Interdisciplinary Workshop on:

Critical phenomena and challenges emerging from dormancy

18th and 19th of December 2023

Prof. Dr. Jay Lennon,
Indiana University Bloomington

Principles of seed banks: complexity emerging from dormancy

Across the tree of life, populations have evolved the capacity to contend with suboptimal conditions by engaging in dormancy, whereby individuals enter a reversible state of reduced metabolic activity. The resulting seed banks are complex, storing information and imparting memory that gives rise to multi-scale structures and networks spanning collections of cells to entire ecosystems. In this introductory talk, I will discuss the fundamental attributes and emergent phenomena associated with dormancy and seed banks, with the vision for a unifying and mathematically based framework that can address problems in the life sciences, ranging from global change to cancer biology

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Maite Wilke Berenguer,
Humboldt University of Berlin

Coalescent models for dormancy and seed banks

This talk is a brief introduction to different coalescents modelling dormancy and seed banks. Starting out from the Kingman coalescent as the standard model for the genealogy of a population without dormancy, we consider the cases of a weak and a strong seed bank, including simultaneous switching in the latter (i.e. the effect of a positive fraction of the population jointly moving in and out of dormancy) as well as the ancient ancestral lines process. The focus is on explaining the different regimes of dormancy times corresponding to each coalescent. We will characterize the differences through key behaviour like the time to the most recent common ancestor or the property of coming down from infinity.

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Prof. Dr. Adrian Gonzales Casanova,
University of California, Berkeley

Effects of Latency in Population Genetics

In this presentation, we will examine some of the mathematical and biological consequences of latency. In the biological context, we will investigate how randomness in the Lag Phase can influence the genealogy of populations during sequential sampling, as well as discuss a model suggesting that dormancy plays a role in speciation. From a mathematical perspective, we will introduce the seed bank random graph and the seed bank lookdown model, and highlight their connections to Fractional Brownian motion and multidimensional diffusions conditioned on fixation.

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Dr. Appoline Louvet,
University of Bath

Dormancy in urban ecosystems: the example of urban tree bases

In this talk, we investigate this question through the lens of dormancy. We introduce a simple stochastic model to describe the presence/absence of plants in urban tree bases, taking into account low-distance dispersal and the potential presence of a seed bank in the soil. We show how this model is associated to a "metric" of the extinction risk for the plant metapopulation, that we apply to a dataset of yearly floristic inventories in 1324 tree bases in Paris, France. Our results show that dormancy makes it possible for plant species to survive and spread through urban tree bases despite high local extinction probabilities. Moreover, taking into account the potential presence of a seed bank when performing inference allows us to identify other biological traits associated to the ability to yse urban tree bases as ecological corridors.

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Dr. Franz Baumdicker,
Eberhard Karls Universität Tübingen

Genome-wide linkage due to clonal reproduction and other challenges for the analysis of dormancy in bacterial populations

Analyzing dormancy in populations with no or low recombination, such as bacteria and cancer poses significant challenges. Particularly genome-wide linkage resulting from clonal reproduction. As an example this talk delves into two critical aspects influencing the analysis of bacterial populations that are also relevant for the analysis of dormancy: Sampling bias in bacterial strain samples sourced from public databases and the evolution of evolutionary rates that are determined by a modifier locus.
Firstly, we investigate the impact of sampling bias on the analysis of various population properties. As databases grow, oversampling becomes a pertinent issue, influencing the reliability of conclusions drawn from the data. We have developed a coalescent theory based method to detect sampling bias in samples of bacterial strains and I will highlight how strong this effect is in the collection of whole bacterial genomes in the NCBI database.
Secondly, we explore the evolution of evolutionary rates and its implications for optimizing dormancy transition rates and mutation rates in bacterial populations. By examining the evolution of of a modifier locus on mutation rates, we show that the principles of population genetics and the canonical equation of adaptive dynamics can be combined to identify the forces that shape evolutionary rates. While our focus has primarily been on mutation rates, we discuss the potential applicability of these findings to dormancy transition rates.

