DYNS3BIO

International Conference on Dynamics in Systems and Synthetic Biology

Online

June 14th to June 18th, 2021

Abstracts Book

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11:30 – 11:45	Break
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12:15 – 12:45	**Application of Genome-wide Association Studies for Detection of Plant Genes Involved in a Defense Response to Virus Infection** Anamarija Butković, *I2SysBio, CSIC-Universitat de València*
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15:00 – 16:00	**Multiscale modelling of the structure, regulation and dynamics of immune responses to virus infections** Gennady Bocharov, *Russian Academy of Sciences; Sechenov First Moscow State Medical University*
16:00 – 16:30	**A systemic view on virus infection fate decisions** Andreas Meyerhans, *Universitat Pompeu Fabra; Institució Catalana de Recerca i Estudis Avançats (ICREA); Marchuk Institute for Numerical Mathematics*
16:30 – 17:00	**An agent-based model with interaction networks, infection dynamics, transmission dynamics, and natural history of infection for evaluation of non-pharmaceutical interventions against COVID-19** Anel Nurtay, *University of Oxford*

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12:15 – 12:45	**Some instances where we can encounter a beyond all order phenomenon** Inmaculada Baldomà, *Universitat Politècnica de Catalunya*
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15:00 – 16:00	**Dynamical Parrondo paradoxes** Armengol Gasull, *Universitat Autònoma de Barcelona; Centre de Recerca Matemàtica*
16:00 – 16:30	**Can ecosystems live in a ghost state?** Blai Vidiella, *ICREA-Complex Systems Lab (UPF-PRBB); Institut de Biologia Evolutiva (CSIC-UPF); Centre de Recerca Matemàtica*
16:30 – 17:00	**Quasi-periodic perturbations of heteroclinic attractor networks in models of bistable perception** Gemma Huguet, *Universitat Politècnica de Catalunya; Centre de Recerca Matemàtica; Institut de Matemàtiques de la UPC - BarcelonaTech (IMTech)*

Wednesday 16th of June

10:00 – 11:00	**Social dispersal in metapopulations** Daniel Oro, *Theoretical and Computational Ecology Lab, CEAB (CSIC)*

11:00 – 11:30	TBA David Alonso
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11:45 – 12:15	**On the basic reproduction number in continuously structured populations** Sílvia Cuadrado, *Universitat Autònoma de Barcelona*
12:15 – 12:45	**Normal forms in Ecology** Josep Sardanyés, *Centre de Recerca Matemàtica*
12:45 – 15:00	Lunch
15:00 – 16:00	**Systemic Risk and Opportunity: Alternative Realities in Social and Ecological Systems** Simon Levin, *Princeton University*
16:00 – 16:30	**Search behaviour in a model organism: a walk on the wild side of diffusion** Frederic Bartumeus, *Theoretical and Computational Ecology Group (CEAB-CSIC)*
16:30 – 17:00	**The dynamics and resilience of ecological networks** Sonia Kéfi, *Institut des Sciences de l'Evolution de Montpellier*

Thursday 17th of June

10:00 – 11:00	**Synthetic transitions: bifurcations, breakpoints and the roads not taken** Ricard Solé, *Complex Systems Lab (UPF-PRBB)*
11:00 – 11:30	**Making sense of a dynamic world: Information processing by recurrent biological networks** Jordi Garcia-Ojalvo, *Universitat Pompeu Fabra*
11:30 – 11:45	Break
11:45 – 12:15	**Implementing Biological Computation with Distributed Multicellular Consortia** Eulàlia de Nadal, *Institute of Research in Biomedicine (IRB Barcelona); Universitat Pompeu Fabra (UPF)*

12:15 – 12:45	**Role of ancient duplicates in the metabolic switching in *Saccharomyces cerevisiae*** Christina Toft, *I2SysBio CSIC-UV*
12:45 – 15:00	Lunch
15:00 – 16:00	TBA Jeff Gore
16:00 – 16:30	**Human Time vs. Mouse Time in Embryonic Development** Miki Ebisuya, *EMBL Barcelona*
16:30 – 17:00	TBA Núria Conde

