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Letter from the President

Dear fellow mathematical and theoretical biologists,

This is the last time I write to you as the president of the ESMTB, after a year where matters were going their good steady pace for the Society. We are gearing up to the 13th ECMTB conference in July 2024 in Toledo. Víctor Pérez is doing a terrific job in organising it — the web page tells it all, see https://ecmtb2024.org/. Our online colloquium, started during the pandemic to provide some minimum of scientific exchange, has established itself as a continuing, well-known, and widely-attended activity. The talks for early 2024 are currently in the planning; they will soon appear on our web page. The first Karl-Peter-Hadeler Prize (for an outstanding paper in our official journal, the Journal of Mathematical Biology) was awarded, and the cooperation contract for the journal was renegotiated with the publisher (SpringerNature); see *News from JoMB* on p. 3. Once more, the Board has been renewed, where four incoming members were elected in September/October with a high quorum, see this page; thanks to all who voted!

On a personal note, let me say that, three years ago, I was not longing to become president of the ESMTB; it took a lot to convince me. But I never regretted it; in contrast, it turned out to be an enjoyable and rewarding experience, simply because the team (Luděk Berec, Sílvia Cuadrado, and Bob Planqué, whose terms are now ending, too; and Tom Britton, José Carrillo, Elisenda Feliu, Tommaso Lorenzi, Benoît Perthame, and Angélique Stéphanou, who will continue for their second term) was fantastic. Always arguing thoughtfully, always constructive, never fighting; always reliable; always willing to share the work; always doing their best to achieve a good balance, both geographically and between research areas. I cannot thank them enough. They have become dear friends, and I will miss them.

But this is also an instance of, as we say in German, 'one should leave when it's best'. With Marie Doumic, Víctor Pérez, Zuzanna Szymánska, and Ezio Venturino, four new, highly engaged, and well-known researchers have come on board. They will officially take up their roles on January 1st, but have already started to contribute fresh ideas. I am absolutely happy to see ESMTB under the new guidance and wish the new and the continuing Board members, and especially their new president Benoît Perthame, a constructive and fruitful term.

With cordial regards

Ellen Baake

Meet our new ESMTB board members

Marie Doumic is the head of MERGE, a joint Inria and Ecole Polytechnique team (at Palaiseau, near Paris), which focuses on "Mathematics for Emergence, Reproduction, Growth and Evolution". She is also part-time professor at Ecole Polytechnique. She did her PhD on advection-Shrödinger equation applied to laser-plasma interaction, before becoming fascinated by biological applications of mathematics and turning to the field of structured population dynamics. She has progressively combined partial differential equations methods with inverse problems, stochastic branching processes and statistics, in order to answer in the most accurate way to molecular biology questions raised by experimentalist collaborators. She has been the principal investigator of an ERC Starting grant (2013-2018). She is co-editor in chief for Esaim Proceedings and Surveys and an associate editor for Kinetic and Related Models, the Bulletin des sciences mathématiques and the Journal of Mathematical Biology.

Víctor M. Pérez García is a professor of Applied Mathematics and director of the Mathematical Oncology Laboratory at University of Castilla-La Mancha (Spain) (https://molab.es). He is editor in chief of Physica D: Nonlinear Phenomena and coordinator of the mathematics panel at the Spanish National Research Agency. After a career in mathematical physics, he switched his interests towards the applications of mathematical models in medicine with special focus on the development of in-silico clinical trials and the discovery of mechanistic-model based biomarkers. He is PI of many projects with the pharma industry, national and international chancer charities

and public funding bodies intended to develop mathematical knowledge of direct applicability in different cancers.

Ezio Venturino, full Professor at the University of Torino, got a Master in Mathematics there, a Master and the Ph.D. both in Applied Mathematics from SUNY at Stony Brook, NY, USA. Held academic positions at the Universities of Iowa, Catania and the Politecnico of Torino; shorter positions at the Universities of Leeds and Huddersfield, England, and medium term visits to many Institutions in Europe, USA, Australia, South America, India. Coauthor of a book for CRC and coeditor of two, for Birkhaeuser and for Springer-SIMAI, currently is serving in the Editorial Board of JoBS, MATCOM, AIMS Mathematics, MBS. Formerly he was Management Committee member for EU COST Action: FA 1405 - Food and Agriculture: "Using three-way interactions between plants, microbes and arthropods to enhance crop protection and production" and main organizer of four conferences held in Torino: MPDE14; CAMo: from Molecules to Models (2015); Ninth DSABNS (2018); MPDEE2022 and chaired or served in a few Italian national committees. Ranked among the top 2% of world scientists by Mendeley Data, 2017-2021, his current interests in mathematical biology concern population theory, focusing on theoretical aspects of ecoepidemiology, ecology, in particular herd behavior, and more recently applying modeling to a variety of real world ecosystems in close connection with biologists, to fight invasive alien species as well as pest control in agriculture and other topics such as wastewater treatement and bioremediation.

Zuzanna Szymańska, PhD, graduated in 2002 in mathematics and in 2003 in computer science from the Faculty of Mathematics, Informatics and Mechanics University of Warsaw. In 2010 she obtained a PhD degree with distinction in biology and a specialization in biophysics from the Polish Academy of Sciences. Currently, she is an Assistant Professor at the Interdisciplinary Centre for Mathematical and Computational Modelling (ICM) at the University of Warsaw. Her main area of research involves developing multi-scale mathematical models in biology and medicine, particularly for processes such as wound healing, and the growth and spread of cancer. Currently, her main research focus and objective is to address the difficulty associated with the use of mathematical models in clinical practice, which is the lack of proper assessment of their range of applicability and model calibration based on empirical data.

Current (2024-2026) board members

- Benoît Perthame, Paris, France (President)
- Víctor Peréz García, Castilla-La Mancha, Spain (Vice President)
- Zuzanna Szymańska, Warsaw, Poland (Secretary)
- Angélique Stéphanou, Grenoble, France (Treasurer)
- Tom Britton, Stockholm, Sweden
- José A. Carillo, Oxford, UK
- Marie Doumic, Paris, France
- Elisenda Feliu, Copenhagen, Denmark
- Tommaso Lorenzi, Torino, Italy
- Ezio Venturino, Torino, Italy

News from the Journal of Mathematical Biology

In a joint venture in 2022, the publisher (Springer-Nature), the Editors in Chief (Anna Marciniak-Czochra and Thomas Hillen), and the ESMTB Board have established the Karl-Peter-Hadeler Prize of the Journal of Mathematical Biology (JoMB). It recognises outstanding publications in the journal.

The prize has now been awarded for the first time. The ESMTB Award Committee unanimously recommend the article entitled *Spatial ecology, optimal control and game theoretical fishing problems* by Idriss Mazari and Domènec Ruiz-Balet (JoMB 85 (2022), 55 (61 pp)). The winners presented their work in the ESMTB online colloquium on March 29, 2023, and also received a material prize from

Springer. See their story on p. 16.

The Board has also renewed its cooperation contract with the publisher; so JoMB will continue to be ESMTB's official journal for the five years to come. Among other things, this implies substantial influence of the Society on the development of the journal; in particular, it means that we are involved in the choice of the Editors in Chief. In the future, ESMTB will also be involved in solliciting and selecting topical collections for the journal.

The Ovide Arino Outreach Award 2023

The Ovide Arino Outreach Award is a joint ESMTB (European Society for Mathematical and Theoretical Biology) and SFBT (Société Francophone de Biologie Théorique) prize, awarded every two years to a young researcher from a Southern country, on the basis of a remarkable contribution in mathematical or theoretical biology, carried out in collaboration with a European or French-speaking country.

The prize awarding committee is happy to announce that **Hari Kishore** has been designated as the laureate for the year 2023 for a work realized in collaboration with colleagues from the University of Milan.

Kishore Hari is a PhD student at the center for BioSystems Science and Engineering (BSSE) at Indian Institute of Science, Bangalore.

He is investigating an aspect of the heterogeneity called Epithelial-Mesenchymal Plasticity, a developmental process with significant implications for cancer metastasis. Using network modelling and population data analysis, he is trying to answer the question of how deterministic and stochastic mechanisms of population heterogeneity interact with each other and possibly lead to improved survival. To this end, he uses mathematical and computational approaches to analyse the networks underlying cancer metastasis.

Hari Kishore's statement

"The study *Identifying Inhibitors of Epithelial-Mesenchymal Plasticity* is an ensemble study of gene regulatory networks that aims to uncover the design principles of the gene regulatory networks (GRNs) underlying Epithelial-Mesenchymal Plasticity (EMP). EMP is a crucial process in cancer metastasis, where cells in primary tumors possessing an epithelial phenotype undergo partial or full EMT to acquire migratory and invasive properties, allowing them to metastasize. While studies have been focused on reducing EMT to reduce metastasis, it must be noted that the transition is bidirectional, and while not much is known about the triggers of MET, the importance of MET in the colonization of cancer cells is undeniable. Furthermore, drugs targeting EMT alone can enhance the metastatic potential of cancer cells.

In this study, we aimed to identify ways to reduce transition in both directions by targeting the GRNs underlying EMP. We collected a set of GRNs underlying EMP from literature and studied the effects of single-edge perturbations to these GRNs on the emergent phenotypic plasticity. We employed a parameter ensemble simulation methodology known as RACIPE. Briefly, RACIPE constructs a system of ordinary differential equations for each node in the network and simulates these ODEs at a large number of randomly sampled parameter sets. The steady states obtained from these simulations serve as phenotypes in our further analysis. We analyzed the best-performing perturbations that reduce the emergent phenotypic plasticity for each network studied and identified the design principles underlying such perturbations. Our ensemble simulation methodology ensures that our predictions are robust to large-scale parametric fluctuations. Notably, given the small scale of the perturbations under investigation, they hold therapeutic feasibility.

We also found the phenotypic space emergent from these networks to be robust to structural (network topology) and dynamical (parameters used for simulating the network) perturbations. Our follow-up study published in Biophysical Journal investigates the design principles of this robustness and finds that an increased fraction of positive feedback loops in a given network correlates positively with the ability to exhibit phenotypic plasticity. In summary, we identify design principles

of the network topology that control EMP, and can robustly be employed to identify therapeutic targets across multiple carcinomas to curb EMP and metastasis."

Kishore will be invited to give a talk at one of the next SFBT virtual seminars.

The OAOA committee,
Julien Arino, Slimane Ben Miled, Rafael Bravo de la Parra, Angélique Stéphanou, Suzanne Touzeau

[1] Kishore Hari *et al.*, Identifying inhibitors of epitelial-mesenchymal plasticity using a network topology-based approach. npj Systems Biology and Applications, 2020, 6(1):15.
https://doi.org/10.1038/s41540-020-0132-1

[2] Kishore Hari *et al.*, Robustness in phenotypic platicity and heterogeneity patterns enabled by EMT networks. Biophysical Journal, 2022, 121: 3600-3615.
https://doi.org/10.1016/j.bpj.2022.07.017

The Reinhart-Heinrich Doctoral Thesis Award 2022

The 2022 Reinhart-Heinrich Doctoral Thesis Award goes to **James Holehouse** for his PhD thesis entitled "Model reduction, mechanistic modelling and transience in models of stochastic chemical kinetics" obtained in October 2022 at the University of Edinburgh.

The prize committee had the following motivation: *James Holehouse receives the prize for his contribution on developing novel analytical and computational techniques for stochastic systems, including model reduction, considering time-dependent processes with applications in gene expression and beyond.*

James will be invited to present his very nice and original work at the next ECMTB conference in Toledo.

James Holehouse Personal Statement

I'm a postdoc at the Santa Fe Institute in New Mexico. I conducted my PhD under Ramon Grima at the University of Edinburgh (2018–2022). My interests typically involve the importance of stochasticity in complex systems, from gene expression to enzyme kinetics in biology and social choice in economics. My PhD work focused broadly on aspects of gene expression and chemical that are subject to stochasticity (i.e., time-dependent random evolution). My current work focuses on first-passage time theory, understanding functional diversity in cities, companies and cells, and volume dependence in mRNA and protein expression. I enjoy finding unexpected complexity in "simple" stochastic models and explaining these phenomena in intuitive ways.

Thesis summary: 'Model reduction, mechanistic modelling and transience in models of stochastic chemical kinetics' by James Holehouse

Introduction and Overview

It is now long known that gene expression and chemical kinetics are subject to random fluctuations. These lead to deviations from deterministic models that do not account for the random nature of biochemical kinetics. Successfully incorporating these stochastic dynamics is of great interest so that one can better model, and more closely understand, the intricate phenomena inherent in biological mechanisms. Many previous studies have been conducted in modelling such processes stochastically, for instance processes such as genetic autoregulation, Michaelis-Menten enzyme action and ant recruitment models. However, the majority of these studies explore only the steady state solutions of such processes while assuming mass-action kinetics, without considering: (1) extrinsic noise, (2) transience from an initial condition, or even (3) the finite, non-continuous nature of molecule or agent numbers.