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Prof. Dr. Ann Zeuner, Dr. Federica Francescangeli
Department of Oncology and Molecular Medicine, National Institute of Health, Italy

Cancer dormancy: a great challenge for scientists, patients and doctors

In industrialized countries, approximately 5,5% of the population lives with a previous diagnosis of cancer. This percentage is going to increase in the next years as cancer cases are increasing steeply, with a 2,4% increase from 2019 to 2022. As solid tumors have been shown to disseminate cells at a very early stage, it is expected that the large majority of people with a previous diagnosis of cancer, even if they underwent successful treatments, carry tumor cells in various tissues and organs. Such cells are usually found in a state of dormancy and are unaffected by anticancer therapies. After a variable period of time (that, in breast cancer, has been shown to extend up to 32 years from diagnosis), dormant cancer cells can reactivate to generate a new and often more aggressive tumor at the primary location or in metastatic sites. In addition, dormant cancer cells can be found in untreated tumors and in tumors undergoing chemo-radiotherapy, where they constitute the prevalent population and are responsible for therapy resistance. Thus, dormant cancer cells represent at the same time a unique biological system (characterized by extreme longevity and resilience) and a great challenge for patients, health professionals and national health systems. In our presentation we will illustrate the characteristics of dormant cancer cells (including relatively unexplored aspects, such as epigenetic memory, dynamicity and depth of the dormant state) and their role in tumor evolution. We will discuss the implications of dormancy for the success of cancer treatment, in terms either of eradication or chronicization of the disease. Finally, we'll highlight the need of a paradigm shift in both theoretical and clinical approaches that takes into consideration the central role of the tumor microenvironment in the establishment, maintenance and breakdown of tumor dormancy.

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Joel S. Brown, PhD,
Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida, USA

The evolutionary ecology of dormancy in nature and in cancer

"I don't think it means what you think it means" from *Princess Bride.* In nature beyond cancer, dormancy generally denotes a metabolic state or life-history state that has all of the following: 1) is non-reproductive, 2) does little to no feeding, 3) has a reduced metabolic rate, and 4) more resistant than feeding or reproductive states to physical harshness or predation. When used in the field of cancer, dormancy rarely imagines a cancer cell exhibiting all these properties simultaneously. The term has become entrenched in the cancer literature referring to reversible cell states. "Dormant" cancer cells may be more resistant to therapy, immune attack, Ph, hypoxia, or resource limitations while continuing to have a high or even higher metabolism, and active nutrient uptake. In nature dormancy can be simply a shift in metabolism such as hibernation in bears or brumation in turtles. Dormancy can entail an entirely different life history state such as seed dormancy or sporulation in bacteria. Cancer dormancy does exhibit some unique states such as polyaneuplid cancer cells, persister cells or giant cancer cells, but the continuum in cancer occupies a narrow portion of the fill continuum seen in the rest of nature. However, through the conceptual and modelling lens of evolutionary ecology there is much opportunity for intellectual cross-fertilization. For, regardless of the term, natural selection universally favors behaviors, physiologies and life-history states that permit an organism to bet-hedge, ride-out unfavorable times and places, face stochastic or predictable stressors and catastrophes.

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Dr. Anna Kraut,
University of Minnesota Twin Cities

