the desired pattern from plausible boundary conditions. Phenomenology of the sort envisioned is essential to bridge the scales from the cell to tissue to embryo, by breaking the system into blocks that can be separately parameterized.

Physics of active surfaces

Frank Julicher

Living matter is an active form of soft matter with extraordinary complexity. Here, active means that energy input at the molecular scale drives force generating and nonequilibrium processes that give rise to patterns, flows, and the generation of structures at larger scales. A key example is morphogenesis of an organism from a fertilized cell. A first step in this process is the establishment of cell polarity and subsequent symmetry-breaking events. Cell polarity is established via a mechanical-chemical switch that involves an active material in which active stress is regulated by molecules that move in the flow. Such activity typically occurs at surfaces where active stresses can generate flows most effectively and where activity also can induce shape changes. the dynamics of such active surfaces can be captured by combining the theory of active matter with the hydrodynamics of deforming fluid surfaces. This approach provides a framework for the active shaping of cells and for the morphogenesis of epithelial tissues.

Chromosomes, contact networks, and 3D gene regulation

Annick Lesne

The relevance of the 3D shape of the genome in the regulatory interactions that control gene expression is increasingly acknowledged. The physical proximity of genome sites (to each other, in 3D space) can be measured in living cells and then represented as a contact map. Such contact maps have also been used to

represent and analyze the structure of proteins. They are closely related to recurrence networks obtained from recurrence plots of dynamical systems, and the same reconstruction methods can be used. The main steps of the reconstruction are (i) to derive a complete distance matrix using shortest-path distance on the weighted contact network, (ii) to use a result of distance geometry based on the three dominant eigenvectors of the metric matrix (yielding the Gram matrix of the structure) (iii) or approximating the 3D structure using multidimensional scaling techniques.

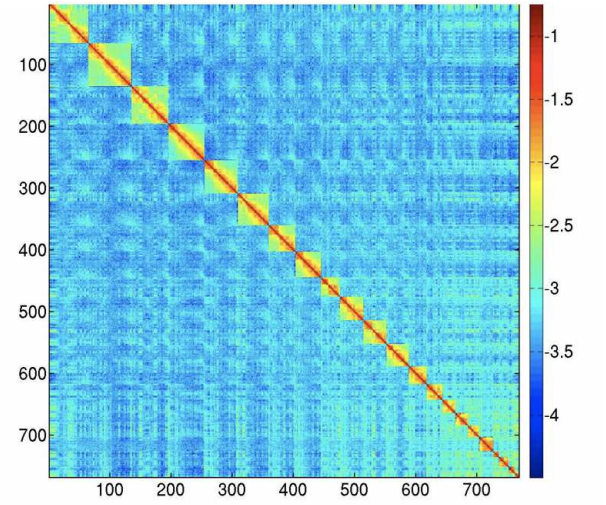

FIGURE 1. **What does a chromosome contact map look like?** Example of a Hi-C contact map obtained from genome-wide chromosome conformation capture in a population of human cells (embryonic stem cells) displaying contact frequencies between any two regions (of size 10kb) along the genome (public data from Dixon et al., Nature 485:376, 2012). Note the yellow squares along the diagonal, each corresponding to a chromosome.

Analogies between the algebraic analysis (principal eigenvector of the correlation matrix) and motif analysis (topological domains seen as squares along the diagonal) of the corresponding contact matrices can also be drawn.

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Dynamical landscapes of cell fate decisions

David Rand

As cells proliferate and assemble into tissues, their molecular identity changes in discrete step-like transitions to produce diverging sequences of distinct cell states that culminate in the differentiation of specific functional cell types. Hence, cellular development can be viewed as sets of branching cell lineages generating increasing diversity and comprising increasingly specialized cell types. This is directed by intercellular signaling between differentiating cells making the process non-autonomous and self-organizing. Each branch-point in a cell lineage represents a choice between alternative distinct cell types. The choice a cell makes at each transition is referred to as a cell fate decision.

I want to discuss this process from the point of view of relatively simple parameterized dynamical systems. When combined with single cell data this allows a new approach to uncovering the mechanisms behind the above cell fate decisions. I will describe an application to early development of the vertebrate neural tube. This approach can also be applied to some problems in spatial patterning in the early embryo and I hope to also include a discussion of this. It also leads to some seemingly new mathematical results where conditions on the boundary of parameter space imply the existence of non-trivial bifurcation sets and dynamics in the interior.