My thesis focuses on the aforementioned complex systems, with an emphasis on how to use toy models in responsible and informed ways. *Responsible* refers to a knowledge of how good our approximations of microscopic dynamics are and their limitations: Do we understand the assumptions that commonly employed approximations rely on? *Informed* refers to whether a model we design is sufficiently minimal or complex to represent the underlying biochemical (or economical) kinetics: Can we use alternative models of similar simplicity (possibly mechanistically informed) to more properly capture the dynamics of the system we are attempting to model? Further issues pursued in this thesis are whether common approximative methods can be extended to effectively include details of more complex underlying dynamics, or whether we can move beyond typical steady state solutions and explore transience from an initial condition.

There are several main findings from my thesis. It is found that for non mass-action Hill-type propensities, often used in biochemical kinetics, that typically only assume time scale separation as the basis of approximation, that finite molecule number effects can greatly perturb their accuracy. Then, I show that the addition of non-Gaussian colored noise to biochemical rate parameters can capture intricate characteristics of gene expression that are not explicitly modelled. For common two-state gene models, I explore why they seem to be so effective at approximating gene expression, where it is known that several key rate limiting steps are ignored. Finally, I develop transient solutions to master equations describing Michaelis-Menten enzyme kinetics and ant recruitment, and we show how to extend the solutions therein to more general forms. The core methods used in the thesis are included in a comprehensive preliminaries, and cover the basics of stochastic simulation (SSA, with and without delays), the chemical master equation (CME), finite state projection, approximation methods for the CME, and transient solutions to the CME. Each chapter has been published, with the bibliography given below in this summary [1, 2, 3, 4, 5]. Please see the extended bibliography in the full thesis [6].

Stochastic model reduction in gene expression

The first chapter of research in my thesis concerns the Hill-type approximation often used to model binding kinetics in genetic autoregulation. Generally, Hill functions have been employed with a derivation reliant on deterministic approaches that do no consider the discrete nature of molecule numbers. This can be an issue when using Hill function in stochastic applications, since the approximation is valid for deterministic kinetics, and becomes a heuristic in stochastic applications. Importantly, it becomes a heuristic that is *misunderstood* in the sense that we do not know *a priori* when the approximation will break down. The results of the chapter elucidate under what situations the heuristic Hill-type propensity breaks down, and provide

a physical justification for its breakdown.

The genetic auto-regulatory reaction scheme is as follows,

$$\begin{aligned} &G \xrightarrow{\rho_u} G + P,\ G + P \underset{\sigma_u}{\overset{\sigma_b}{\rightleftharpoons}} G^\star, \\ &G^\star \xrightarrow{\rho_b} G^\star + P,\ P \xrightarrow{d} \varnothing, \end{aligned} \tag{1}$$

where G is the species denoting the unbound gene state, $G^\star$ is the bound gene state, and P denotes the proteins that degrade with rate d. Each reaction in this scheme denotes an event with an exponentially distributed waiting time with a rate indicated on the arrow. There is a single gene that can either be in state G or $G^\star$. Using deterministic arguments this reaction scheme can be approximated by the simpler (albeit non mass-action) reaction scheme

$$\tilde{G} \xrightarrow{\frac{L\rho_u + \rho_b n}{L+n}} \tilde{G} + P,\ P \xrightarrow{d} \varnothing, \tag{2}$$

where the production rate is a Hill function and there is a single effective gene state $\tilde{G}$, $L = \sigma_u/\sigma_b$ and n is the number of proteins in the system. The deterministic derivation of the Hill function is reliant on a quasi-steady state assumption that states that the gene is a fast species compared to the dynamics of the protein. The key to understanding any disparities between Eqs. (1) and (2) comes from the discovery that in the rigorous fast gene switching limit in Eq. (2) actually corresponds to

$$\begin{aligned} &G \xrightarrow{\rho_u} G + P,\ G \underset{\sigma_u}{\overset{\sigma_b n}{\rightleftharpoons}} G^\star, \\ &G^\star \xrightarrow{\rho_b} G^\star + P,\ P \xrightarrow{d} \varnothing, \end{aligned} \tag{3}$$

with the protein dependence now in the propensity to switch. Importantly, this ignores the *protein-binding fluctuation* between gene state switching, which leads to significant disagreement between the schemes in Eqs. (1) and (2) when protein-gene binding is much faster than the unbinding rate ($L \ll 1$). The origin of the disagreement can be explained by the dynamics of the schemes around $n \gtrapprox 0$ (for a full explanation see p. 42–43 of [6]).

Chapter 5 investigates other aspects of model reduction. In particular, I investigated why telegraph-like models (two gene-state models of transcription) fit mature and nascent mRNA numbers so well *given that they exclude key rate limiting steps in transcription*. Such steps include activator binding, RNA Pol II pause and release and nascent mRNA elongation. To compare to the telegraph-like models I introduced the mechanistic scheme shown in Fig. 1. This mechanistic scheme has three stochastic species: the state of the gene, the nascent mRNA and the mature mRNA. The telegraph-like models we considered were separate for the nascent mRNA and mature mRNA dynamics. For the mature mRNA the reaction scheme is,

$$G \xrightarrow{\rho_u} G + M,\ G \underset{\sigma_b}{\overset{\sigma_u}{\rightleftharpoons}} G^\star,\ M \xrightarrow{d} \varnothing, \tag{4}$$

where $G^\star$ is the transcriptional off-state, G is the on-state, σ_b and σ_u are the rates of activator binding/unbinding and mRNA degrades at rate d. For the nascent mRNA dynamics the scheme is similar, but due to the many (approximately Markov) steps of the RNA Pol II stepping along the gene we model the removal of nascent mRNA as a *deterministic process*, giving the scheme

$$G \xrightarrow{\rho_u} G + N,\ G \underset{\sigma_b}{\overset{\sigma_u}{\rightleftharpoons}} G^\star,\ N \underset{\tau}{\Longrightarrow} \varnothing, \tag{5}$$

where the double arrow denotes a non-Markovian delayed reaction which fires after a time τ has elapsed. Note that in the thesis itself we instead refer to the nascent mRNA as "active RNA Pol II", although for the purposes of this summary this distinction is unimportant. The master equations of both these telegraph-like models have been previously solved in the literature, and in this thesis chapter we solve for the marginal dynamics of both the nascent and mature mRNA from the full mechanistic reaction scheme in Fig. 1.

To answer our question as to why telegraph-like models are so successful I proceeded to investigate different mappings of the two models based on (i) waiting time distributions for mRNA production, (ii) moment matching and (iii) distribution matching using the Hellinger distance. The first of these methods gives analytic regions of mapping between the mechanistic and telegraph-like models, whereas the latter

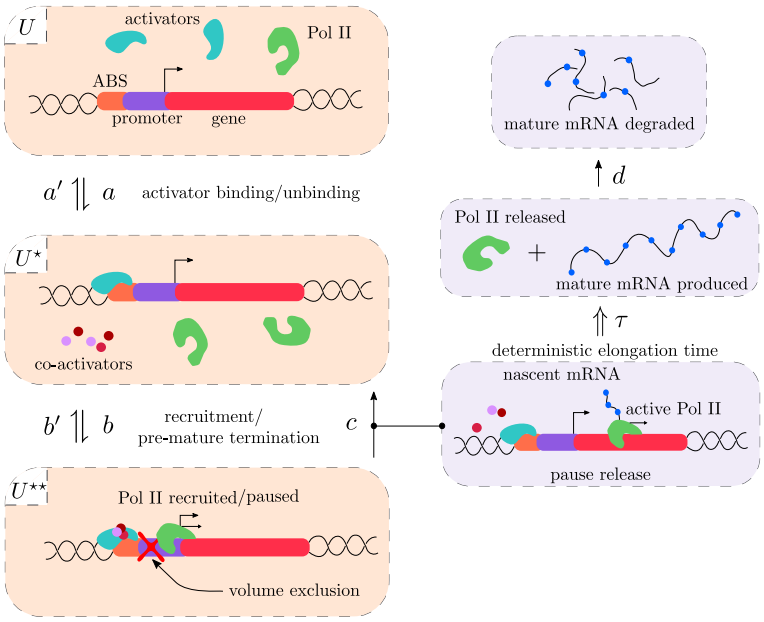

Figure 1: Illustration of the mechanistic model of mRNA expression, including activator binding/unbinding, RNA polymerase II pause and release, (deterministic) nascent mRNA elongation, mRNA production and degradation.

two can only be conducted numerically. The key feature that led to an understanding of why the telegraph-like models generally perform so well is that the mapping is only possible where the Fano factor (a measure of noise or "Poissonianness") of mRNA expression is ≥ 1. This coincides with the fact that most (although not all [7]) mRNA expression profiles across many genes have a Fano factors ≥ 1, therefore explaining why telegraph-like models have performed so well.

Analytics and noise induced modalities in autoregulation

A popular direction of research in the stochastic gene expression literature concerns the decomposition of noise seen in experimental gene expression data to *intrinsic* and *extrinsic* components following the pioneering work of Swain *et al.* [8]. In this sense, intrinsic refers to variation arising from the stochasticity of cellular kinetics and low molecule number, whereas extrinsic refers to stochasticity in a population of cells arising from different cellular environments. We investigated a separate aspect of extrinsic noise in a *single cell* that arises from unresolved processes that are not normally included in models of gene expression such as multi-stage protein degradation and multi-stage protein production.

The toy model that I conducted the analysis on is the cooperative autoregulatory feedback loop seen in Fig. 2. Unresolved processes are included by adding a colored noise term $\eta(t)$ to each reaction rate (meaning that the reaction rates themselves are stochastic quantities). This colored noise term is characterized by two features (i) τ, the correlation time between noise impulses and (ii) D, which is the strength of the noise. The correlator of this colored noise is defined by $\langle \eta(t)\eta(t')\rangle = (D/\tau)\exp(-|t-t'|/\tau)$. Typically systems subject to colored noise are difficult to approach analytically, and this is were the novelty of this chapter lies. By approximating the chemical master equation describing the scheme in Fig. 2 as a Fokker-Planck equation and employing the *unified colored noise approximation* (UCNA, [9]), I show how to derive semi-analytic solutions of the probability distribution of proteins at steady state as a function of the D and τ that characterize each reaction.

This solution allowed us to observe several aspects of the effects induced by colored noise on

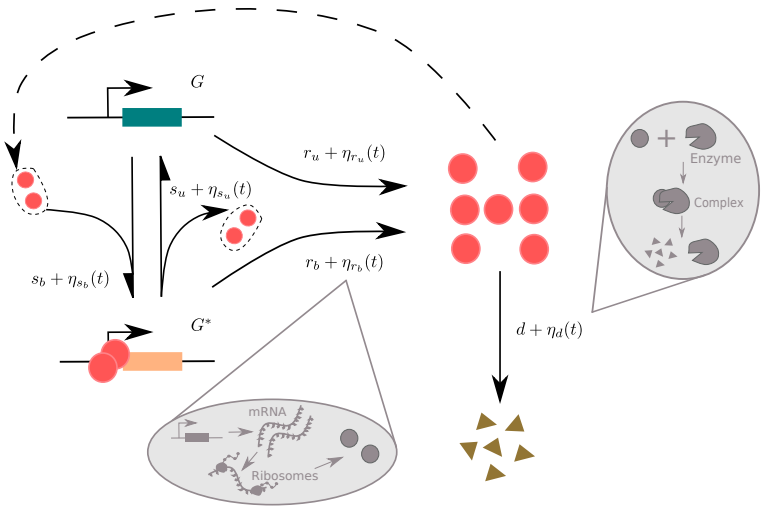

Figure 2: Illustration of the cooperative auto-regulatory reaction scheme with colored noise included on each individual reaction, the model explored in Chapter 4 of the thesis. The addition of noise onto rate parameters can be thought of as accounting for processes that are not explicitly included in the gene expression model. Here we show two examples, where colored noise on the rate parameters of the reduced model can be used to account for mRNA number fluctuations during protein translation, or the degradation of proteins via an enzyme catalytic mechanism.

varying system rates. For example, where gene switching is fast, increasing the strength of noise on the degradation rate can induce multimodality in the steady state probability distribution (see Fig. 3A). On the contrary, if gene switching rates are the slowest system timescales, increasing D can remove multimodality from the steady state distribution. This ability to induce bimodality through a more detailed description of the details of the degradation process is important in the context of cellular decision-making. It is hence possible for regions of the reaction rate parameter space previously thought unable to induce multiple phenotypic states to do so with an increasing influence of more complex degradation mechanisms. Finally, we show how to find the values of D and τ corresponding to specific unresolved processes, in this case, multistage protein production and degradation. The results of this chapter constitute rare cases of analytics for systems subject to both intrinsic and extrinsic noise, that can be extended beyond the cooperative auto-regulation example shown.