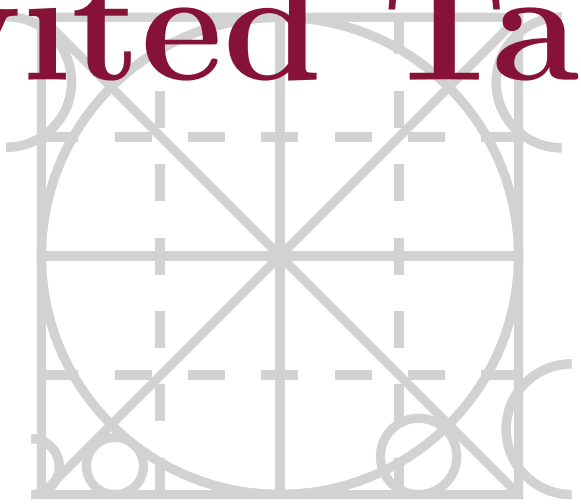
Friday 18th of June

10:00 – 11:00	**Cancer Virotherapy with Oncolytic Adenoviruses** Ramon Alemany Bonastre, *Catalan Institute of Oncology/IDIBELL*
11:00 – 11:30	**Beating cancer "escape room": let's use mathematical modelling to unlock cells!** Núria Folguera Blasco, *The Francis Crick Institute*
11:30 – 11:45	Break
11:45 – 12:15	**Metabolic circuits operability and cancer immunotherapy efficacy** Javier A. Menendez, *Program Against Cancer Therapeutic Resistance (ProCURE); Girona Biomedical Research Institute (IDIBGI)*
12:15 – 12:45	**Multiscale approach to understanding cell rearrangements in early angiogenesis** Daria Stepanova, *Centre de Recerca Matemàtica*
12:45 – 15:00	Lunch

Abstracts

of the

Invited Talks



Cancer Virotherapy with Oncolytic Adenoviruses

Ramon Alemany Bonastre

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Cancer virotherapy seeks to eliminate cancer cells with tumor-selective or "oncolytic" viruses. Lysis of tumor cells by oncolytic viruses is highly immunogenic and it can revert the immune suppression developed by tumors. Among different oncolytic viruses, human adenoviruses are non-enveloped DNA viruses with a cellular tropism and life cycle particularly suitable for oncolysis of tumors of epithelial origin. However, limited efficacy in clinical trials indicates that oncolytic adenoviruses need to be improved at different levels. For a successful systemic tumor targeting of the virus, issues such as neutralizing antibodies, fast clearance from blood, liver tropism, and tumor penetration, need to be addressed. Once in tumors, intratumoral spread of the virus is hampered by diffusion barriers formed by an extracellular matrix and stromal cells. Finally, the ability to induce antitumor immune responses is limited by the dominant immunogenicity of viral proteins compared to tumor antigens. This talk will present strategies aimed to overcome these limitations.

Predictability: Can the turning point and end of an expanding epidemic be precisely forecast?

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No, they can't [1]. Epidemic spread is characterized by exponentially growing dynamics, which are intrinsically unpredictable. The time at which the growth in the number of infected individuals halts and starts decreasing cannot be calculated with certainty before the turning point is actually attained; neither can the end of the epidemic after the turning point. An SIR model with confinement (SCIR) illustrates how lockdown measures inhibit infection spread only above a threshold that we calculate. The existence of that threshold has major effects in predictability: A Bayesian fit to the COVID-19 pandemic in Spain shows that a slow-down in the number of newly infected individuals during the expansion phase allows to infer neither the precise position of the maximum nor whether the measures taken will bring the propagation to the inhibition regime. There is a short horizon for reliable prediction, followed by a dispersion of the possible trajectories that grows extremely fast. The impossibility to predict in the mid-term is not due to wrong or incomplete data, since it persists in error-free, synthetically produced data sets, and does not necessarily improve by using larger data sets. Our study warns against precise forecasts of the evolution of epidemics based on mean-field, effective or phenomenological models, and supports that only probabilities of different outcomes can be confidently given.

Acknowledgments: This research has been funded by the Spanish Ministerio de Ciencia, Innovación y Universidades (MICINN)-Fondo Europeo de Desarrollo Regional funds of the European Union support, under Projects FIS2016-78883-C2-2-P and PID2019-106339GB-I00 (to M.C.), PGC2018-098186-B-I00 (to J.A.C.), FIS2017-89773-P (to S.M.), FIS2016-78313-P (to S.A.), and PID2019-109320GB-100 (to S.A.). The Spanish MICINN has also funded the "Severo Ochoa" Centers of Excellence (to Centro Nacional de Biotecnología (CNB)) SEV 2017-0712 and Special Grant Proyecto Intramural Especial 2020-20E079 (to CNB, S.M. and S.A.) entitled "Development of protection strategies against SARS-CoV-2."

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Some instances where we can encounter a beyond all order phenomenon

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In this talk we want to show three different settings where a beyond all order phenomenon occurs by means of exponentially small quantities with respect to a suitable parameter. It summarizes different joint works with Maria Aguareles, Oriol Castejón, Mar Giralt, Marcel Guardia, Santiago Ibáñez and Teresa M. Seara.