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Control of cisternal size, shape, and number in the trafficking pathway

Madan Rao

A defining feature of eukaryotic cells is compartmentalisation in the form of Membrane bound organelles. Such organelles, especially those participating in trafficking pathways, form as a consequence of nonequilbrium self assembly driven by active fission and fusion processes. Examples include organelle systems, such as the Golgi, Endosomes and Mitochondria. In my talk I focussed on the Golgi system - a collection of cisterna betwixt the endoplasmic reticulum and the plasma membrane which is subject to an incessant flux of cargo vesicles which fuse and fission off it. Individual fission and fusion processes are associated with energy consuming mechano-chemical cycles which we treat as nonequilibrium Markov cycles. Upon completion of each cycle, membrane area, lumenal volume and momentum

is transferred to (fusion) / from (fission) the cisterna. We use this to first study the control of cisternal size, both of a single and multiple cisternae. Amongst the various phases that we obtain, are the stable cisternae (in the presence of a finite flux of material) and limit cycles that we identify with the onset of cisternal progression. The crucial implication here is that vesicle transport and cisternal progression are but two different phases of the same underlying physics. We next explore the shapes and shape instabilities of a Golgi cisterna subject to active fission and fusion using an active hydrodynamics formalism for a closed membrane embedded in a viscous solvent. We write down covariant hydrodynamic equations describing the mass and force and torque balance, with appropriate boundary conditions. We solve these resulting equations perturbatively about a uniform sphere keeping the net mass fixed and show that the cisterna is spontaneously unstable to drift ($l = 1$), flattening ($l = 2$) and tubulation ($l > 2$). An important implication is that the driving force for cisternal progression is the imbalance in the active stresses arising from fission and fusion, and that here again the vesicle transport and cisternal progression are two different phases of the same underlying physics. The next part of the talk addressed the question of the driving force for the control of cisternal number – for instance there are 3-4 cisternae in mammalian cells, 20 in plants, 100 in green algae. Here we argue that Golgi function, namely Glycosylation, is the driving force for cisternal number control. We pose this problem as an optimisation problem, and determine optimised parameters for the sequential glycosylation machinery, namely chemical reaction and cisternal transport rates, cisternal number, and enzyme number and specificity, that drive the synthesis of complex Glycan profiles. Towards the end I briefly touched upon our attempts to build a non-equilibrium dynamics that couple non-equilibrium self-assembly and enzymatic kinetics that describes the control of number, morphology, size and chemical identity of the Golgi system.

Mathematical models of communities of synthetic microbes

Kresmir Josic

Synthetic microbial consortia consist of two or more engineered strains that grow together and share the same resources. Such consortia can exhibit complex spatiotemporal patterns that we are only beginning to understand and control. I will discuss different models of such systems, including a Moran-type model, and PDEs, and some open questions about their formulation and behavior.

On Turing & mechanical instabilities in vertebrate skin patterning

Michel Milinkovitch

Skin colour patterning in vertebrates emerges at the macroscale from microscopic cell-cell interactions among chromatophores. Taking advantage of the convergent scale-by-scale skin-colour patterning dynamics in five divergent species of lizards, we have quantified the respective efficiencies of stochastic (Lenz-Ising and cellular

automata, sCA) and deterministic reaction-diffusion (RD) models to predict individual patterns and their statistical attributes. We have shown that all models capture the underlying microscopic system well enough to predict, with similar efficiencies, neighborhood statistics of adult patterns. Second, we have shown that RD robustly generates, in all species, a substantial gain in scale-by-scale predictability of individual adult patterns without the need to parametrize the system down to its many cellular and molecular variables. Third, using 3D numerical simulations and Lyapunov spectrum analyses, we quantitatively demonstrated that, given the non-linearity of the dynamical system, uncertainties in colour measurements at the juvenile stage and in skin geometry variation explain most, if not all, of the residual unpredictability of adult individual scale-by-scale patterns. I suggest that the efficiency of RD is due to its intrinsic ability to exploit mesoscopic information such as continuous scale colours and the relations among growth, scales geometries, and the pattern length scale. Our results indicate that convergent evolution of CA patterning dynamics, leading to dissimilar macroscopic patterns in different species, is facilitated by their spontaneous emergence under a large range of RD parameters, as long as a Turing instability occurs in a skin domain with periodic thickness. I then also discuss the fact that morphogenesis can involve mechanical instabilities such as in the development of face and jaws scales in crocodiles. A full quantitative understanding of development will require to integrate signaling and mechanics into a single mathematical model.

Protein as a mathematical problem

Tsvi Tlusty

Recent advances in computation brought a breakthrough in the protein folding problem - predicting the 3D structure from the gene sequence. But other fundamental questions about proteins remain open, in particular, how genes are mapped to biochemical functions and how this mapping is linked to dynamics and conformational changes in the protein. We will discuss physical approaches to this problem, combining predictive theoretical models, AI tools, and experimental observations. Our focus will be on a mechanical view that links mutations to collective physical interactions among the amino acids. These theoretical ideas will be demonstrated in an experimental study of the enzyme guanylate kinase. Altogether, this study paints a physical picture of proteins as viscoelastic machines with sequence-encoded specifications, and we will discuss its general implications for understanding proteins and designing new ones. The present geometric approach is proposed as a framework for analyzing protein and for other living systems in which physics and evolution are entangled.

Criticality, "ghost" memory state, and semi-stability in biological networks

Aneta Koseska

A fundamental characteristic of living systems is sensing and subsequent robust response to a continuously changing environment. We have described how "ghosts" can be utilized as a memory generating mechanism to integrate information from time-varying signals, and identified experimentally such "ghost" states are an emergent feature of cell surface receptor networks organized at criticality. I will discuss a development of theoretical framework for computation with "ghost" states as well as open questions on the emergence and identification of such states in large scale networks, and the definition of semi-stability in this context.