Time-dependent solutions in reaction kinetics

The final two chapters of research in my thesis concern time-dependent solutions to master equations. In general, time-dependent solutions are rare, since the time-dependence compounds analytic difficulties where even steady-state solutions are challenging. We outline two particular methods for solving master equations in time in the preliminaries, one of which utilizes the properties of the resolvent of the master operator, the second which utilizes methods from spectral theory to find the associated eigenvalues and eigenvectors of the master operator.

Chapter 6 takes a fresh look at Michaelis-Menten enzyme kinetics described by the scheme,

$$S + E \underset{k_1}{\overset{k_0}{\rightleftharpoons}} C \xrightarrow{k_2} E + P. \tag{6}$$

Previously, the master equation describing this reaction scheme had not been solved in time, aside from the case of a single enzyme and a single substrate molecule. We solve it for the realistic case where the enzyme action is inefficient (i.e., $k_1 \gg k_2$), there are multiple enzyme

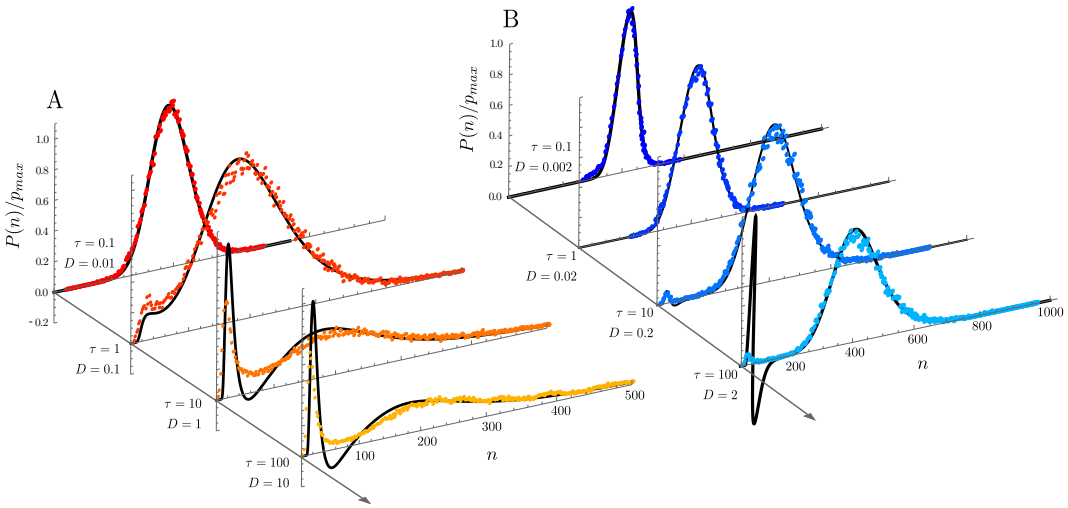

Figure 3: Comparison of the UCNA (black line) against stochastic simulation (colored dots) as the correlation time τ of the noise on the degradation rate is increased at constant noise size D/τ. Note that the y-axis shows $P(n)/p_{max}$, where $P(n)$ is the solution to the Fokker-Planck equation and p_{max} is equal to the maximum value of $P(n)$. Deterministically this system is monostable with an equilibrium point at $n = 194.7$, however as τ is increased a shift towards a lower mode is observed. When τ is sufficiently large, the UCNA breaks down and predicts a negative probability. (B) This too is a deterministically monostable system with equilibrium point $n = 406.0$.

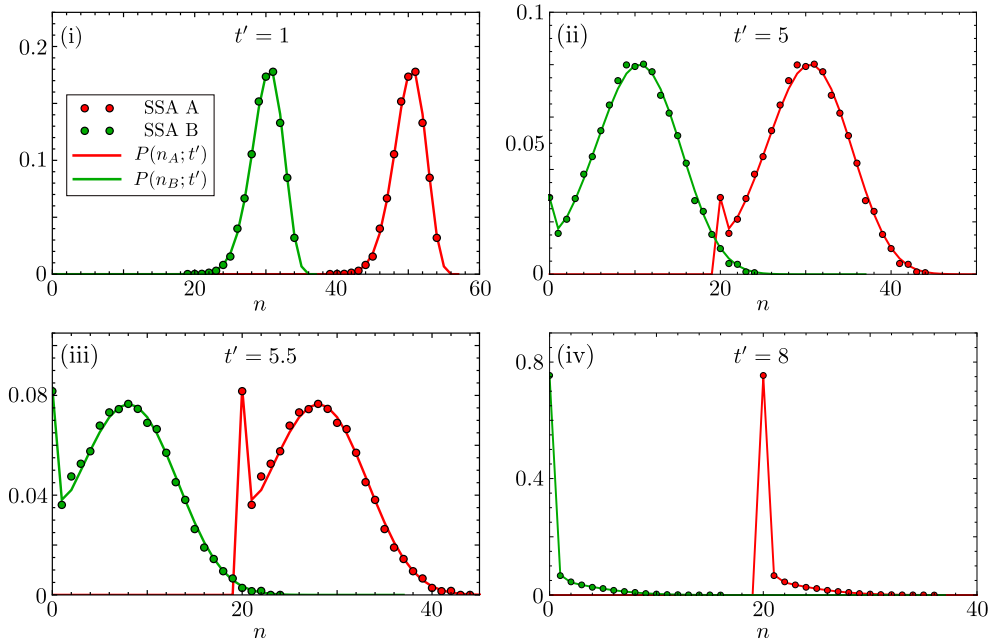

Figure 4: Comparison of the analytic distribution of two types of substrate species A and B, involved in the ternary complex formation, against the distributions obtained using the SSA (stochastic simulation). Note that SSA A and SSA B denote the SSA predictions for species A (red dots) and species B (green dots), respectively. In the panels (i)–(iv) we plot the probability distributions $P(n_A;t')$ (red line) and $P(n_B;t')$ (green line) for four different time points from near the initial condition (i) to near the absorbing state (iv). Each SSA probability distribution is constructed from 10^5 individual reaction trajectories.

and substrate molecules, and for general initial conditions. Additionally, we extend our analyses to other related enzyme mechanisms, such as ternary complex formation which is described by the scheme,

$$E + A + B \underset{k_1}{\overset{k_0}{\rightleftharpoons}} C \xrightarrow{k_2} E + P + Q. \qquad (7)$$

Exploring the behavior of the solutions in time, I found the occurrence of *transient bimodality* in regions of the parameter space with an initially large number of substrate, small numbers of enzymes and $k_1/k_0 \ll 1$. The origin of this behavior cannot be explained by the finite nature of molecule numbers, and is thought to be generally resultant from a complex mix of high variance and slowly relaxing kinetics (explaining this phenomenon is still an open problem). An example of transient bimodality seen in ternary complex formation can be seen in Fig. 4 (although it is also seen in standard Michaelis-Menten kinetics too). Notably, *transient bimodality does not have a deterministic counterpart and is a purely stochastic phenomenon.*

The final chapter of research in my thesis deviates away from chemical kinetics and into economic toy models. I investigated Kirman's model of ant recruitment, which is popular in economics since its steady state solution describes how populations of ants (or in economics, people) can become polarized exclusively due to endogenous dynamics without the need for external forces. In this classic narrative, ants are allowed to access two sources of food, one on the left and one on the right, and the ants can 'recruit' each other to the opposing food source or otherwise randomly switch between them. The model is fully characterized by two rates, the rate of interaction between the ants μ and the rate of random switching ε, all occurring in a finite population of ants of size N (where n denotes the number of ants on the right-hand food source). In Fig. 5 we show the steady state behavior of this model for varying values of the parameters. Note that this model is also isomorphic to the Moran process that describes genetic drift in population genetics.

The aspect of this problem I explored was the time-dependence of the solution of the master equation. Using methods from spectral theory I showed that the rates of relaxation are indistinguishable from those of the Fokker-Planck equation describing the limit of $N \to \infty$. Additionally, the slowest timescale dictating the relaxation to equilibrium is simply the the random switching rate ε, which can be interpreted as saying that the switching of a single ant to the opposing food source is enough to start an avalanche of switching. I then extend this analysis to models of ant recruitment of increasing asymmetry, and also to voter models with third-order interactions.

Conclusions

For many outside the field, studies in stochastic gene expression and more widely in reaction kinetics may be viewed as "professionalized" and an end unto themselves. But the truth is far from that. There are still many unresolved problems that relate to real aspects of empirical data, whose analytic complexity allows for simple kinetics to give rise to *a priori* non-intuitive phenomena. In gene expression such problems include (i) time-dependent solutions and relaxation to steady state behavior, (ii) understanding the effects of volume dependence on prokaryotic and eukaryotic gene expression, (iii) the influence of the cell-cycle on gene expression profiles [11], (iv) the thermodynamics of gene expression [10], and (v) models of stochastic gene expression integrated into global regulation networks [12]. These points provide many interesting future directions for young researchers, such as myself, in an exciting field of study.

Acknowledgments

I thank Ramon Grima for his unwavering support during my PhD studies. This thesis is dedicated to my father, Michael Holehouse, for sparking my interest in science.

References

[1] James Holehouse and Ramon Grima. Revisiting the reduction of stochastic models of genetic

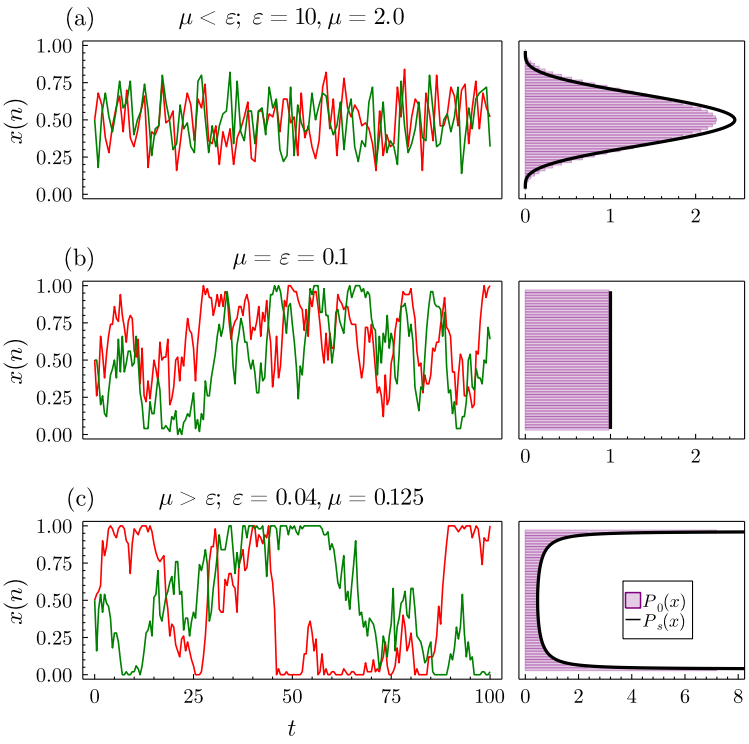

Figure 5: Sample of two different trajectories (left) of the fraction of ants $x(n) = n/N$ on the right-hand source, with the red and green lines showing two different realizations for $N = 50$ ants, along with the corresponding stationary densities (right). Purple bars are the exact stationary distribution for finite N, and the black lines correspond to the symmetric Beta distribution. Notice that in the high imitation regime $\varepsilon < \mu$, corresponding to plot (c) the ants tend to concentrate in one of the food sources for a time of order $1/\varepsilon$ before switching collectively to the other source. The case $\varepsilon = \mu$ in (b) corresponds to the situation where the Beta distribution is a uniform distribution over $[0, 1]$.

feedback loops with fast promoter switching. Biophysical Journal, 117, 1311–1330, 2019.

[2] James Holehouse, Abhishek Gupta and Ramon Grima. Steady-state fluctuations of a genetic feedback loop with fluctuating rate parameters using the unified colored noise approximation. Journal of Physics A: Mathematical and Theoretical, 53, 405601, 2020.

[3] Svitlana Braichenko and James Holehouse* and Ramon Grima **(* joint first-author)**. Distinguishing between models of mammalian gene expression: telegraph-like models versus mechanistic models. Journal of the Royal Society Interface, 18, 20210510, 2021.

