# RISE project 690817: FourCModelling
# Year 3 workshop report

The third annual workshop for the FourCModelling project took place at the University of Torino in Italy on July 16-19, 2018. The workshop again contained a number of central elements, including 23 presentations, with a focus on dissemination and communication, andn in particular on integrating research from the different work packages. Events included:

(i) specialist sessions on the background and research carried out to date on each of WPs 1-4; these were comprised of a central main talk and associated questions, but there were also smaller talks from project participants that expanded on this;

(ii) sesssions including presentations of related work from researchers from outside of the project. There was a total of 31 participants in the workshop, including 13 from outside of the project (some of which had attended previous workshops);

(iii) a keynote presentation by External Advisory Board member Ben Allen;

(iv) extensive research discussion sessions within the workpackages, and in particular cross work package sessions exploring synergies in the project, and the development of research for the unifying WP5, which was the central focus of the meeting;

(v) project review including reports from all of the WP coordinators on any issues relating to non-research aspects (and research aspects not already discussed in the main presentations);

(vi) project planning, identifying priorities for the coming year and towards the end of the project. This included finalising/updating plans for the last secondments, cross work package work, dissemination and communication, and the annual workshop, after which the project will have approximately five months left to run.

A full programme for this event is also attached.

Once again we had an enjoyable and successful meeting, and we would like to thank all of the participants for contributing to our workshop.

# Conflict, Competition, Cooperation and Complexity: Using Evolutionary Game Theory to Model Realistic Populations

## Torino, July 16-19, 2018

Universita' di Torino    Via Po 17 / via Verdi 8

**Scope of the Workshop:** This workshop is the annual event that brings together all the partners of the FourCModelling EU project, funded under the H2020-RISE program. The participants share among them the research results they obtained thanks to the collaboration within the program. The event offers a cross-fertilization opportunity across different work packages, and encourages scientific exchange also with other researchers attending the event, although not directly participating in the project exchange program.

# Programme

All the presentations and the meetings in the morning will be in the room "sala Principe d'Acaja" at the street level in the main University building, with entrance from Via Po 17 or (equivalently) via Verdi 8 (via Po and via Verdi are parallel streets, the front entrance of the building is from via Po).

For afternoon coffee break and the following sessions we will move to the "sala multifunzione" of the Cavallerizza Reale, entrance from via Verdi 9 (just across the street from the University main building); where lunches will also be served.

## Monday July 16

9.00 – 9.15  Welcome

9.15 - 10.15  Mark Broom:  (Main talk from WP1) Modelling evolution in structured populations involving multiplayer interactions

10.15 - 10.40  Igor Erovenko:  The evolution of cooperation in mobile populations on multiplayer stochastic networks

10.40 - 11.10  Coffee Break

11.10 - 11.35  Matteo Sereno:  Energy Efficiency & Game Theory: Applications to Network Management Policies

11.35 - 12.00  Peter Bayer:  Best-Response Dynamics in Network Games with Asymmetric Interaction.

12:00 - 12:25  Zhijun Wu:  Equilibrium Distributions of Populations of Biological Species on Networks of Social Sites

12.30 - 14:00  Lunch Break

14.00 - 15.00  Vlastimil Krivan and Tamas Varga:  (Main talk from WP2) Matrix games with time constraints

15:00 - 15.25  Ted Galanthay:  A game-theoretic approach to foraging dynamics

15.25 - 15.50  Monica Salvioli:  A Stackelberg Approach To Cancer Treatment

15.50 - 16.20  Coffee break

16.20 - 17.30  Discussion


## Tuesday July 17

9:00 - 10.00  K. Selcuk Candan:  (Main Talk from WP3) Discovering Context Sensitive Impact in complex systems

10:00 - 10.25  Marco Beccuti:  A computational model to study the effects of different vaccine policies on Pertussis epidemiology

10.30 - 11:00  Coffee Break

11.00 - 12.00  Ben Allen:  (Keynote talk) Evolution in spatially structured populations: from models to theorems

12.00 - 12.25  Amira Kebir:  A general dynamical game model for structured population and applications

12.30 - 14.00  Lunch Break

14.00 - 15.00  Katerina Stankova and Joel Brown:  (Main Talk from WP4) Modeling and Treating Cancer using Game Theory

15.00 - 15.25  Francesca Cordero:  Computational models to inspect intratumor heterogeneity

15.30 - 16.00  Coffee break

16.00 - 17.30:  Administrative Aspects of the project

## Wednesday July 18

9.00 - 9.25  Li You:  Including blood vessel in a game theoretical model of cancer dynamics

9.25 - 9.50  Pietro Landi:  Adaptive Dynamics and evolutionary diversification: Theory and applications

9.50 - 10.15  Tomas Revilla:  Plant coexistence under adaptive exploitation and mutualism

10.15 - 10.45  Coffee break

10.45 - 12.30  Discussion in groups  (in 2 rooms)

12.30 - 14.00  Lunch Break

14.00 - 14.25  Karan Pattni: Framework for studying evolution in structured populations with fixed and variable size.