Mathematical models for dormancy and therapy evasion in cancer

Therapy evasion, often caused by tumor cell heterogeneity, is a major challenge in current oncology. Cancer cell dormancy plays an important role in this context since many treatment strategies target the cancer cells' reproduction pathways, which are down-regulated in dormant cells, making treatment ineffective. The underlying mechanisms of cancer cell dormancy - and even a precise definition of cell dormancy itself - are complex and an abstract study using mathematical models can be helpful in analyzing the resulting population-level dynamics and identifying the most important scenarios and mechanisms.
In this talk, I present an idealized mathematical individual-based model for cancer cell dormancy. We focus on the short-term effects of both spontaneous and drug-induced dormancy, which can lead to therapy failure even for small proportions of dormant cells. With the optimization goals of shrinking the tumor size and avoiding mutations that result in permanent treatment resistance, we compare a range of treatment strategies. We study different dosing protocols under constraints on the total drug dose and including multi-drug approaches that aim to specifically target the dormant cells and either keep them in a dormant state or revert them back to their active (drug-sensitive) form.
The presented results are from joint work with Jochen Blath, Tobias Paul and András Tóbiás.

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Herr Manuel Esser
University of Bonn

Dormancy in fitness valleys and changing environment

Often, mutations are unbeneficial events meaning that fitness decreases. But accumulating several mutations might lead to an advantage. This is what describes a fitness valley. However, larger individual fitness could also mean larger splitting rates of a single cell line in e.g. a human body, which is a phenomenon related to cancer emerge.

In our work we analyse this in the context of stochastic individual-based models. The typical evolutionary behaviour can be studied by looking at limits of large populations and rare mutations. While early works have shown a separation of time scales of ecology and evolution, younger articles give contributions to elaborate a broader picture of evolution in terms of a multi-scale analysis on general finite trait graphs also including fitness valleys and the expected time for a crossing.

To depict repeating changes of the environment, all of the model parameters vary over time as piecewise constant and periodic functions, on an intermediate time scale between those of stabilization of the resident population (fast) and exponential growth of mutants (slow). This can biologically interpreted as the influence of seasons or , more practically, the deviation of drug concentration during medical treatment.

Bringing together fitness valleys and changing environments already brought us to some interesting behaviour. Going beyond it seems to be really exiting to also include the possibility of dormancy, because of its big difference on key quantities e.g. equilibrium size, invasion fitness/probability, effective growth rates, etc. One aim is to understand how changing environments and dormancy interact and what is the joint impact on evolution.
Most of this is work of an ongoing collaboration with Anna Kraut.

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Dr. Nathan Wisnoski,
Mississippi State University

The spatial ecology of dormancy in multispecies communities

Dormancy is evolutionarily advantageous in variable environments because it reduces population declines during suboptimal times and enables populations to rebound during favorable times. In ecological communities containing multiple species, dormancy can promote coexistence if it allows different species to be favored at different times. While these effects of dormancy on biodiversity have been well studied at local spatial scales, they overlook the broader spatial context of communities in the landscape. Local communities are connected to one another through the process of dispersal, forming a metacommunity. Dispersal is a fundamental process influencing the composition of local communities and the maintenance of biodiversity in metacommunities. In addition to dispersal, dormancy can have a multitude of effects on biodiversity and community dynamics at different spatial scales. In certain conditions, dormancy can substitute for dispersal (e.g., maintaining local and regional diversity when dispersal is limiting). In other cases, dormancy could amplify the effects of dispersal by modify dispersal rates or the spatial structure of seed banks. I will provide an overview of how multispecies communities can be influenced by dispersal and dormancy. In particular, I will demonstrate how dormancy may be particularly important for maintaining biodiversity and promoting stability at large spatial scales in disturbed landscapes consistent with anthropogenic change.

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Dr. András Tobiás,
Budapest University of Technology and Economics

Invasion and fixation of microbial dormancy traits in models of stochastic population dynamics