[4] James Holehouse, Augustinas Sukys and Ramon Grima. Stochastic time-dependent enzyme kinetics: Closed-form solution and transient bimodality. The Journal of Chemical Physics, 153, 2020.

[5] James Holehouse† and José Moran **(† corresponding author)** Exact time-dependent dynamics of discrete binary choice models. Journal of Physics: Complexity, 3, 035005, 2022.

[6] James Holehouse Model reduction, mechanistic modelling and transience in models of stochastic chemical kinetics. The University of Edinburgh, 2022.

[7] Douglas E. Weidemann, James Holehouse, Abhyudai Singh, Ramon Grima and Silke Hauf. The minimal intrinsic stochasticity of constitutively expressed eukaryotic genes is sub-Poissonian. Science Advances, 9, eadh5138, 2023.

[8] Peter S. Swain, Michael B. Elowitz and Eric D. Siggia. Intrinsic and extrinsic contributions to stochasticity in gene expression. Proceedings of the National Academy of Sciences, 99, 12795–12800, 2002.

[9] Peter Jung and Peter Hänggi. Dynamical systems: A unified colored-noise approximation. Phys. Rev. A, 35, 4464(R), 1987.

[10] Jeremy L. England. Statistical physics of self-replication. J. Chem. Phys., 139, 121923, 2013.

[11] Casper H. L. Beentjes, Ruben Perez-Carrasco, and Ramon Grima. Exact solution of stochastic gene expression models with bursting, cell cycle and replication dynamics. Phys. Rev. E 101, 032403, 2020.

[12] Feng Jiao, Jing Li, Ting Liu, Yifeng Zhu, Wenhao Che, Leonidas Bleris and Chen Jia. What can we learn when fitting a complex gene expression model to a simple telegraph model? bioRxiv, 2023.

Reinhart-Heinrich Doctoral Thesis Award

ESMTB announces the annual Reinhart Heinrich Doctoral Thesis Award to be presented to the student submitting the best doctoral thesis within the current year 2023 in any area of Mathematical and Theoretical Biology, see `https://esmtb.org/Reinhart-Heinrich-Award`.

Professor Reinhart Heinrich (1946 – 2006) started his research career in theoretical physics and then moved into biochemistry, becoming a full professor and head of theoretical biophysics at the Humboldt University, Berlin in 1990. He is considered a father of the field that is now named Systems Biology, since he investigated various topics such as modelling metabolic networks and metabolic control theory, modelling of signal transduction networks, nonlinear dynamics as applied to biological systems, protein translocation, lipid translocation, vesicular transport, and even DNA repair. Reinhart Heinrich was always searching for the principles that underlie observations, looking for different perspectives and connecting theoretical abstraction with biological evidence. In this way, he inspired numerous students, gave them insight and direction for future research in modern mathematical and theoretical biology, and organized a large number of memorable conferences. Gratefully acknowledging his stimulating support of our interdisciplinary field and, in particular, his way of guiding students and young scientists, the Board of ESMTB decided to offer a Doctoral Thesis Award annually to commemorate Reinhart Heinrich and his legacy in mathematical and theoretical biology.

Prize Awarding Committee
Tom Britton (chair of the committee, Stockholm University), Helen Byrne (University of Oxford), Mirjam Kretzschmar (UMC Utrecht), Josep Sardanyes (Centre de Recerca Matemàtica, Barcelona), Jana Wolf (MDC Berlin)

Award

- Invitation to give a plenary talk at the next ECMTB (European Conference on Mathematical and Theoretical Biology), or alternatively, a limited travel grant from ESMTB for a scientific visit of the winner's own choice;
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- Free membership of ESMTB for one year;

Application

Potential applicants may be nominated by any ESMTB member.
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1. Name, address, phone number, affiliation, and email address of **nominator**.
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3. A detailed **statement** describing why the nominee should be considered for the award.
4. The acceptance date of the thesis.
5. An **extended summary** of the thesis (ca. 2-5 pages).
6. A **CV** of the nominee.

Closing date for applications is ***31st March 2024.***

Shortlisted applicants will be asked to send their full thesis.

The Karl-Peter-Hadeler Prize 2023

Population dynamics, fisheries and the tragedy of the commons: A first mathematical analysis

by Idriss Mazari-Fouquer and Domènec Ruiz-Balet

Introduction

Fisheries are a cornerstone of modern societies, whether they be considered from the point of view of the economy-given how many countries rely on fishing as as source of activity and revenue-, of food security-defined as the access to sufficient food-, or of global ecological threats to marine populations across the world. Of particular importance, then, is the *management of fisheries*, whichever meaning we choose to give this expression. Indeed, one can think of fishing companies competing to extract the most resources possible, but this might come at the cost of a greater toll being imposed on fishing populations, and might lead to *overfishing*, which, in this context, is nothing but an instance of the *tragedy of the commons*: the unregulated competition over finite common resources can result in the depletion, and even extinction, of these resources. This is a significant threat to the survival of entire ecosystems, in turn threatening the livelihoods of those who depend on them. On the other hand, a possibility would be for companies to *cooperate*. This might mediate difficulties arising from competition, but this has a strategic cost: every fishing company must be certain that the others are fully in.

In our paper [13], we propose a game-theoretical approach to such overfishing problems, so as to provide a qualitative understanding of these issues. As is often the case when tackling such multifactorial real world issue, we settled on a simple, yet paradigmatic model for the fishes' population, inspired by the seminal works of Fisher, Kolmogorov, Petrovskii and Piskunov [5, 9]. In this model, we only factor in three phenomena: first, the *motion of individuals within the environment*. Second, the *intrinsic reaction of individuals*, which live in a heterogeneous environment but are also competing for the resources available in the environment. Finally, the *action of fishing companies* on the fishes' population.

In this framework, we set out to investigate four main questions:

Q_1 A basic building block is first to consider the case where only one company is fishing. In this case, can we obtain a qualitative description of *overfishing* phenomena? Is *geometric information* (*e.g.* where should we fish in the domain) available? Although not our primary goal, this constitutes the foundation of later questions related to multi-agents situations.

Q_2 When fishing companies are *competing*, can they reach an equilibrium situation? Here, by equilibrium, we mean "Nash equilibrium" [14]. When discussing the competition between actors, Nash equilibria is a concept that basically states that no player has any interest in changing unilaterally their strategy.

Q_3 If Nash equilibria exist, *what do they look like*? Should we expect different fishing companies to fish at exactly the same spot? Should they rather fish in one spot, or spread out their strategies to fish in different locations?

Q_4 Can we illustrate the tragedy of the commons? In other words, can we give examples of situations where, if players fish according to a certain Nash equilibrium strat-

egy, the population goes extinct while, if they coordinated, the population would not only survive, but each player would get a higher outcome than if they were competing?

Regarding such game theoretical questions, let us mention that other authors have considered related questions, albeit within a different framework; we refer for instance to [2, 3].

In the last part of this article, we will present a new, related line of research, focused on a qualitatively different approach, where we adpot a travelling-front approach to understand the tragedy of the commons in game theory.

What happens when a single fishing company is acting (Q_1)?

Our study relies on the most basic, yet extremely useful and paradigmatic, equation in population dynamics, the (steady) logistic diffusive equation. This equation models the behaviour of a population density θ by taking into account the different factors outlined in the introduction.

It reads

$$\underbrace{-\Delta\theta_\alpha}_{\text{Diffusion}} = \underbrace{K(x)\theta_\alpha}_{\text{Reproduction}} - \underbrace{\theta_\alpha^2}_{\text{Intrinsic competition}} - \underbrace{\alpha(x)\theta_\alpha}_{\text{Harvested Fish}}$$

The function $K(x)$ describes the resources available at a particular point x, and $\alpha(x)$ models intensity of fishing at this specific location. This function α is the *strategy* of the fishing company. Natural constraints are imposed on it: at any given point, the total fishing can not exceed certain values, and the overall fishing capacity of the player is limited. Let us insist upon the fact that here *the harvester has a macroscopic influence on the function* θ_α. The harvester's objective is to maximise the functional:

$$J(\alpha) = \int \alpha(x)\theta_\alpha(x)dx.$$

Now, quantifying the *overfishing phenomenon* amounts to understanding whether *the functional J is monotonous or not*: should a fishing company always fish as much as possible, or rather, should it limit its own action to increase its harvest?

In our paper, we prove rigorously that the answer to this query depends on the overall fishing capacity of the company: when this capacity is very large (*i.e.* the company can fish a lot), increasing the fishing can yield a lower harvest. This intuitive outcome highlights the negative consequences of overfishing. In contrast, for low fishing capacities, intensifying fishing efforts does lead to an increased quantity of harvested fish. This nuanced interplay between fishing intensity and harvested quantity highlights the importance of maintaining a balanced and sustainable approach in fisheries management.

At a geometric level, we focus on two properties; the first one, dubbed "bang-bang property" amounts to investigating whether the company should focus all of its fishing capacity in one spot, in essence acting as much as it can in a certain region, or rather spread its forces a bit everywhere. The second one, on the other hand, has to do with where the company should fish: should it focus on one particular region, or rather spread its boat fleet? For this question, while we can offer theoretical proofs in certain limited settings, we resorted to numerical simulations to showcase the diversity of possible outcomes, depending on the overall fishing ability and other parameters:

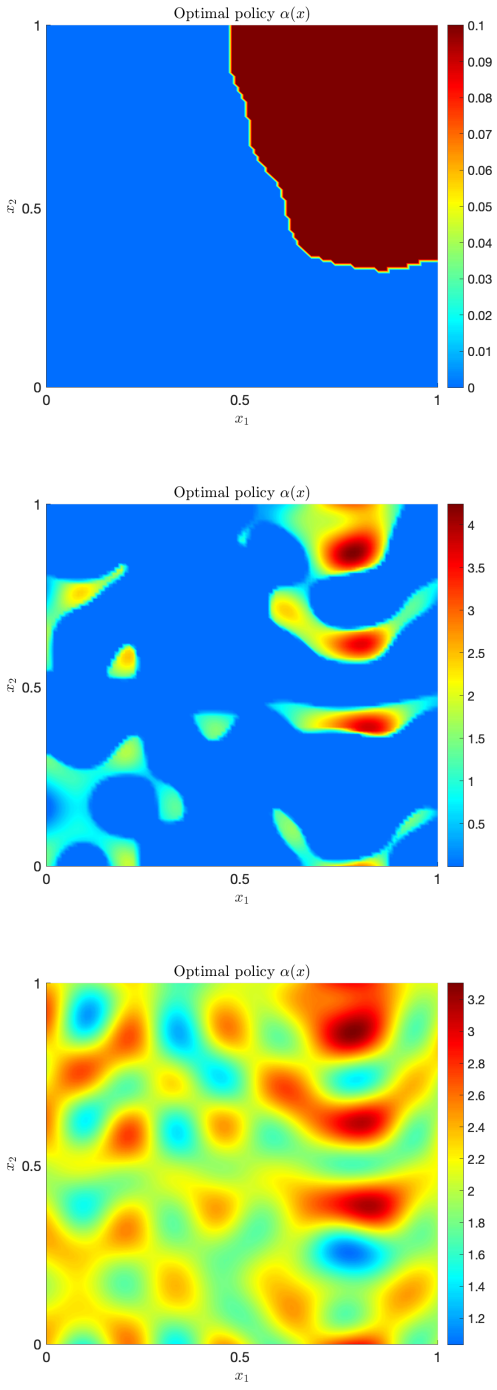


Figure 6: Examples of different behaviours of the optimal policy depending on the fishing ability

Nash equilibria

Nash equilibria (Q_2) Next, we turn our attention to a game-theoretical scenario. Here, two companies, or players, (1 and 2) are fishing, the i-th fishing with a strategy α_i satisfying the same type of bounds. The overall equation on the population density now depends on (α_1, α_2) and satisfies

$$-\Delta\theta_{\alpha_1,\alpha_2} = K(x)\theta_{\alpha_1,\alpha_2} - \theta^2_{\alpha_1,\alpha_2} - \underbrace{\alpha(x)\theta_{\alpha_1,\alpha_2}}_{\text{Player 1}} - \underbrace{\alpha(x)\theta_{\alpha_!,\alpha_2}}_{\text{Player 2}}.$$

Here, the i-th player is trying to maximise

$$J_i(\alpha_1, \alpha_2) = \int \alpha_i(x)\theta_{\alpha_1,\alpha_2}(x)dx$$

with respect to its own strategy α_i. The main difficulty is that the outcome for one player also depends on the action of the other player. The main question we raise is: *does there exist an equilibrium situation?* Here, equilibrium means "Nash equilibrium" [14]. We described this fundamental concept in plain words in (Q_2); mathematically, a Nash equilibrium is a pair of strategies (α_1^*, α_2^*) such that, for any other admissible pair of strategies (α_1, α_2), we have

$$J_1(\alpha_1, \alpha_2^*) \leq J_1(\alpha_1^*, \alpha_2^*)\,, J_2(\alpha_1^*, \alpha_2) \leq J_2(\alpha_1^*, \alpha_2^*).$$

Our main findings, here, are that Nash equilibria exist when each player has a small fishing capacity; this is intimately linked to the overfishing phenomena described in the previous paragraph. Beyond this result, we were also able to fully characterise some of these Nash equilibria in certain scenarii, in particular when the domain is relatively small. Our research thus contributes to the understanding of the intricate at play and, we believe, offers valuable qualitative insight for the management strategies. The study concludes with a discussion on the "price of anarchy"—the potential loss of total outcome when players adopt competitive strategies rather than cooperative ones.