The first one is about the occurrence of Shilnikov bifurcations in analytic unfoldings of some Hopf-Zero singularities through a beyond all order phenomenon: the exponentially small breakdown of invariant manifolds which coincide at any order of the normal form procedure. The conditions we provide, are computable and satisfied by generic singularities and generic unfoldings. *Joint work with Oriol Castejón, Santiago Ibáñez and Teresa M. Seara.*

The second one deals with the existence of spiral wave solutions in oscillatory models having a rotational symmetry, such as generic λ-ω systems. These can be derived as the normal form of oscillatory reaction-diffusion systems near a Hopf bifurcation. Rigidly rotating spiral waves are commonly found in many chemical systems and biological processes [1, 2, 3, 4]. In these systems, we prove that the asymptotic wavenumber is an exponentially small quantity with respect to the the (small) twist parameter. *Joint work with Maria Aguareles and Teresa M. Seara.*

In the last instance we consider the Restricted Planar Circular 3-Body Problem (RPC3BP) with primaries mass ratio μ small. This configuration has a saddle-center equilibrium point called L_3 (collinear with the primaries and beyond the largest one) with a 1-dimensional stable and unstable manifold. Since the modulus of the hyperbolic eigenvalues are smaller than the elliptic ones by a factor of $\sqrt{\mu}$. As a consequence, when $\mu \to 0$, the 1-dimensional stable and unstable coincide at any order of μ. However, we can prove that they are not equal but its distance is exponentially small with respect to $\sqrt{\mu}$. *Joint work with Mar Giralt and Marcel Guardia.*

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Search behaviour in a model organism: a walk on the wild side of diffusion

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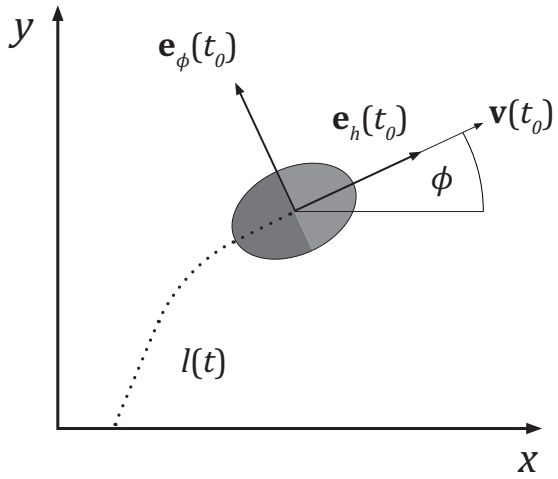
Search under large environmental uncertainty requires to solve the spatial exploration-exploitation tradeoff. Combining intensive and extensive sampling efforts, the searchers increase the chances to find both nearby and faraway targets from any given initial search position. Based on a high-throughput tracking system we study the search behaviour of *Caenorhabditis elegans* in a cue-deprived arena. This roundworm is a free-living transparent nematode of about 1 mm in length that is massively used as a model organism in genetics, neurosciences, and biomedicine research.

C.elegans exploratory behaviour combines both stereotyped strong reorientations, which abruptly break directional persistence, with smooth curvature control that is executed while crawling. Complex movement patterns and heterogeneous spatial sampling emerge from the combination of these two elements. Here, we use stochastic differential equations (Eq. 1, Eq. 2) to model *C.elegans* search trajectories. Our model reproduces the observed dynamics and allows us to investigate how motor control influences macroscopic properties of movement and search efficiency at much broader scales. We found that *C.elegans* combines periods of extensive spreading with local sampling, transiting between sub/super-diffusive regimes, and solving key tradeoffs related to optimal spatial sampling. Exploratory behaviour can be interpreted widely as a walk on the wild side of diffusion.

Mathematical notes:
In our movement model (Fig. 1), we distinguish the dynamics in the direction of



motion (h, according to the figure) from the normal direction (ϕ). Then we apply a Langevin framework (stochastic differential equations) with different forces in the mentioned directions. Basically, we consider that there is a propulsive force in the direction of motion that tries to keep the speed constant at a given speed v_s, then there is a constant force in direction ϕ (which induces a constant curvature in the motion) and finally we have Gaussian white noises is both directions with intensities σ_h and σ_ϕ. In consequence, the model reads:

$$\frac{d\mathbf{v}}{dt} = -\gamma(v - v_s)\mathbf{e}_h - \beta\mathbf{e}_\phi + \sigma_h\mathbf{e}_h + \sigma_\phi\mathbf{e}_\phi \tag{1}$$

where γ and β are constant parameters that determine the intensity of the propulsive force and the curvature force, respectively. The prevalent direction, $\mathbf{e}^*$ can be alternatively represented in terms of the angle of movement ϕ^*.

When we expand the equations in the direction of motion and the normal direction separately, and for simplicity we assume $\mathbf{e}^* = \mathbf{i}$ (this is, the preferential direction of motion in the direction x) so that:

$$\begin{aligned} \frac{dv}{dt} &= -\gamma(v - v_s) + \sigma_h \\ \frac{d\phi}{dt} &= \frac{\beta + \sigma_\phi}{v} \end{aligned} \tag{2}$$

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Multiscale modelling of the structure, regulation and dynamics of immune responses to virus infections