14.25 - 14.50  Silvestro Poccia:  Meta-data driven algorithms for detecting  robust multi-dimensional motifs

14.50 - 15.15  Karl Sigmund:  Outbreaks of Corruption - an evolutionary perspective

15.15 - 15.45  Coffee break

15.45 - 17.30  Discussion in groups


## Thursday July 19

9.00 - 9.25  Anthony Sun:  A social-ecological model for lake pollution dynamics

9.25 - 9.50  Yannick Viossat:  Modeling adaptive therapy

9.50 - 10.15  Fei Xu:  Sexual predation preference in a predator-prey system

10.15 - 10.45  Coffee break

10.45 - 12.30  Discussion in groups  (in 2 rooms)

12.30 - 14.00  Lunch Break

14.00 - 15.30  Discussion in groups

15.30 - 16.00  Coffee break

16.00 - 17.00 Plenary discussion and concluding remarks

# Abstracts (all talks except the main WP1-WP4 talks)

Ben Allen

Title: Evolution in spatially structured populations: from models to theorems

Abstract: Spatial population structure has a variety of consequences for evolution, the extent of which is gradually coming into focus. Spatial structure can affect the rate of genetic change, the balance of selection versus drift, and the evolution of cooperation and other forms of social behavior. Mathematical modeling of this question has become increasingly sophisticated, with a recent focus on heterogeneous spatial structures that were once thought to be mathematically intractable. However, the proliferation of models and results makes it challenging to draw general, broadly applicable conclusions. After reviewing recent progress on this question, I will outline a mathematically general approach, in which the objects of study are classes of models defined by minimal assumptions. Any theorem proven from these assumptions is valid for all models in the class. I will show how this approach can be used to prove equivalence between evolutionary success criteria and formalize the method of weak selection.

Peter Bayer

Title: Best-Response Dynamics in Network Games with Asymmetric Interaction.

Abstract: This paper studies network games with linear best response functions. This class of games includes applications like pollution, industrial organization, and evolutionary game theory. The case of symmetric weight matrices, representing reciprocity between agents, is widely studied with several existing results for the structure of Nash equilibria and the convergence of simple learning processes. In this paper we consider games with asymmetric weight matrices which represent non-reciprocal interactions between pairs. We show that in this case even the simplest learning processes such as the best-response dynamic can diverge. We present known subclasses of games where convergence/divergence is assured and present conditions of convergence for the general case.

Marco Beccuti

Title: A computational model to study the effects of different vaccine policies on Pertussis epidemiology

Abstract: Pertussis is a highly contagious respiratory disease caused by bacterium Bordetella pertussis and characterized by uncontrollable, violent coughing which often makes hard the breathing. Although recently studies provided an its better characterization, it remains a challenging public health problem because many aspects of its infection, disease and immunity are still poorly understood. In particular, even if the implementation of vaccination programs in many countries has decreased substantially its diffusion and mortality, the pertussis-related hospital admissions and fatalities are still evident particularly in young infants. In this context, computational-mathematical models can be exploited (a) to provide new insights into drivers of pertussis epidemiology, (b) to investigate different explanations of this observed resurgence, and (c) to predict potential effects of different vaccination strategies as well as prenatal vaccination and booster vaccinations.

In this presentation we describe a preliminary work in which we extended the classical SIRS infection model to include the peculiarities of the pertussis infection and the relative vaccination cycle. To provide a parametric model considering sub-populations with different infection and immunity characteristics over time, we employed Stochastic Symmetric Net (SSN)--a high-level Petri Net formalism. Indeed, SSN allows us to describe the system as a parametric graphical diagram that makes easier and faster the derivation of the underlying SIRS model and its comprehension without requiring advanced skills in mathematics and modeling. It also provides the possibility of automatically deriving qualitative and quantitative properties of the system. The model behavior is thus obtained by numerically solving a set of Ordinary Differential Equations (ODE) automatically derived by our SSN model; while Latin Hypercube Sampling, a well-known sampling technique to scan input parameter spaces, is exploited for model calibration and sensitivity analysis.