Geometric information regarding Nash equilibria (Q_3) We now turn to (Q_3), namely: what do Nash equilibria look like? This is a multifaceted question. As we outlined, in certain scenarii, we are able to establish that there exist scenarii where the fishing companies should

always be fishing in the same spot, while, in others, this is no longer true. We resorted to numerical simulations to exemplify these complex behaviours (see Fig. 6-7-8).

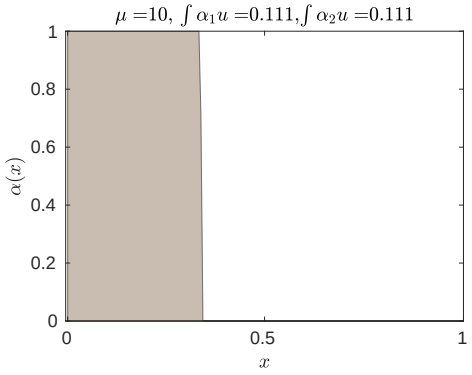
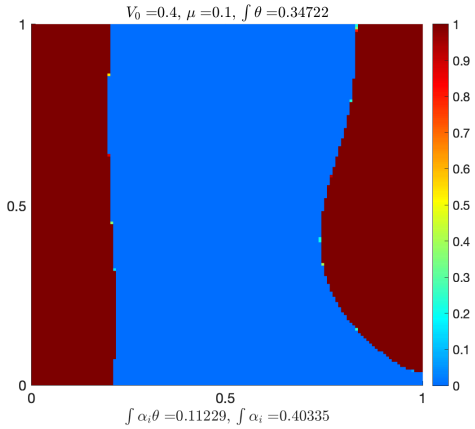
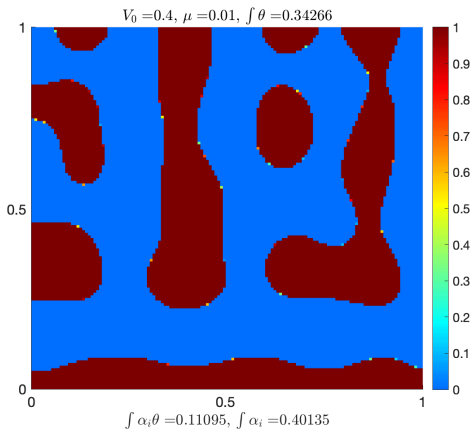


Figure 7: Both players fish at the extreme of one spot when the domain is small.





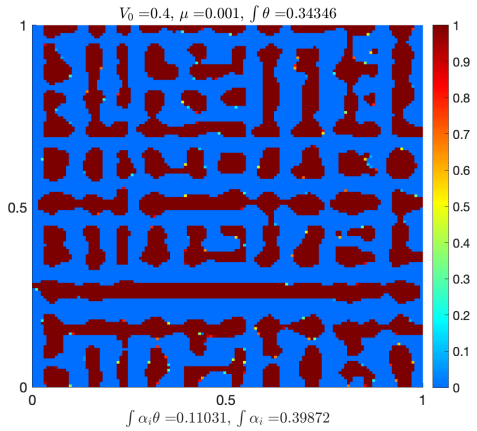
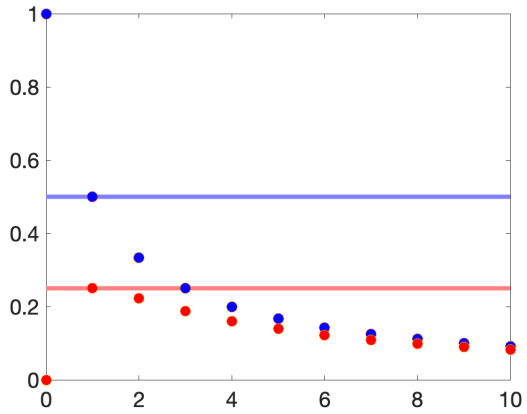


Figure 8: Fragmentation of the Nash equilibria for very large domains

The tragedy of the commons (Q_4) A last result in our paper is devoted to the understanding of the tragedy of the commons. Here, we were unable to prove a fully general theoretical result, but we provided a telling example in the context of an $N \gg 1$ players game. Namely, we proved that, for N large, there exists a Nash equilibrium that almost completely extinguishes the fishes' population, and where each player gets a quantity $\approx 1/N^2$ of fishes, while there exists a cooperative strategy, where not only does the fishes' population survive, but where each player gets a quantity $\approx 1/N$ of fishes! This is illustrated in Fig. 9. This last observation prompted our following study, in collaboration with Z. Kobeissi, where we investigate the case of infinitely many players.



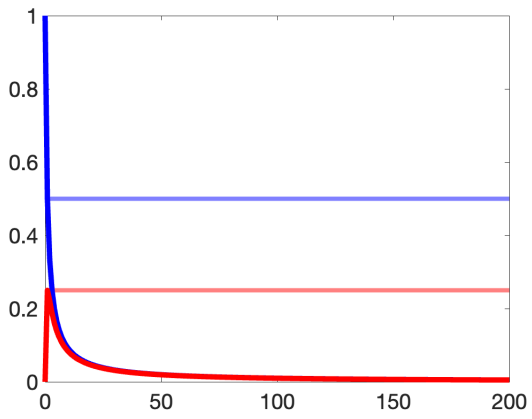


Figure 9: Harvested fish and total population of fish at a N-player Nash equilibrium for homogeneous reproduction

Blending travelling waves & mean-field games

In order to shine a different light on the tragedy of the commons, we studied in [8] a different type model, using the methodology of *Mean Field Games* [10, 11, 7, 6, 12]. A key assumption is that *each individual player has a negligible impact on the overall population*, but that *the resulting action of all fishermen has a macroscopic influence*. The fishes' population, still denoted by θ, solves the evolution equation

$$\partial_t \theta - \Delta\theta = f(\theta) - \underbrace{m\theta}_{\text{Harvested fish}} \tag{8}$$

where m is the density of all fishermen, and f is a particular reaction term made precise below. Each of these fishermen is modelled by its position $x = x(t)$, and controls its trajectory using a control v according to the equation

$$x'(t) = v(t)\,, x(t_0) = x_0.$$

The control v is chosen to maximise the functional

$$\int_0^{+\infty} e^{-\lambda t} \left(\underbrace{\theta(x(t),t)}_{\text{Harvested Fish}} - \underbrace{\frac{1}{2}v(t)^2}_{\text{Control cost}} \right) dt. \tag{9}$$

The constant $\lambda > 0$ simply models the fact that the player might not want to wait for too long. We let $V(t_0, x_0)$ be the optimal value of this optimisation problem (*i.e.* the value function, or the optimal outcome reachable at time t, starting from x_0). Just like in the two players setting, solving this problem requires a knowledge of θ, in turn hinging on the overall distribution of players m. In this setting, the MFG framework allows to write down the system that should be satisfied for the "Nash equilibria" of this system.

$$\begin{cases} \partial_t \theta - \partial_{xx}\theta = f(\theta) - m\theta \\ \partial_t m + \partial_x \left(\partial_x V m\right) = 0 \\ -\partial_t V - \frac{1}{2}\partial_x V^2 + \lambda V = \theta. \end{cases} \tag{10}$$

A fascinating aspect of the above system is the existence of traveling waves; these particular solutions, which write $\theta(x,t) = \Theta(x - ct)$, $m(x,t) = \mathcal{M}(x - ct)$, and $V(x,t) = \mathcal{V}(x - ct)$, are central in the qualitative theory of reaction-diffusion equations [4], as their existence and speed can help predict the outcome in "generic" situations. It should be noted that the study of harvesting problems through the use of travelling wave phenomenology has recently been developed [1], but with a different perspective on the matter.

In [8] we settle for a *bistable non-linearity* f that models the Allee effect: when individuals are not in high enough numbers, the population dies out, while when the density is high enough, they can survive. This non-linearity is well-suited to our qualitative endeavours, as it comes equipped, in the absence of fishermen (take $m = 0$ in (8)) with a *unique* travelling wave solution $\theta = \theta(x - ct)$ that can either be invasive or extinctive (*i.e.*, generically, either the population survives in large times, or it dies out, and this behaviour is fully encapsulated in the behaviour of the travelling wave solution). We reformulate our question as: assume that when $m = 0$ the travelling wave solution of (8) is invasive. Is it possible that the action of fishermen will lead to the existence of an extinctive travelling wave. In other words: *can a competition situation lead to a reversal of a travelling wave?*

We proved that this was indeed the case in a variety of settings, and we further elaborated on the tragedy of the commons in this setting. The typical profiles we get are represented in Fig. 10. While we do not extend further on this in the present paper, we think that this last contribution offers valuable insights in (over)fishing phenomena and opens up new research paths, both mathematically and from an applied perspective.

Concluding remarks and observations

In conclusion, we decided to investigate the management of fisheries by using a blend of optimal control, reaction-diffusion equations and game theory. By exploring these venues, we showed that our seemingly simple models could showcase key phenomena.

The existence of Nash equilibria, their qualitative properties and the tragedy of commons lent themselves to a substantial mathematical analysis, and led us to investigating other facets of this phenomena in MFG systems. Beyond the captivating mathematical intricacies, we believe that these directions are substantially relevant for real-world applications, by helping to better asses the management of fisheries.

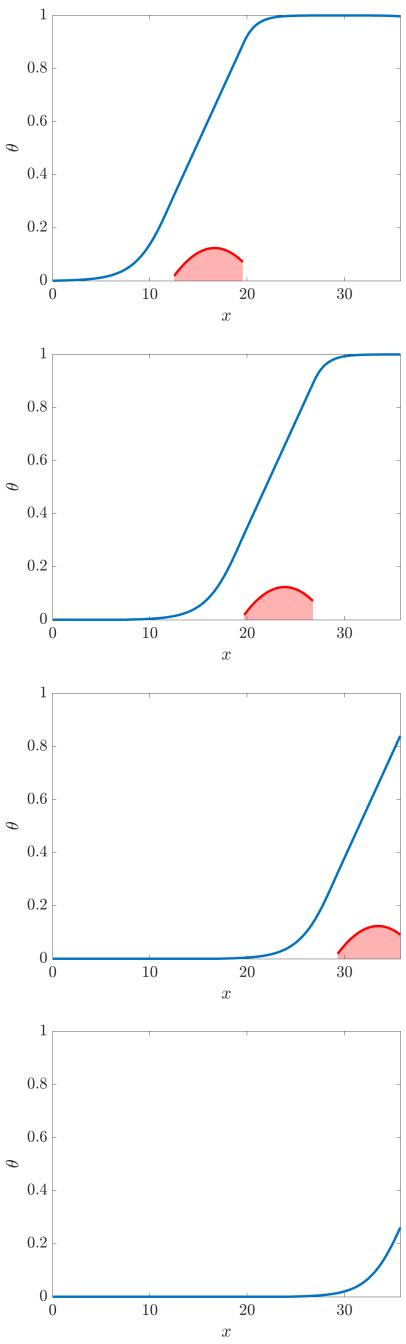


Figure 10: An example of a reversed travelling wave: in blue, the density of fishes, in red, the density of fishermen

References

[1] Alberto Bressan, Maria Teresa Chiri, and Najmeh Salehi. On the optimal control of propagation fronts. *Mathematical Models and Methods in Applied Sciences*, 32(06):1109–1140, 2022.

[2] Alberto Bressan and Wen Shen. Measure-valued solutions to a harvesting game with several players. In *Advances in Dynamic Games: Theory, Applications, and Numerical Methods for Differential and Stochastic Games*, pages 399–423. Springer, 2010.

[3] Alberto Bressan and Vasile Staicu. On the competitive harvesting of marine resources. *SIAM Journal on Control and Optimization*, 57(6):3961–3984, 2019.