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The course and outcome of publicly relevant human infections depend on the immune system. It functions as an hierarchically organized, spatially structured and pleiotropically regulated ensemble of recirculating cells and humoral factors that function to control antigenic homeostasis of a host organism. To understand the pathogenesis of infectious diseases and to predict their progression after therapeutic interventions, a range of challenges exist. These include the curse of dimensionality of a systems state space, the multiplicity of dynamics trajectories of pathological processes, the nonlinearity of regulation loops, and the heterogeneity and variability of innate- and adaptive immunity. To overcome these challenges, the deployment of mathematical and computational tools combining the rigor of mechanistic description and power of machine learning algorithms is needed. This shall enable a quantitative description of the immune system dynamics in the multidimensional space of physical and phenotypic traits, to allow a cause-and-effect type of analysis of

pathological processes and to robustly predict the system's reaction to multi-modal therapies. A systematic approach to the development of multiscale multiphyiscs models of the immune system with a special focuss on the structure, regulation and dynamics is presented [2, 1]. Our fundamental and translational studies are placed around two major immune-dependent disease classes, i.e., human infections (HIV-1, SARS-CoV-2) [3, 4, 6] and experimental animal infections (LCMV and MHV) [5].

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Application of Genome-wide Association Studies for Detection of Plant Genes Involved in a Defense Response to Virus Infection

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Genome wide association studies (GWAS) link specific genetic variants with particular diseases and they are becoming increasingly popular in the last decade. These discoveries have helped us to identify genes responsible for different diseases or medical conditions. In GWAS we scan the genomes of many, often up to thousands, individuals of the same species, taking into consideration healthy individuals and the individuals with a disease we are interested in. Then using statistical methods, such as, linear mixed models (LMM), look for places in the genome that are consistently different between diseased and healthy individuals [1]. Once we identify genetic markers associated with our disease of interest we can focus more on experimental studies to clarify the exact role of this region and develop appropriate prevention measures.

In our GWAS project we have characterized Arabidopsis thaliana genes involved in the response to infection with Turnip mosaic virus (TuMV), a prototypical RNA plant virus. Arabidopsis is a great model organism to perform GWA analyses on since it is small, easy to work with, very well studied and a lot of genetic data is readily available. TuMV is an interesting virus to study because it causes a lot of economic loses in agricultural production each year and is commonly used and

well characterized in our laboratory. With the help of LMM [2], genes that are correlated with TuMV infection were found and further characterized. Using the bayesian sparse linear mixed model (BSLMM) [3], that is a hybrid of LMM and the Bayesian variable selection regression models (BVSR), we inferred the genetic architecture of the infection-related trait. This approach has helped us to understand if several disease-related traits of interest are well explained with the genomic information available.

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On the basic reproduction number in continuously structured populations

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In a deterministic epidemic model, the basic reproduction number $\mathcal{R}_0$ is defined as the expected number of new infections a newly infected individual will produce in a wholly susceptible population over the full course of the disease. In an ecological model, the basic reproduction number $\mathcal{R}_0$ is, by definition, the expected number of offspring that an individual has during its lifetime. In constant and time periodic environments it is calculated as the spectral radius of the so-called *next-generation operator* ([1, 2]). In continuously structured populations defined in a Banach lattice X with concentrated states at birth one cannot define the next-generation operator in X. In this talk we present an approach to compute the basic reproduction number of such models as the limit of the basic reproduction number of a sequence of models for which $\mathcal{R}_0$ can be computed as the spectral radius of the next-generation operator. We will show an application of these results to some examples.

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Virus-induced codon-specific reprogramming to favor viral RNA translation

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Codon usage bias regulates gene expression, as synonymous codons are not decoded with the same efficiency (1). How viruses, such as the emerging mosquito-borne Chikungunya virus (CHIKV), express their genomes at high levels despite an enrichment in rare codons remains a puzzling question. Using ribosome footprinting, we analysed translational changes at the ER and the cytosol, the two major translation compartments, in CHIKV-infected cells. Here we show that CHIKV infection induces a codon-specific reprogramming of the host translation machinery to favor translation of viral RNA genomes over host mRNAs featuring optimal codon usage. This reprogramming was specifically apparent at the ER, whereăCHIKV RNA efficiently translates. Mechanistically, it involves CHIKV-induced overexpression of KIAA1456, an enzyme that modifies the wobble U34 position in the anticodon of tRNAs required for proper decoding of a specific set of codons highly enriched in CHIKV RNA. Our findings demonstrate an unprecedented interplay of viruses with the host tRNA epitranscriptome to adapt the host translational machinery to the viral codon usage.

Towards a phage therapy against multi-drug-resistant *Klebsiella pneumoniae*

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The emergence of multi-drug-resistant bacteria is a major threat nowadays. *Klebsiella pneumoniae* is considered by the WHO as a priority pathogen to be treated, due to its high levels of resistance emergence [1]. Alternative treatments are needed, and bacteriophages, viruses that kill bacteria, have been proposed as promising therapeutic tools [2]. Understanding phage-host interactions of *Klebsiella phages*, and their combination with antibiotics, will help us in the fight against *Klebsiella pneumoniae* and in the development of future phage-based treatments. Mathematical modelling will provide an excellent tool for understanding the dynamics of bacteriophage infections and determining the fate of populations. Interestingly, the inclusion of complex parameters such as the emergence of resistant bacteria [3] and coinfection [4] will produce a qualitative description of these biological processes.