Microbial dormancy is an evolutionary trait that has emerged independently at various positions across the tree of life. It describes the ability of a microorganism to switch to a metabolically inactive state that can withstand unfavorable conditions. However, maintaining such a trait requires additional resources that could otherwise be used to increase e.g. reproductive rates. In this paper, we aim to gain a basic understanding under which conditions maintaining a seed bank of dormant individuals provides a "fitness advantage" when facing resource limitations and competition for resources among individuals (in an otherwise stable environment). In particular, we wish to understand when an individual with a "dormancy trait" can invade a resident population lacking this trait despite having a lower reproduction rate than the residents.
To this end, we follow a stochastic individual-based approach employing birth-and-death processes, where dormancy is triggered by competitive pressure for resources. In the large-population limit, we identify a necessary and sufficient condition under which a complete invasion of mutants has a positive probability. Further, we explicitly determine the limiting probability of invasion and the asymptotic time to fixation of mutants in the case of a successful invasion.
If time permits, we also discuss further kinds of dormancy traits in recently introduced models of stochastic population dynamics, such as contact-mediated host dormancy in microbial host-virus models. The content of this talk is based on joint work with Jochen Blath (Goethe-Universität Frankfurt).

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Herr Tobias Paul,
Humbold-Universität Berlin

The impact of dormancy on speciation and the species abundance distribution

This talk focuses on the role of dormancy on speciation and species diversity: In the first part of the talk we investigate an adaptive dynamics model that was used by Diekmann and Doebeli (1999) to demonstrate sympatric speciation which is a mode of speciation which does not require geographic separation. We will show that the introduction of a competition-induced dormancy mechanism may increase the parameter ranges for sympatric speciation and therefore support the diversification. In addition, we will consider other measures which could be influenced by dormancy such as the speed of adaptation and the (genetic) distance in trait space between species. The second part then discusses the impact of dormancy on the species abundance distribution (SAD) which is a measure of ecological diversity. Using the approach employed by Hubbell (2001) in his unified neutral theory of biodiversity, we use coalescent models with a strong or weak seed bank effect to understand how dormancy may affect the shape of the SAD."

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Andreas Geven
Friedrich-Alexander-Universität Erlangen-Nürnberg

Spatial systems of interacting Fisher-Wright diffusions with seedbanks: finite system scheme

We consider a population of individuals migrating in geographic space, resampling in colonies and at each colony becoming dormant and waking up again. The seedbank is structured, so that we can model non-Markovian processes with non-exponential wake up times/times to become dormant. The goal is to study the question how the longtime behavior of the populations in finite geographic space is related to the behavior of systems with countable geographic space .We work with the infinite per site diffusion limit and new universality classes are appearing for that class of population models, w.r.t. the question of relating infinite-finite space longtime behavior and this is entirely due to dormancy and structured seedbank."

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Ashley Shade, Ph.D.,
University of Bath

Exploring reactivation as a mechanism of microbiome resilience

Soils have the highest known microbiome diversity and include thousands of unique bacterial and archaeal taxa. Soil microbiomes are critical for global carbon and nutrient cycles and support terrestrial plant health by forming beneficial relationships. Of all microbial habitats, soils have the largest reservoir of dormant cells (>80%) and taxa (>55%). However, there are fundamental unknowns in understanding the dormant component of the microbiome for soils. Critically, we do not know how the members of the dormant microbial pool will respond, individually or collectively, to environmental stressors associated with climate change. Motivated by my lab's previous results showing that 18% of soil microbiome resilience to thermal stress can be supported by reactivation, I hypothesize that dormant microbial taxa contribute to community resilience by activating and substituting or complementing disturbance-sensitive members. In this talk, I will present a working conceptual framework of the relationship between microbial activation from dormancy and resilience to environmental disturbances.

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Prof. Dr. Christian Giardinà,
Modena and Reggio Emilia University

Complexity emerging from dormancy in models of transport

One of the major success of interacting particle systems (IPS) has been the mathematical rigorous derivation of classical laws of transport for diffusive systems (Fick's law for mass transport, Fourier's law for heat transport) via the so-called thermodynamic limit procedure. However, when we consider the multi-type setting and include dormancy, new unexpected macroscopic behaviours emerge from the microscopic models. For instance, one may obtain a non-Fickian transport with uphill diffusion, i.e. the mass moves from a lower density region to a higher density region. We discuss multi-type IPS [1] whose hydrodynamic limit is a coupled linear reaction-diffusion system showing such anomalous behavior as a consequence of the switching mechanism beyond dormancy.