[4] Paul C. Fife and J. B. McLeod. The approach of solutions of nonlinear diffusion equations to travelling front solutions. *Archive for Rational Mechanics and Analysis*, 65(4):335–361, dec 1977.

[5] R. A. Fisher. The wave of advances of advantageous genes. *Annals of Eugenics*, 7(4):355–369, 1937.

[6] Minyi Huang, Peter E. Caines, and Roland P. Malhamé. Large-population cost-coupled LQG problems with nonuniform agents: individual-mass behavior and decentralized ϵ-Nash equilibria. *IEEE Trans. Automat. Control*, 52(9):1560–1571, 2007.

[7] Minyi Huang, Roland P. Malhamé, and Peter E. Caines. Large population stochastic dynamic games: closed-loop McKean-Vlasov systems and the Nash certainty equivalence principle. *Commun. Inf. Syst.*, 6(3):221–251, 2006.

[8] Ziad Kobeissi, Idriss Mazari-Fouquer, and Domenec Ruiz-Balet. The tragedy of the commons: A mean-field game approach to the reversal of travelling waves, 2023.

[9] A. Kolmogorov, I. Pretrovski, and N. Piskounov. étude de l'équation de la diffusion avec croissance de la quantité de matière et son application à un problème biologique. *Moscow University Bulletin of Mathematics*, 1:1–25, 1937.

[10] Jean-Michel Lasry and Pierre-Louis Lions. Jeux à champ moyen. I. Le cas stationnaire. *C. R. Math. Acad. Sci. Paris*, 343(9):619–625, 2006.

[11] Jean-Michel Lasry and Pierre-Louis Lions. Jeux à champ moyen. II. Horizon fini et contrôle optimal. *C. R. Math. Acad. Sci. Paris*, 343(10):679–684, 2006.

[12] Jean-Michel Lasry and Pierre-Louis Lions. Mean field games. *Jpn. J. Math.*, 2(1):229–260, 2007.

[13] Idriss Mazari and Domènec Ruiz-Balet. Spatial ecology, optimal control and game theoretical fishing problems. *Journal of Mathematical Biology*, 85(5), oct 2022.

[14] John Nash. Non-cooperative games. *The Annals of Mathematics*, 54(2):286, September 1951.

European Teams in Mathematical Biology

In each issue we present some of the European groups working in the field of mathematical biology. We try to cover different subjects and geography. If you think some group should be portrayed in the next issue, please let us know. Enjoy!

Unit of Theoretical Chronobiology - Université Libre de Bruxelles (ULB)

The Unit of Theoretical Chronobiology (UTC) was founded by Albert Goldbeter in the early nineties. Our research focuses on the spatio-temporal organization of living systems. We study, through computational modeling, the molecular mechanisms underlying oscillatory phenomena in biochemical, genetic, and signalling networks (biological rhythms) and cellular decision making (cell differentiation). The models we build are closely based on experimental data and typically take the form of nonlinear differential equations which we analyze by means of numerical methods or stochastic approaches. Models help to unravel the design principles of biological networks and their role in cell physiology, and lead to predictions that can be tested experimentally. In 2023 the group was composed of 3 PI, 2 honorary professors, 1 post-doc, 1 visiting researcher and 5 PhD students. Main research axes are described below, followed by a brief presentation of the group members.

Calcium dynamics
Calcium is a signalling ion used by most cell types to convey information from the stimulus to its physiological response. Much of this information is encoded in the spatio-temporal characteristics of the calcium signal, which often takes the form of oscillations. To decipher the mechanistic origin of these highly organized calcium changes, computational models are widely used. They allow us to address questions related to the transition from stochastic, localized signals to regular, global calcium changes; the link between calcium oscillations and mitochondrial metabolism; the activation of the Unfolded Protein Response in response to a calcium decrease in the endoplasmic reticulum; or the dysregulation of calcium signalling during the development of diseases such as cancer or Alzheimer's disease. Most of these studies are performed in close collaboration with experimental labs, among which the lab of Laurent Combettes in the Integrative Biology Institute (Paris-Saclay, France).

Cell specification in early development
During embryonic development, cells from a population of common progenitors evolve towards different fates characterized by distinct levels of specific transcription factors, a process known as cell differentiation. This evolution is governed by gene regulatory networks modulated by intercellular signalling. In the group, we focus on two differentiation processes associated with early development. During pre-implantation murine embryogenesis, cells from the inner cell mass (ICM) can be specified in epiblast (Epi, future embryonic tissues, from which embryonic stem cells are derived) or primitive endoderm (PrE, future placenta and other extra-embryonic tissues). The specification is controlled by a gene regulatory network, involving Erk signalling through extracellular Fgf4. In collaboration with the lab of Claire Chazaud (University of Clermont-Ferrand, France), we developed a model describing the specification process in terms of tristability (coexistence between three stable steady states) in the gene regulatory network. We use bifurcation diagrams and numerical simulations, both deterministic and stochastic, to investigate the mechanism that controls the cell specification process. We also analyse scRNA-seq data to get insight into the initial source of heterogeneity triggering cell differentiation.
A second line of research pertains to ascidians, which are marine invertebrate chordates belonging to a sister group of vertebrates. Uniquely among chordate models, the embryogenesis of ascidians proceeds with an invariant cell division pattern, such that cellular configurations and cell cycle progression are quasi-invariant. During the initial step of ascidian neural induction, precisely 2 out of a total of 8 anterior ectoderm cells are selected as neural precursors at the 32-cell stage. This choice is dictated by the cell surface contacts with other, FGF-expressing cells. In collaboration with the lab of Hitoyoshi Yasuo (Oceanographic Lab of Villefranche-sur-mer, France), we use computational modelling to understand how the observed switch-like pattern of expression of the neural Otx gene can be explained by the embryonic morphology. We also investigate if this mechanism allows the embryo to optimise the transfer of information.

Circadian clocks
Circadian oscillations originate at the cellular level from interlocked gene regulatory feedback loops. We develop computational models to unravel the molecular mechanism underlying circadian oscillations in gene expression in plants and in mammals, to study

their entrainment by light-dark cycles, and to investigate the synchronization resulting from inter-cellular coupling. These models provide theoretical bases to understand the causes of sleep disorders and the impact of jet lag on the sleep-wake cycle. We also study the dynamics of clock-regulated metabolic processes with a particular focus on the interplay between the circadian clock and glucose homeostasis. These models help to understand the effect of ill-timed feeding in the onset of obesity and diabetes.

Cell cycle
In mammals, the progression of the cell through the different phases of the cell division cycle is governed by a complex network of cyclin-dependent kinases, which are sequentially activated. By means of detailed mathematical models we study the regulatory logic of this network, its dysregulation in case of cancer, and its control by the circadian clock. We also aim at using these models to guide the development of chronopharmacological protocols to optimize the effect of anti-cancer drugs.

Dynamics of microbial communities
The composition of microbial communities is dynamic. The relative abundances of species within a community vary with time and change with environmental conditions. In collaboration with the group of Karoline Faust (KU Leuven, Belgium), we develop models to study the response of such microbial communities to environmental perturbations or to explain the emergence of various community types. Experimentally-based models further allow us to back up the time-dependent nutrient-mediated interactions between selected bacterial species grown in co-cultures.

Generic properties of regulatory networks
Considering the importance of the notion of feedback circuits in biological systems, we address the general question of the relation between the logical structure of a network and its main qualitative dynamical properties. Combining dynamical systems theory and Boolean or multileveled logic, we study the generic properties of typical regulatory modules, i.e. properties relying on the combination of feedback circuits. This approach leads to the formulation of general laws concerning the relation between structure, dynamics and function in regulatory networks. The development of new concepts such as logical bifurcation diagrams enables us to identify key control points in such networks. In the framework of the model of cell specification developed in the group we apply our logical bifurcation diagrams concept for a systematic characterization of the asymptotic behaviors compatible with a given set of regulatory interactions.

STAFF MEMBERS

Geneviève Dupont is a theoretical chemist. Her PhD, performed under the supervision of Albert Goldbeter, focussed on modelling calcium oscillations and waves. She then moved to Cambridge (UK) to perform a post-doctoral stay in the lab of Michael Berridge, for an experimental study of the mechanism of calcium oscillations observed at fertilisation in mouse oocytes. Together with James Sneyd, Martin Falcke and Vivien Kirk, she is author of the book entitled "Models of calcium signalling". Besides pursuing her research on calcium signalling, she also works on the mechanisms underlying cell specification in early development in mammals and in ascidians. She is Research Director at the Belgian National Fund for Scientific Research" (FRS-FNRS).

Didier Gonze trained as a chemist, he turned to computational biology during his PhD thesis undertaken under the supervision of Albert Goldbeter. During his post-doctoral stay in the group of Hanspeter Herzel in Berlin (Germany), he focused on the synchronization of circadian oscillators. Now, as Associate Professor, he develops ODE-based and stochastic models for circadian clocks, for the cell cycle and its control by the circadian clock, and for cell differentiation. In collaboration with Karoline Faust (KU Leuven), he also contributes to studies on bacterial dynamics.

Jean-Christophe Leloup studied chemistry. His PhD, under the supervision of Albert Goldbeter, focused on modeling the circadian clock of Drosophila. He then moved to the CNRS of Gif-sur-Yvette (France) to perform a post-doctoral stay in the lab of François Rouyer for an experimental study of the mechanisms that underlie the perturbation of the circadian rhythms in Drosophila by light pulses. He then returned to Brussels and focused his research on modeling the circadian clock in mammals and studying

the physiological impacts of perturbations of these rhythms. He also investigated the circadian mechanism in plants.

Albert Goldbeter studied chemistry. After his PhD in the group of Ilya Prigogine, he performed one post-doctoral stay at the Weizmann Institute of Science (Israel), followed by a research stay at the University of California (Berkeley, US) a few years later. He played a pioneering role in the field of modelling cellular rhythms such as glycolytic oscillations, cAMP oscillations in Dictyostelium amoebae, calcium oscillations, cell cycle, circadian rhythms, etc. Together with D. Koshland, he also predicted the phenomenon of "zero order ultrasensitivity", which was later validated experimentally. He is author or co-author of about 220 research papers, and 3 books. Among these, his 1996 book entitled "Biochemical Oscillations and Cellular Rhythms. The molecular bases of periodic and chaotic behaviour" has become a key reference in the field.

Marcelle Kaufman, trained as a chemist, started her research in the field of pattern formation and multiple bifurcations in reaction-diffusion systems. Later on she shifted toward Theoretical Biology, and in particular Theoretical Immunology, focusing on how regulatory mechanisms at various scales (from molecular and cellular to intercellular) act synergistically or competitively to achieve high degrees of regulation. She directed the unit of Theoretical and Computational Biology. Some specific research themes include T cell signalling and development, neural development and sex determination in Drosophila, oscillations in the p53-mdm2 network involved in the control of the proliferation of abnormal cells in mammals.

Aurore Woller is physicist by training (ULB). She did her PhD under the supervision of Marc Lefranc in Lille (France) where she studied the interplay between the circadian clock and metabolism. She then did a first post-doc in Paris where she studied bacterial dynamics with Claude Loverdo and a second post-doc in the group of Uri Alon in Israel where she focused on the glucose-insulin-beta cell circuit and its impairement leading to (pre)diabetes. Back as a senior post-doc at UTC, she currently investigates the coupling between the circadian clock and the regulation of glucose.

Marcelo Ramirez obtained his PhD at ULB in 2004, where he worked under the supervision of JL Deneubourg on nonlinear systems and the study of synchronization in light-controlled oscillators. Between 2010 and 2012, he got a post-doc position in the group of Prof. J. Kurths at HU in Berlin. He has been a lecturer and researcher at the Instituto de Investigaciones Físicas of the University of La Paz (Bolivia) and a professor since 2019. His research interests encompass nonlinear dynamics, complex networks, self-organization, synchronization, and statistical mechanics. He is currently a scientific collaborator at UTC, focusing on the entrainment and control of chaotic systems.

Mehrosh Ahmed studied Bioinformatics at the University of Islamabad, in Pakistan. She is starting a new PhD project on the role of calcium signalling in the development of glioblastoma, one of the most aggressive brain tumour.

Rossana Bettoni got her Master in Material Science and Engineering at the University of Padova in Italy. She also followed courses in Biology at the Institut Pasteur and Institut Curie in Paris. After her MA project in cellular biology, she joined the group to perform a PhD on modelling cell differentiation in the ascidian embryo. Her thesis is co-supervised by Sophie de Buyl (VUB, Brussels).