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Human Time vs. Mouse Time in Embryonic Development

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Different species have different tempos of development: larger animals tend to grow more slowly than smaller animals. My group has been trying to understand the molecular basis of this interspecies difference in developmental time, using the segmentation clock as a model system. The segmentation clock is the oscillatory gene expressions that regulate the timing of body segment formation during early embryogenesis. We have recently succeeded in recapitulating the segmentation clock from both human and mouse pluripotent stem cells, detecting oscillations and traveling waves in vitro. Interestingly, the oscillation period of human segmentation clock was 5-6 hours while that of mouse was 2-3 hours. Taking advantage of our in vitro system and simple mathematical models, we have been comparing the genome sequences and molecular processes of the segmentation clock between human and mouse to explain the interspecies difference in the oscillation period.

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Beating cancer "escape room": let's use mathematical modelling to unlock cells!

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The inherent capacity of differentiated cells to switch their phenotype in vivo in response to damage stimuli might have a pivotal role in ageing and cancer. However, how the mechanisms of phenotype reprogramming are established remains poorly understood. In order to elucidate such mechanisms, we present a stochastic model of combined epigenetic regulation (ER)-gene regulatory network (GRN) to study the plastic phenotypic behaviours driven by ER heterogeneity. Our analysis of the coupled system reveals the existence of pluripotent stem-like and differentiated steady-states. Crucially, ER heterogeneity is responsible for conferring abnormal robustness to pluripotent stem-like states, which cause the locking of the cells in a stem cell-like state prone to cancer development. By analysing the ER heterogeneity, we formulate epigenetic heterogeneity-based strategies capable of unlocking and facilitating the transit from differentiation-refractory (pluripotent stem-like) to differentiation-primed epistates. Our results suggest that epigenetic heterogeneity regulates the mechanisms and kinetics of phenotypic robustness of cell fate reprogramming. The occurrence of tunable switches capable of modifying the nature of cell fate reprogramming from pathological to physiological might pave the way for new therapeutic strategies to regulate reparative reprogramming in ageing and cancer.

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Making sense of a dynamic world: Information processing by recurrent biological networks

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Living organisms must monitor the dynamics of their environment continuously, in order to adapt to present conditions and anticipate future changes. But anticipation requires processing temporal information, which in turn requires memory. We have recently shown that both cells [1] and simple nervous systems [2] can perform such dynamical information processing by leveraging the recurrent architecture of gene regulatory and neuronal networks, respectively. Here we review these studies, showing in particular how recurrent network architectures enable the long-term storage of information, through a phenomenon reminiscent of generalized chaos synchronization. We also discuss the size requirements that recurrent networks must fulfill under realistic biological conditions.

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Dynamical Parrondo paradoxes

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We start showing that for planar periodic non-autonomous discrete dynamical systems, even when a common fixed point for each of the autonomous associated dynamical systems is repeller, this fixed point can became a local attractor for the whole system, giving rise to a Parrondo's dynamical type paradox. This result can be easily extended to even dimension.

Afterwards we study a similar situation, involving two planar homeomorphisms. This planar construction can also be extended to any dimension greater than 2 and shows the appearance of the dynamical Parrondo's paradox in odd dimensions.

Finally this paradox is proved to appear also in two other situations:

- Some iterated function system generated by two maps f and g, where each of them appears with a certain probability; and
- Some planar alternating ordinary differential equations, which can be used to model systems with seasonality.

This talk based on the works [1, 2, 3].

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Quasi-periodic perturbations of heteroclinic attractor networks in models of bistable perception

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Bistable perception is characterized by alternation of percepts under a steady sensory input. Alternatively to the profusely used two-attractor models for bistable perception, heteroclinic networks have been considered successfully to model this phenomenon [1]. Heteroclinic networks consist of the union of several heteroclinic orbits between saddle points. In bistable perception models, noise plays a leading role to explain the statistics of dominance times of percepts observed in experiments. Thus, trajectories of heteroclinic networks are characterized by long periods in neighbourhoods of saddle points from which they escape thanks to noise. In fact, noise is meant to model a diversity of inputs impinging on the areas represented in the model.

In this talk we consider quasiperiodic perturbations of heteroclinic networks, assuming that the system is receiving events, either internal or from other brain areas,

that include only a finite number of (incongruent) frequencies. We show how these systems can achieve good agreement with gamma distributions of the dominance times observed in bistable perception, and we compare these results with those obtained with noise. We present a methodology based on the separatrix map to model the dynamics close to heteroclinic networks with quasi-periodic perturbations. Our methodology considers two different approaches, one based on Melnikov integrals and another one based on variational equations. The perturbed system shows chaotic behaviour while dominance times achieve good agreement with Gamma distributions. Results can be found in [2].