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Simone Floreani,
University of Oxford

Time non-locality from long dormancy

In this talk we will analyze the effect of long sleeping times in some classical interacting particle systems, the exclusion process and the inclusion process. We will show how at the hydrodynamic scale, time non-locality emerges in the form of fractional time derivatives or fractional integrals in time. Transition from Markovian to Non-Markovian dynamics as a consequence of dormancy will be discussed.

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Herr Michel Reitmeier,
Department of Mathematics,
Goethe University Frankfurt

The Contact Process with switching

In this talk, we introduce a type switching mechanism for the Contact Process. That is, we allow the individual particles/sites to switch between two types independently of one another, and the different types may exhibit specific infection and recovery dynamics. Such type switches can e.g. be motivated from biology, where `phenotypic switching' is common among micro-organisms. Our framework includes as special cases systems with switches between `active' and `dormant' states (the Contact Process with dormancy, CPD). After constructing the process from a graphical representation, we first establish basic properties, including the existence of a non-trivial invariant distribution and existence of a phase transition. Then, we introduce some weak form of duality in our system. Subsequently, we investigate scaling limits for the process as the switching parameters tend to ∞ (fast switching regime).In an outlook, we shift focus to a modified model where renewal processes with heavy-tailed inter-arrival distributions, as opposed to Poisson Point processes, trigger the type switches.

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Jan-Lukas Igelbrink,
Johannes Gutenberg University Mainz,
Goethe University Frankfurt

Hammond and Sheffield's power law Pólya's urn

For the renormalised sums of the random ± 1-colouring of the connected components of $\mathbb{Z}$ generated by a coalescing renewal processes, Hammond and Sheffield (PTRF 2013) proved convergence towards fractional Brownian motion. They conjectured that a voter model on $\mathbb{Z}$ with long range interactions rescales to a fractional Gaussian field. Recently, this has been proved by R. Drogin (arxiv 2023). Under a suitable rescaling, Drogin finds a limiting field of fractional Brownian motions.
We show that the methods developed in Igelbrink and Wakolbinger (ALEA 2023) can be used to generalise this result to $\mathbb{Z}^d$. In particular for $d = 2$ we find a space-time field of correlated fractional Brownian motions.
Variations of those methods can be applied to extend results by Bramson and Griffeath (Ann. Probab. 1979), see also Zähle (Ann. Probab. 2001), on the nearest-neighbour voter-model in $\mathbb{Z}^d, d \geq 3$.
Furthermore, we suggest a combination of a voter model on $\mathbb{Z}^d$ with a temporal seedbank-genealogy: In this combination an individual is allowed to copy its opinion from a distant position as well as from the distant past, such that the ancestral lines in time correspond to those in a Hammond-Sheffield urn.

Based on joint work with Adrián González-Casanova and Alan Hammond.

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Prof. Dr. Franziska Matthäus,
Frankfurt Institute for Advanced Studies &
Faculty of Computer Science and Mathematics,
Goethe University Frankfurt

Is subdiffusion a useful concept to model dormancy?

The talk will introduce the general concept of anomalous diffusion, its properties and relation to classical diffusion, and in particular the two subtypes superdiffusion and subdiffusion. Both types of anomalous diffusion can be derived from a generalised random walk model (continuous time random walk, CTRW), have interesting solution behavior, and represent optimal search strategies in different scenarios. Subdiffusion is a classical approach to model movement in porous or adhesive media, or movement in crowded environments. Its main characteristic is the heavy-tailed waiting time distribution. With the presented formalism and analogies to dormancy the talk is intended to stimulate a discussion if - on a conceptual level - subdiffusion in the state space might be a suitable approach to model dormancy in biological systems and provide further insights into this fascinating phenomenon.