A mathematical model for the regeneration of planarians

Angela Stevens
(joint work with Arnd Scheel and Christoph Tenbrock)

Our mathematical model for the regeneration of planarian flatworms consists of a system of partial differential equations, which incorporates the dynamics of head and tail cells. These express positional control genes that in turn translate into localized signals that guide stem cell differentiation. Orientation and positional information is encoded in the dynamics of a long range wnt-related signaling gradient. The model relates to experimental data, and it correctly reproduces typical cut and graft experiments. In particular, the system improves on previous models by preserving polarity in regeneration, over orders of magnitude in body size during cutting experiments and growth phases. The model relies on tristability in cell density dynamics, between head, trunk, and tail. In addition, key to polarity preservation in regeneration, the system includes sensitivity of cell differentiation to gradients of wnt-related signals relative to the tissue surface. This process is particularly relevant in a small tissue layer close to wounds during their healing, and modeled in a robust fashion through dynamic boundary conditions.

Central to our modeling efforts are two observations from experiments: (i) sharply increased activity including stem cell proliferation near wound healing sites; (ii) global gradients of chemical signals, related to the wnt-signaling pathway.

The first observation is translated into dynamic boundary conditions, modeling changed reaction kinetics in a boundary compartment. The second observation has often been discussed in connection with the regulation of tissue size, expanding on the idea of the French-flag model. The role of this global signal gradient is different in our mathematical model: we postulate that the gradient, rather than absolute levels of the signal are sensed by stem cell populations and, at wound sites, translated into directed differentiation.

Sensing of the gradient of wnt-signaling can be accomplished by stem cells in many ways, for instance during their (directed) movement towards the wounding site. During their movement, they may measure the signal at different time steps

or different locations. We do not attempt to model details of this sensing process but simply include a lumped reaction term for the differentiation of stem cells that depends sharply on the sign of the normal derivative of the wnt-signal. We suspect that within a rather general modeling context, such a gradient sensing is necessary in order to reproduce robust preservation of polarity in cutting experiments.

Our reaction-diffusion system describes 6 species, 3 cell type populations, and 3 chemical signals. Through model reduction to an order parameter for cell types and one long-range chemical signal, only, we exhibit how these two ingredients organize the regeneration process. In the reduced model, we can point to regeneration as an instability mechanism for a trivial, unpatterned state and identify analytically limits of robust regeneration. The process is fundamentally different from Turing's mechanism, and driven by the boundary compartments.

Since experiments appear to point to a significant role of directed motion, a model that takes such effects into account could potentially improve both qualitatively and quantitatively on the results presented so far.

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Phase transitions and universality in neural circuit evolution

Fred Wolf

The information processing machinery of the biological brain emerged through sequences of key innovations from the origins of the first neurons to the neural circuits of the primate and human brains. A key task for mathematical theories of brain circuits is to understand the nature of these inventions, why they offered advantages, and how as complex a system as brain could reconfigure itself. After reviewing some aspects of nervous systems evolution, I presented an account of the transformation of the primary visual cortex at the origin of modern primates. I mapped the problem of co-optimizing the input and the intrinsic connection of the cortical neurons to a pattern formation/equivariant bifurcation problem in 2D or 3D. I showed that symmetries decompose the space of all utility functions of the system into 4 distinct classes. The class of highest symmetry predicts a parameter free circuit architecture with a signature of on average $\pi = 3.14$ topological orientation defects per unit area. I reported that in 9 different species, these and more signature have been confirmed with small error morphs, indicating biological universality of this mathematically defined architecture. A direct phase transition (first order) connects this circuit design to the presumably ancestral salt and pepper design found in many small non-visual mammals. The primate architecture exhibits neutral degrees of freedom. These seem to be functionally disable shifting the circuit by perturbation in the living brain. Our theory and

these observations suggest that the neural circuits could be viewed as large complex dynamical systems and their evolution is partially explained by bifurcations and phase transitions of these dynamics.

Impact of population spatial structure on mutant fixation, from models on graphs to the gut

Anne-Florence Bitbol

Microbial populations often have complex spatial structures, with homogeneous competition holding only at a local scale. Population structure can strongly impact evolution, in particular by affecting the fixation probability of mutants.

I will first discuss a general model for describing structured populations on graphs [1]. I will show that by tuning migration asymmetry in the rare migration regime, the star graph transitions from amplifying to suppressing natural selection. I will also discuss the impact of increasing migration rates [2]. The results from our model are universal in the sense that they do not hinge on a modeling choice of microscopic dynamics or update rules. Instead, they depend on migration asymmetry, which can be experimentally tuned and measured.

Then I will show that the specific structure of the gut, with hydrodynamics and gradients of food and bacterial concentrations, can increase the fixation probability of neutral mutants [3]. Our results can be rationalized by introducing an active population, which consists of those bacteria that are actively consuming food and dividing. Thus, the specific environment of the gut enhances neutral bacterial diversity.

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