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The dynamics and resilience of ecological networks

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Understanding the stability of ecological communities has proved to be a challenging task. In particular, while the need to consider the multidimensionality of stability has been clearly stated in the ecological literature for decades, little is known about how different metrics of stability relate to each other in ecological communities. Indeed, our understanding of stability has remained fragmented and is limited largely to simple or simplified systems. I'll present results of dynamical simulations of multispecies communities under different perturbation scenarios, in which we measured how frequently used stability metrics relate to each other. I'll discuss how these results may contribute to improve the quantification of stability in theory and in practice.

Scaling laws for stochastic ghosts explained by Hamiltonian dynamics

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Universal scaling laws occur in deterministic dynamical systems. Several of these scaling laws arise (in many cases) from long transients at the vicinity of local bifurcations. In these situations time transients τ follow laws of the form $\tau \sim |\mu - \mu_c|^{\alpha}$, where μ is the bifurcation parameter and μ_c the value at which the bifurcation takes place. The exponent α depends on the bifurcation type, being $-1/2$ for the saddle-node bifurcation. Multitude of research has focused on this slowing down phenomenon, the so-called *ghost*, using deterministic approaches, which conserve such a scaling behaviour. However, the impact of stochasticity (i.e., intrinsic or demographic noise) on ghosts still remains poorly explored.

Reference [4] explored the impact of intrinsic noise in the vicinity of a local saddle-node bifurcation in one- and two-dimensional dynamical systems including cooperation, competition, and species decay. They numerically found that this scaling law was more intrincated than the one for deterministic systems, and that an increase of noise stabilised the dynamics producing longer transients. To the best of our knowledge, there is no yet a satisfactory theoretical body to this explain this phenomenon from a dynamical point of view.

In this talk, we will provide an analytical approach to evaluate how intrinsic noise shapes these stochastic transients and their associated scaling law by means of a Hamiltonian approach. This approach, based upon conservative dynamical systems, will be applied to a simple model for autocatalysis and to a cooperative system modelled with a Hill function.

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Systemic Risk and Opportunity: Alternative Realities in Social and Ecological Systems

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Phase transitions between distinct states are common throughout our world, from physical systems to financial systems and our societies. Understanding these transitions and their consequences is crucial for efforts at sustainability and for the development of effective management regimes. I will discuss the nature of the challenges, the search for early warning indicators of impending changes, and implications for the design of management strategies.

Metabolic circuits operability and cancer immunotherapy efficacy

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Targeting the "don't eat me" signals that cancer cells employ to evade detection and destruction by the immune system with cancer immunotherapy has revolutionized cancer treatment, but efficacy remains limited in major cancer types and clinical settings. Given that only 1 in 8 cancer patients would obtain a therapeutic benefit from this potentially curative modality, further progress towards more broadly effective immunotherapeutic strategies urgently requires an unbiased identification of novel mechanisms of tumor cell-intrinsic immune evasion.

While most efforts to biologically rationalize and clinically broaden the utility of immunotherapeutics have mostly revolved around the genetic aberrations of cancer cells, relatively little information exists on how cancer cell-intrinsic metabolism might operate as a self-autonomous barrier against antitumor immunity and cancer immunotherapy. We recently envisioned that the operability of metabolic circuits might drive the composition and/or functionality of immune-escape mechanisms and consequently fine-tune the responsiveness of cancer cells to T-cells and immunotherapeutics. We have proposed that a molecular-level delineation of the metabolic blueprint shaping the balance between "eat me" and "don't eat me" signals in cancer cells should provide an unforeseen perspective on the frequently overlooked relevance of basic metabolism research in the post-genomic era of cancer research.

To functionally interrogate the contribution of tumor-intrinsic metabolic circuits to tumor immune evasion we can take advantage of the versatility of the CRISPR-Cas9 technology for functional gene screening. We here illustrate how CRISPR/Cas9-based drop-out of single or combinatorial perturbations of metabolic circuits working patterns in combination with automated, real-time measurements of the cytolytic

interactions between T-cells and cancer cells at different effector-to-target ratios (as representative grades of T cell-selection pressure), can unbiasedly identify cancer cell-autonomous metabolic traits as tumor-intrinsic factors regulating sensitivity to T cell-mediated killing and cancer immunotherapy. Using small molecule drug-responsive metabolic circuits, we exemplify also how we can couple perturbations of metabolic circuits operability with the activation of endogenous chromogenic reactions in drug-resistant cellular states that self-promote their escape from the immune system but at fitness cost to the cancer cell that can be exploited for therapeutic benefit (i.e., the so-called 'one-two punch' model for cancer therapy).

The development of mathematical models and computational tools to run 'metabolic machines' capable of generating immunotherapy efficacy maps based on metabolic circuits operability would provide not only a highly innovative resource to discover and manipulate novel metabolic regulators of immune evasion but also to accelerate the translation and implementation of lab-based discoveries on tumor/T-cell basic metabolic science into immuno-oncology clinical trials.