Roberto Ornelas-Guevara graduated as a Processes Engineer at the UAM in Mexico. He joined the group as a PhD student, to model calcium dynamics with a special emphasis on sophisticated spatially-resolved models. He also collaborates on a project aiming at deciphering the relation between Ca2+ changes in the endoplasmic reticulum and the adaptative stress response known as the Unfolded Protein Response.

Francisco Prista von Bonhorst obtained a master's in physics in 2019 and a complementary master's in bioinformatics and modeling in 2020 (ULB). During his bioinformatics master, he worked on modeling calcium dynamics, and its dysregulation during Alzheimer's disease. He then joined the lab as a PhD student where he analyses single cell RT-qPCR and RNA-seq data in order to feed and refine the mathematical models currently developed in the group related to cell specification during early embryonic development in mammals.

Corentin Robert obtained his master in chemistry in 2020 (ULB). He then joined the lab as a PhD student where he studies through numerical simulations, bifurcation analyses, and stochastic approaches molecular mechanisms ensuring robust cell differentiation. His thesis is co-supervised by Yannick De Decker (ULB).

For more information, please visit:
`https://utc.ulb.be`

ECMTB 2024

July 22-26 - Toledo, Spain

With great pleasure, we extend our warmest greetings to each of you as we come together to celebrate the **13th European Conference on Mathematical and Theoretical Biology!**

Organized under the banner of the European Society for Mathematical and Theoretical Biology (ESMTB), this conference represents a new step in the series of events that have been advancing the intersection of biology and mathematics. The ESMTB, as a learned society, has been at the forefront of nurturing and promoting theoretical approaches and mathematical tools in the realms of biology and medicine across Europe and beyond.

We are delighted to welcome all of you, esteemed researchers, scholars, and enthusiasts, to join us in this intellectual endeavor. The ECMTB conferences represent the pinnacle of our community's collective efforts, providing a platform for sharing research, fostering collaboration, and igniting new ideas. Your presence here not only enriches this event, but also contributes to the larger purpose of driving scientific progress and innovation.

As we embark on this journey together, we encourage you to actively participate by sending proposals for minisymposia, contributed talks, or posters. Your contributions will play a vital role in shaping the diversity and richness of the conference program, furthering our collective knowledge and exploration at the interface of mathematics and biology.

Once again, a warm welcome to all of you! Let us make the 13th European Conference on Mathematical and Theoretical Biology an unforgettable gathering that inspires us to reach new heights in our understanding of this fascinating discipline.

Ellen Baake
Víctor Manuel Pérez García

`https://ecmtb2024.org`

Deadline for mini-symposia : January 31, 2024

ESMTB
European Society for Mathematical and Theoretical Biology

Call for the organisation of ECMTB 2026

This is a call to submit a proposal for the organisation of ECMTB in 2026. Hosting an ECMTB conference is a great opportunity to increase visibility of the local mathematical and theoretical biology community.

The guidelines for proposals can be found here:

`https://www.esmtb.org/resources/Documents/guidelines_proposal_ECMTB_2024.pdf`

The deadline for submission is **May 1, 2024**.

Travel grants report

Fifteen travel grants were awarded in 2023 to help predominantly young researchers visit conferences, workshops or summer schools. About 4550 EUR was provided in total in this support. We have now received travel reports from some of the awardees and are glad to share their experience with you. The year 2023, wedged in between two ESMTB conferences, obviously allowed a rich spectrum of events in which to support participation.

All awardees emphasize the fact that reception of a travel grant helped them to participate in a meeting at all, and are very grateful for that opportunity, enabling them in-person contacts and discussions much needed for their further career. As Martina Conte puts this, "The ESMBT Travel Grant allowed me to participate in the ECCOMAS Young Investigators Conference (YIC2023) [the main purpose of which was to bring] together young researchers developing their work in all areas related to computational science and engineering and providing them with a unique environment for knowledge exchange and establishment of future scientific collaborations." Daniel Galvis, attending the SIAM Conference on Applications of Dynamical Systems (DS23) in Portland, Oregon, adds: "I am immensely grateful to the ESMTB for funding my trip to attend this inspiring conference. I learned a lot, developed projects, engaged with new friends and future collaborators, promoted my newly-minted research, and organised an inspiring minisymposium. I couldn't have done this without your support. ... Moreover, I was inspired by some of the techniques that hold promise for advancing my own research, such as uncertainty quantification in mathematical model fitting." And Ranjini Bhattacharya, visiting the 50th Annual Meeting for the Society of Mathematical Biology held at the Ohio State University, says: "This was a significant milestone for me, as it marked the first time I had the privilege of attending the conference in person. ... Being invited to speak at this session was a wonderful opportunity for me to connect with peers at similar career stages and receive valuable feedback from experts in the field ... As a young scientist, I greatly appreciated the chance to interact with fellow researchers, exchange ideas, and build valuable connections with colleagues from around the world."

Young researches, still not much anchored in a specific topic, also appreciated seeing a methodology that they use yet applied in different contexts. Going on with Martina Conte's words: "At the same time, it was very interesting to see how models and methods I use within my research can be applied to other areas, also quite far from the biomedical field, as well as how very different approaches can be used to address problems close to the ones I currently work on. In my opinion, one of the strongest aspect of the conference lies in its multidisciplinary character. In fact, it brought together people from several different fields and allowed them to expand their scientific network, getting to know many other early career researchers and having fruitful conversations with them, potentially leading to future collaboration and research studies." Multidisciplinarity is also emphasized by Joan Saldaña Meca who visited the workshop "Epidemic modelling: current challenges" at the University of Girona: "The event brought together researchers in the field of epidemics with different backgrounds (mathematicians, physicists, computer scientists, environmentalists, and biologists) who presented current problems as well as potential avenues of future research in epidemiology. The topics covered a wide range of computational and modelling issues, including, among others, the impact of non-pharmaceutical interventions and human behaviour on epidemic spreading, empirical human proximity data, non-Markovian epidemic models, inferring contact network properties from epidemiological data, and models for the spread and

control of vector-borne diseases". And Ranjini Bhattacharya adds: "Although my primary research area is mathematical oncology, this conference offered me a unique opportunity to broaden my horizons and explore other fascinating domains. I attended talks from the cell development, neuroscience, and ecology-evolution subgroups, drawing inspiration from these diverse fields and incorporating new ideas into my work."

Similarly, Giulio Lucci, visiting the European Conference on Numerical Mathematics and Advanced Applications (ENUMATH 2023) that took place at the Instituto Superior Técnico in Lisbon, Portugal, says: "I particularly appreciated the choice of the organizers to put together in the Mini-Symposium both young and expert researchers with different backgrounds: some of them concentrated on the theoretical aspects of the models, whereas others provided more detailed insights into the numerical part of their work." And Pierre Roux, attending the "Topics on Neuroscience, Collective Migration and Parameter Estimation" conference at the University of Oxford, favours discussion of also applied aspects of the contributions: "The attendees seemed to particularly appreciate that the questions featured could be from the most applied point of view to the most theoretical, some talks more centred on one side and others covering the full range."

Visiting conferences, workshops or summer schools is of course not only about research and passionate scientific discussions. It is also about life and ability to get to know new places and culture. "Having the possibility of walking around Porto, discovering the amazing Portuguese culture as well as their typical food was undoubtedly a bonus to the conference.", closes Martina Conte her report. And Pierre Roux adds: "The United Kingdom bestowed upon the conference a mildly hot weather and a fairly reasonable dose of rain, ideal for exploring the architectural treasures of the city and the green palette of the surrounding countryside.".

ESMTB Travel Support

The ESMTB provides travel support to mathematical/theoretical biology events such as meetings, conferences, workshops or schools. Support is provided only to ESMTB members, so that an applicant needs to be member at the moment of submitting the application. The maximum amount of travel support per single application is currently 350 euro. However, funding will in most cases be only partial, in order to support a greater number of applicants. In general, preference will be given to:

- applicants who have been members of the ESMTB for a longer time,
- doctoral students and post-docs, but graduate students and senior scientists may also apply,
- applicants who present a paper or poster at the attended event,
- applicants who did not receive travel support from the ESMTB before,
- applicants in conditions of economic hardship.

Details and the application form are available at `https://www.esmtb.org/Travel-Support`

Minutes of the ESMTB board meeting via videoconference

January 10, 2023, 12:00-13:35

Members present: Ellen Baake (EB), Luděk Berec (LB), Tom Britton (TB), José Antonio Carrillo (JAC), Sílvia Cuadrado (SC), Elisenda Feliu (EF), Benoît Perthame (BP), Bob Planqué (RP), Angélique Stéphanou (AS).
Invited guest: Víctor Pérez (VP).

- ECMTB 2024 Toledo: The scientific committee will be composed by 4 board members (JAC, EF, RP and SC) and 4 external members. It is proposed to invite Reinhard Bürger, Eva Loecherbach, Andrea Pugliese and Marie Rognes. VP and EB will jointly send the invitation.
- ICIAM 23 Tokio: JAC will represent ESMTB at the conference. He informs that the call for posters and minisymposia and the one for financial support have been extended. A reminder about it will be sent in the next newsletter.
  JAC also reports that ICIAM is planning to expand their number of officers (people in the executive committee). There will be elections for officers in 2023 and 2024 (two that will be replaced and two "new" ones).
- Treasury: RP informs that there have been some technical difficulties with the bank account. As a consequence, the financial administration at this moment is being kept by the treasurer and is being made effective by AS.
  The society has received from Springer the partial sponsorship for meetings and conferences corresponding to 2022.
- Agenda for 2023: The board discusses some points on the agenda for 2023 which include:
  - Select the winning paper for the Karl-Peter Hadeler prize.
  - Cooperation between the ESMTB and the SMB: The text about the collaboration of the societies is currently with the SMB board.
  - Renegotiate the contract with Springer (it will be handled by JAC, BP and EB).
  - Prepare the election for the new board members that will take place in October. An open call will be sent to all ESMTB members.
- Committee for the Karl-Peter Hadeler prize: The editors in chief of the Journal of Mathematical Biology have nominated 3 papers. It is approved by acclamation that LB, TL and BP will form the committee that will choose the winning paper.
- Communications: The present issue of the Communications is ready to go on the web page. It is decided that hard copies will be printed on offset paper as the previous time.
- Colloquium: The next talk will be given by Víctor Perez in February 22. Some speakers are suggested for the next sessions.
- European Mathematical Society: BP informs that EMS has released a new initiative consisting in creating topics within EMS to work on for four years (by creating activity around it). One of the topics is Mathematical Biology. In order to organize such a group at least 7 persons from EMS are needed. The board agrees to follow closely this initiative and possibly in the long run encourage members to participate.
- Various: BP informs that some journals of Springer have a webinar as a way to promote the journal. This could give ESTMB an alternative way to stream the colloquium by asking JMB if ever needed.

May 4, 2023, 12:00-13:15

Members present: Ellen Baake (EB), José Antonio Carrillo (JAC), Sílvia Cuadrado (SC), Elisenda Feliu (EF), Bob Planqué (RP), Angélique Stéphanou (AS), Tommaso Lorenzi (TL).
Absent (with apology): Luděk Berec (LB), Tom Britton (TB), Benoît Perthame (BP).

- E-vote decisions: Decisions taken via email since the previous meeting (January 10, 2023)

- April 20, 2023. The board agrees to give the winners of the KPH prize the possibility to make a contribution to the Communications.

- Financial situation. RP reports that the society currently has a balance of EUR 63.000 plus the surplus from ECTMB in Heidelberg.
  It has been agreed to make a lump sump payment to the ECMTB Toledo 2023 account to sponsor some activities, which will be specifically decided later. The Board agrees on the convenience of having some external administrative support, primarily for treasury tasks. EB will seek information on how this procedure can be technically carried out. It has also been decided to maintain the reduced fees as long as the financial situation allows. If the

society's financial situation worsens in the future, the travel support that was increased in 2022 will be reduced.
The possibility of creating a networking tool for biomathematicians has been discussed. RP will explore whether it can be done within the society's current website.

- Board Election. SC informs that there are currently two applications. A reminder of the call will be sent to all members.
- ECMTB in Toledo. The list of plenary speakers is almost finalized with six confirmed plenary speakers. The scientific committee is now in the process of agreeing on at least one more plenary speaker.
- Colloquium. The colloquium is running successfully. The audience has not been lower than during the pandemic. As the conference period begins the colloquium will pause for a few months and resume in autumn.

June 29, 2023, 12:00-13:30

Members present: Ellen Baake (EB), Luděk Berec (LB), Tom Britton (TB), José Antonio Carrillo (JAC), Sílvia Cuadrado (SC), Elisenda Feliu (EF), Benoît Perthame (BP), Bob Planqué (RP), Angélique Stéphanou (AS), Tommaso Lorenzi (TL).