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A systemic view on virus infection fate decisions

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The immune system usually fights an invading virus until it is eliminated. Such an infection course is named an acute infection. Alternatively, if the pathogenic threat is very high, the immune system may surrender by immune cell exhaustion to establish a co-existence with the virus, a chronic infection. Neither the decisive elements of this infection fate decision nor the elements that partly control viremia in the chronic phase are completely understood. In our laboratory, we therefore aimed to analyze the sequential events underlying acute and chronic virus infection fate decisions and understand their regulatory mechanisms. Studies of acute and chronic infections of mice with the Lymphocytic Choriomeningitis Virus (LCMV) will be described and possible points of therapeutic interventions discussed.

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Implementing Biological Computation with Distributed Multicellular Consortia

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Engineering approaches to synthetic biology have shown that several strategies can be used to build complex functional constructs with computational abilities. In this regard, efforts have been devoted to build artificial computational devices for a wide range of applications, including bioremediation, food production or biomedicine. Using yeast as a model organism, we have successfully implemented complex circuits by distributing computation within cellular consortia. This approach to biological computation paves the way for the design and development of a novel method, which can be combined in multiple ways to create complex computational circuits. The potential use of this approach is demonstrated by the implementation of complex logical functions responding to up to six inputs, the building of a synthetic biological memory switch or a circuit with an incoherent feed-forward loop architecture (FFL) to generate single pulse responses, or the implementation of reprogrammable biological devices. Our results might serve as a blueprint for the future development of biocomputing cellular devices.

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An agent-based model with interaction networks, infection dynamics, transmission dynamics, and natural history of infection for evaluation of non-pharmaceutical interventions against COVID-19

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In the absence of pharmaceutical interventions, novel infectious diseases such as COVID-19, apart from causing deaths and illness in millions, have proven to demand strict restrictions on social and economic activity in order to be contained. Various computational models are being employed by policy makers to estimate the effects of different interventions and to predict spread of infection. One of the tools that has been developed to help asses the effects of public health measures is OpenABM-Covid19: an agent-based simulation of the epidemic which includes detailed age-stratification and realistic social networks. The model can be parametrised to demographics of any country, and can evaluate non-pharmaceutical interventions. Interaction networks, infection dynamics, transmission dynamics, and natural history of infection are taken into consideration in the model to assure it being a flexible yet precise tool. It can simulate a population of one million people in seconds per day, which allows parameter sweeps if necessary and formal statistical model-based inference. OpenABM-Covid19 is an open-source project with Python and R interfaces, which allows scientists and policy makers to evaluate and compare different combinations of interventions.

Social dispersal in metapopulations

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In perturbed patches, a behavioural response of individuals in populations is to disperse to more suitable patches to increase fitness prospects. Dispersal is known to affect metapopulation dynamics, but in social species where social copying is common, dispersal may be non-linear. This non-linearity may result from a behavioural dispersal avalanche once a threshold value of perturbation is attained [1]. We assess here the difference between nonsocial and social dispersal and the consequences for the population under perturbation. We explore the nontrivial steady states of a logistic model depending on the dispersal strategy and found the existence of an Allee effect. This suggests that in social species, there is a minimum critical size for a population to successfully colonize an empty patch.

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Normal forms in Ecology

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Normal forms are the simplest equations or formulas explaining mathematical phenomena. They are extremely useful in dynamical systems theory to illustrate, understand and investigate dynamics and bifurcations. In this talk I will develop the concept of biological normal forms, focusing on ecological systems, and introducing an extremely simple differential equation capturing dynamics of intra-specific cooperation (or facilitation) together with competition and decay. This particular equation has been used to investigate the population dynamics of autocatalytic replicators or metapopulations with facilitation. I will explain this ecological normal form, introducing its main dynamical features and how these characteristics change upon the consideration of explicit metapopulations and spatially-extended dynamics of facilitation.

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Synthetic transitions: bifurcations, breakpoints and the roads not taken

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Evolution is marked by well-defined events involving profound innovations: the so-called Major Evolutionary Transitions. They involve the integration of autonomous elements into a new, higher-level organization whereby the formerly isolated units interact in novel ways, losing their original autonomy. All major transitions, which include the origin of life, cells, multicellular systems, societies, or language (among other examples), took place millions of years ago. Are these transitions unique, rare events? Have they instead universal traits that make them almost inevitable when the right pieces are in place? Are there general laws of evolutionary innovation? Are there alternative paths? Can mathematical models involving bifurcations points help to understand their origins? In order to approach this problem under a novel perspective, we argue that a parallel class of evolutionary transitions can be explored involving the use of synthetic biology and artificial evolutionary experiments and a proper theoretical approach. These alternative scenarios could help us to understand the underlying laws that predate the rise of major innovation and the presence of universal principles.

Multiscale approach to understanding cell rearrangements in early angiogenesis

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Angiogenesis is the process whereby endothelial cells (ECs) migrate from a pre-existing vascular bed guided by local environmental cues and interacting with each other to eventually create a new vascular network. We introduce a multiscale model of migration-driven angiogenic sprouting which accounts for the individual phenotype selection of ECs, cell-cell and cell-extracellular matrix interactions [1]. The model, calibrated and validated against various experimental data, captures the characteristic behavior of ECs: branching, cell mixing and, chemotactic sensitivity. These properties, rather than being hard-wired into the model, emerge naturally due to accounting for heterogeneous behavior of ECs depending on their gene expression pattern. This allows us to use the model to investigate the role of cell rearrangements during angiogenic sprouting on the vascular network structure. In particular, we show how cells with impared gene expression of a specific receptor are characterised by reduced levels of cell rearrangement which influences the branching pattern of vascular networks. Overall, our results support the hypothesis that cell rearrangements play a central role in angiogenesis.

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Role of ancient duplicates in the metabolic switching in *Saccharomyces cerevisiae*

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Gene duplication events have been associated with increasing biological complexity throughout the tree of life, but also with illnesses, such as cancer. Early evolutionary theories indicated that duplicated genes could explore alternative functions due to the relaxation of selective constraints in one of the copies, as the other remains an ancestral-function backup. In unicellular eukaryotes like yeasts, it has been demonstrated that the fate and persistence of both duplicated copies in the genome depend on the duplication mechanism (whole-genome or small-scale events). Although it has been shown that small-scale duplicates tend to innovate and whole-genome duplicates specialize in ancestral functions, the implication of ancient duplicates transcriptional plasticity and transcriptional divergence on environmental and metabolic responses remains largely obscure. Here we subject Saccharomyces cerevisiaeăto a metabolic switch by enforcing acute and chronic growth on a non-fermentative carbon source (including ethanol, lactic acid and glycerol) unrevealing the central and common role, the ancient duplicates have in these kinds of metabolic shifts. In particular, the duplicates respond by transcriptional rewiring, depending on their transcriptional background. Our results shed light on the mechanisms that determine the role of duplicates, and on their continued evolvability.

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Can ecosystems live in a ghost state?

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Current ecosystems are threatened by anthropogenic activities. Growing human societies are increasing their demand of resources (such as water, minerals, or food), promoting dangerous effects for wildlife due to water pollution, CO_2 emissions, and habitat destruction. As a result, ecosystems are suffering transition towards degraded states (e.g. loss of species, desertification and coral bleaching, among others). These perturbations in natural systems may push them to their sustainability limits. Once an ecosystem is perturbed beyond a critical boundary, it can shift to a degraded state. Depending on the nonlinearities raised from ecosystem's species interactions, the ecosystem will be able to exhibit different response behaviours. For instance, a change from a stable state to an oscillatory one. After a tipping point (or bifurcation), the dynamics can get trapped into a non-existing previously stable state. This can make the ecosystem to remain stable but actually being trapped in a transient state (delayed transition) transitioning towards an undesired state e.g., extinction or highly degraded status. In this talk, we will show different transients arising in a variety of transitions. We will explore local bifurcation effects like the so-called critical slowing-down (typical from transcritical and pitchfork bifurcations) and the so-called ghosts, which appear close to saddle-node bifurcations. Furthermore, we will explain our adventures in more complex dynamics, such as transients induced by an heteroclinic bifurcation from a resource-consumer model, to the one induced by a normally hyperbolic invariant manifold (NHIM) identified in a cooperator-parasite system.

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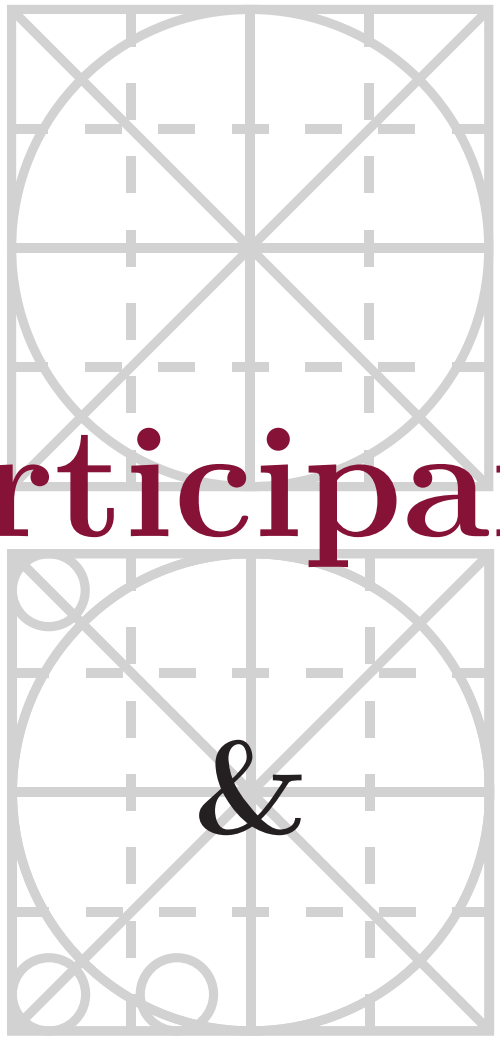

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