- Board elections.

  The board discusses the upcoming elections that will take place in October 2023 in which the ESMTB members will elect four new Board members, whose period of office will run from January 2024 through December 2029.
- Web page

  The society's current website allows to create a networking tool for biomathematicians. RP will explore whether a link to the home page of members can be added.
  An item on the history of ESMTB will be included on the website.

October 27 , 2023, 13:00-14:05

Members present: Ellen Baake (EB), Luděk Berec (LB), Tom Britton (TB), Sílvia Cuadrado (SC), Elisenda Feliu (EF), Tommaso Lorenzi (TL), Benoît Perthame (BP), Bob Planqué (RP), Angélique Stéphanou (AS).

Absent (with apology): José Antonio Carrillo (JAC).

- E-vote decisions: Decisions taken via email since the previous meeting (June 29, 2023).

  September 4, 2023. The board agrees to subsidize the Toledo conference by 30.000 EUR in order to reduce the fees.
- Springer.

  On October 5, EB, JAC and BP had a meeting with Springer in order to discuss the extension of the contract between ESMTB and Springer.

  Springer aims at increasing high-quality content for JOMB. It is suggested that the Board reaches out to its members to solicit proposals for topical collections, which are pre-screened by the Board; high-quality proposals will be forwarded to Springer and the JOMB EiCs. One person in the Board will take responsibility for this process. The ESMTB board is in favor of starting this collaboration, provided that topical collections are used sparingly and are carefully selected according to high quality.
- Request of summer school funding.

  The board received a funding request for a European summer program in infectious disease modelling. The board agrees to grant it conference support and also will inform the applicants about the possibility for participants to apply for travel support.
- Board election.

  The ESMTB board election is closed and the new 4 ESMTB board members that will start their term in 2024 are: Marie Doumic, Victor Peréz, Zuzanna Szymańska and Ezio Venturino. The results of the election will be published in the next newsletter. A meeting of the present board with the new members will be scheduled in December.

December 15 , 2023, 12:00-13:25

Participants: Ellen Baake (EB), Luděk Berec (LB), Tom Britton (TB), José Antonio Carrillo (JAC), Sílvia Cuadrado (SC), Marie Doumic (MD), Elisenda Feliu (EF), Tommaso Lorenzi (TL), Víctor Pérez (VP), Benoît Perthame (BP), Bob Planqué (RP), Angélique Stéphanou (AS), Zuzanna Szymanska (ZS), Ezio Venturino (EV).

EB, LB, SC and RP are outgoing board members (2018-2023 term).

TB, JAC, EF, TL, BP and AS are continuing board members (2021-2026 term).
MD, VP, ZS and EV are incoming board members (2024-2029 term).

The incoming members were elected by electronic ballot open from September 16 to October 16 2023, https://www.esmtb.org/ESMTB-Board-elections

- The current board members report on the activities, namely the ECMTB conferences, prizes, online colloquium, travel and conference support, summer schools and educational matters, communication (webpage, newsletter, social media), administration, Communications, umbrella organizations and partner societies.
  RP (current treasurer) reports on financial matters and EB (current president) informs about the new cooperation contract with Springer about JOMB.
- Election of ESMTB board officers.
  BP, VP, ZS and AS are elected president, vice president, secretary and treasurer, respectively, by acclamation. The passage of remaining responsibilities, to be decided in the upcoming board meeting, is discussed.

  The new board of the ESMTB for 2024-2026 is therefore constituted as follows: Benoît Perthame (President), Víctor Pérez (Vice president), Zuzanna Szymanska (Secretary), Angélique Stephanou (Treasurer), Tom Britton, José A. Carrillo, Marie Doumic, Elisenda Feliu, Tommaso Lorenzi, Ezio Venturino.

Sílvia Cuadrado
ESMTB Secretary

ESMTB Online Colloquia

The ESMTB online colloquia were established to promote and facilitate scientific interactions during and after the COVID-19 pandemic. In view of the success of these recurring events, evidenced by a consistently good turnout, we decided to continue organising them.

All the details of the colloquia will be shared with the members of the ESMTB mailing list and through the dedicated page on the ESMTB website (`https://www.esmtb.org/ESMTB-online-colloquium`).

Practical information:

- *When:* last Wednesday of the month at 1pm (CET).
- *Where:* colloquia are live streamed on Zoom – the Zoom link is distributed to the members of the ESMTB mailing list.
- *After the colloquium:* colloquia are recorded (provided the speaker agrees) and a link to the recording is made available on the ESMTB webpage.

2023 speakers :

- Víctor Manuel Pérez García (University of Castilla-La Mancha), Mathematical oncology for the clinics: predicting cancer's behavior and optimizing treatments
- Idriss Mazari and Domenec Ruiz-Balet, Spatial ecology, harvesting and game theory: a qualitative approach
- Vincent Calvez (CNRS), Modeling crowd of bacteria
- Paul Jenkins (Warwick), Using the Wright-Fisher diffusion for statistical inference of evolution

Educational corner

by Luděk Berec

This time I would like to share with you a few topics that have recently attracted my attention and interest (and apologize if you know them or find them not that interesting).

Reed-Frost epidemic model

I am sure every math epidemiologist today knows this model that historically inspired theoretical thinking in infection dynamics and affected much work since it has become known. Interestingly, Lowell Reed, a biostatistician, and Wade Hampton Frost, an epidemiologist, did not develop this model for getting a scientific inquiry, but rather as to explain fundamental epidemic principles in their lectures at the Johns Hopkins University in Baltimore, in times when epidemiology as an autonomous discipline has begun to constitute. The model itself is very simple. Assuming S_t susceptible, I_t infectious and R_t recovered individuals at time t, time step corresponding to the length of infectious period, probability p of infection transmission upon a contact, and that anyone during each time step meets everyone, one can write the following equations for the system state at time $t+1$:

$$\begin{aligned} S_{t+1} &= S_t - B_t, \\ I_{t+1} &= B_t, \\ R_{t+1} &= I_t, \end{aligned}$$

where B_t is the number of new cases at time step t. It is easy to realize that when considered stochastically, B_t is a binomially distributed random variable with the parameters S_t and $P_t = 1-(1-p)^{I_t}$, which for a mean-field model version can be replaced by $B_t = (1-(1-p)^{I_t})\, S_t \approx p\, S_t\, I_t$.

What I have recently learned is a mechanical model analogue or, if you want, a Reed-Frost mechanistic model, apparently serving as an outstanding didactic tool to demonstrate the basic assumptions behind its mathematical version and as an imaginative connecting link between math and reality (Engelmann 2021). The mechanistic model consists of a box with marbles of different colors and a linear trough. Put N marbles into the box, one red (infectious) and the rest green (susceptible) – an initial state, shake the box (random mixing of the population), and spill the balls into the trough. Now observe the balls in the trough, replace susceptible green balls by infectious red ones if the former have a red ball just next to themselves, and then replace original red balls by blue ones (recovered). This sequence of events forms one time step. Clearly, ball color dynamics obeys the above model, yet with slightly different formula for B_t. Now, the probability that a susceptible ball has an infectious one to the right or to the left is $I_t/(N-1)$, for N representing the total number of balls present, and hence the probability that it gets infected at time step t is $P_t = 1-(1-I_t/(N-1))^2$. Therefore, B_t is now binomially distributed with the parameters S_t and P_t, which for the mean-field model version can be represented as $B_t = (1-(1-I_t/(N-1))^2)\, S_t \approx (2/(N-1))\, S_t\, I_t$; p in the above model now corresponds to $2/(N-1)$. I use this mechanistic model now to demonstrate epidemic dynamics to (potential) students virgin to the subject. This mechanistic model can be further modified to account for features such as exposed class of individuals or vaccination. Much more on how the Reed-Frost model, and its authors, influenced epidemiology is given in Engelmann (2021).

Engelmann L (2021) A box, a trough and marbles: How the Reed-Frost epidemic theory shaped epidemiological reasoning in the 20th century. History and Philosophy of the Life Science 43: 105

The way of plague transmission in medieval times

The way of plague transmission we commonly read about or are taught is linked to rats. An infected rat or another rodent is brought to a city full of (susceptible) rats. Rat fleas then transmit the bacteria *Yersinia pestis* between the rats and if infected rats die, fleas, in search of another host individual, may jump onto humans. Humans here are a dead end for *Y. pestis*, having rats (and many other rodent species in the wild) as reservoir species. The way of transmission thus resembles the Lyme disease, for example, albeit with much higher intensity due to much closer relationship of rats and humans as opposed to forest vertebrates and humans. We are also well aware of the pneumonic form of plague, where pathogens are transmitted directly through inhalation of infected droplets produced through coughing by infectious persons, technically resembling common respiratory infections.

Perhaps surprisingly, written medieval sources are frequently silent about rat overabundance at times of plague epidemics. On the other hand, they often report about prohibition of buying and selling second-hand clothes. Why is that? One reason could be the miasma theory, originating in China, advanced in Europe by Hippocrates, stating that it is a kind of bad air emanating from decay of organic matter and in fact surrounding infectious persons that is responsible for disease transmission, and persisting until the germ theory has eventually replaced it by the end of 19th century.

In their paper, Dean et al. (2018) propose another explanation: while the plague epidemic necessarily starts with rats and rat fleas, soon human fleas and lice become infected, too, and transmit the infection directly between people, thus resembling e.g. mosquitoes transmitting yellow fever in urban settings. Could this transmission pathway explain at least some of the Second plague pandemic outbreaks? This is precisely the question Dean et al. (2018) addressed. And even though this idea is viewed as controversial by some and may eventually turn to be rejected, I see this study as a very nice piece of modeling work, more than clearly justifying the use of models in situations where we seek explanations of past events.

So, Dean et al. (2018) proposed three transmission hypotheses, rat-flea-human, direct-pneumonic and human-ectoparasite, developed a mathematical model for each, and estimated parameters of each model using observed data and Bayesian inference for nine medieval urban plague epidemics between 1348 and 1813. Model comparison was then performed using the Bayesian information criterion (BIC) and the model with the lowest BIC considered as the preferred one. For seven outbreaks, the human-ectoparasite model had by far the lowest BIC, while in the remaining two cities one of the other models could not be excluded. But Dean et al. (2018) went one step further. They applied their models also to three Third plague pandemic outbreaks for which the transmission route was known. In all these cases, the 'correct' model was selected. Obviously, no math model can provide any conclusive evidence on any such question, but generates plausible hypotheses that when combined with other pieces of evidence may contribute to developing a sound theory.

Dean KR, Krauer F, Walløe L, Lingjærde OC, Bramanti B, Stenseth NC, Schmid BV (2018) Human ectoparasites and the spread of plague in Europe during the Second Pandemic. PNAS 115: 1304-1309

Grey and red squirrels in Europe

Many mathematical ecologists sooner or later come across what might be one of the best documented cases of competition and subsequent replacement of a native species by an introduced one. Grey squirrels, initially introduced to England from North America in 1876 as an ornamental species, sooner or later escaped or were released into the wild and since then they spread and colonise much of mainland, due to their competitive advantage evicting and causing decline of native red squirrel. Later, grey squirrels were introduced also to the continental Europe, to Italy, with analogous consequences. Much modeling work has been done to understand this competition and to attempt to break or at least slow down grey squirrel expansion.

Later, it was found that the interaction between red and grey squirrels is modulated by the parapoxvirus, highly pathogenic in the red squirrels and with actually no detectable effect on the grey one (Tompkins et al. 2002). Modeling showed that this modulation dramatically speeded up the rate of competitive replacement (Tompkins et al. 2003). Recently, pine martens have been found to predate on grey squirrels more than on red ones. Exact reasons for this apparent preference are still not completely clear, ranging from larger size and overabundance of grey squirrels up to an ability of red ones to 'smell' pine martens from larger distances and thus having more time to escape. A recent modeling study by Slade et al. (2023) suggests that pine marten may reverse the outcome of squirrel competition and extirpate the parapoxvirus. I am sure a lot of room remains for modeling studies in this direction, and look forward to reading some once they appear.

Slade A, White A, Lurz PWW, Shuttleworth C, Tosh DG, Twining JP (2023) Indirect effects of pine marten recovery result in benefits to native prey through suppression of an invasive species and a shared pathogen. Ecological Modelling 476: 110216

Tompkins DM, Sainsbury AW, Nettleton P, Buxton D, Gurnell J (2002) Parapoxvirus causes a deleterious disease in red squirrels associated with UK population declines, Proceedings B (2002) 269, 529–533

Tompkins DM, White AM, Boots M (2003) Ecological replacement of native red squirrels by invasive greys driven by disease. Ecology Letters 6: 189–196

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