Francesca Cordero

Title: Computational models to inspect intratumor heterogeneity

Abstract: The IntraTumor Heterogeneity (ITH) is an essential determinant of tumor progression, diagnosis and treatment. It is the result of the action of the evolutionary forces of mutation and selection that lead to cancer cell populations with distinct genotypic and phenotypic profiles. The high level of ITH contribute to the failure of cure, by initiating phenotypic diversity and enabling more aggressive and drug resistant clones. In this presentation I will give a general overview of about the presence of ITH in the cancer samples and which are the technologies and methodologies to inspect it.


Igor Erovenko

Title: The evolution of cooperation in mobile populations on multiplayer stochastic networks

Abstract: We create stochastic simulations of a finite evolving population of individuals on a network. Individuals move around the network following a Markov process and interact with each other via a public goods game. We investigate how the population size, movement cost, exploration time, and network structure affect the evolution of cooperation. This modeling framework allows to extend the analytic approach of Pattni, Broom, and Rychtar for complete graphs to arbitrary networks.


Ted Galanthay

Title: A game-theoretic approach to foraging dynamics

Abstract: The Hawk-Dove game has been used to model the evolution of aggression in animals. This is a frequency-dependent, but density-independent, two-strategy game with well-known results. In the classical game, interactions between players take the same amount of time. R. Cressman and V. Krivan found qualitatively different results when interaction times depended on the strategies. Recent work extended this time-dependent Hawk-Dove game by incorporating foraging dynamics, from ecology, by including payoffs to singles from foraging on an implied underlying resource where resource levels were assumed to be fixed. In this talk, we present preliminary results on how predictions of aggression are affected by including resource dynamics.

Amira Kebir

Title: A general dynamical game model for structured population and applications

Abstract: In this work we study a generalized form of a dynamical game elaborated in Kebir et al (2015) for hermaphrodite species. This general dynamical game includes a finite number of strategies and a finite number of physiological structures. For this model we prove the existence and find sufficient conditions of stability in a particular equilibrium state that describes well mixed population with pure strategies. We then analyze these results for a spatially structured hawk and dove game model and a new model for hermaphrodite population called the residual game (RG) model (Kebir et al, 2018).

A.Kebir, N.H.Fefferman, and S.Ben Miled (2015). Understanding hermaphrodite species through game theory J. Math. Biol. 71 1505-1524.
A.Kebir, N.H.Fefferman, and S.Ben Miled (2018). A general structured model of a hermaphrodite population J.Theor.Biol. 449 53-59.

Pietro Landi

Title: Adaptive Dynamics and evolutionary diversification: Theory and applications

Abstract: Adaptive Dynamics is a mathematical framework for the study of phenotypic evolution driven by selection in ecological context. One of its main innovative features is the formalization of evolutionary branching, that is, the sympatric diversification of two morphs under disruptive selection from a single phenotype. Subsequent evolutionary branching events are thus responsible for the increase of polymorphism in the community and, possibly, sympatric speciation.
The mathematical conditions for evolutionary branching were introduced in the late Nineties, but the formalization of critical branching events has only recently been developed. Moreover, such critical condition triggering evolutionary branching has been systematically used to study the evolution of polymorphism in prey-predator communities, in bio-economic models of fisheries, and social systems (fashion evolution). Current work is addressing the emergence of sympatric diversity in life-history strategies and its role in the emergence of intransitive competitive interactions, as well as the concurrent evolution of dispersal and self-fertilization in plant communities.

Karan Pattni

Title: Framework for studying evolution in structured populations with fixed and variable size.

Abstract: In this talk a framework that allows the modelling of structured populations with fixed and variable size is described. It is then shown that the fixation probability of a mutant in a resident population of fixed size is a special case of the fixation probability in a population with variable size. As an application of this modelling framework, the fixation probability as studied in the evolutionary graph theory framework is derived from a model with Lotka-Volterra type competitive interactions.

Silvestro Poccia

Title: Meta-data driven algorithms for detecting robust multi-dimensional motifs

Abstract: The unsupervised discovery of recurring pattern (Motifs) in time series data is a well known challenge. The discovery of motifs in uni-variate time series is a well studied problem and, while being a relatively new area of research, there are also several proposals for multi-variate motif discovery. Unfortunately, motif search among multiple variates is an expensive process as the potential number of sub-spaces in which a pattern can occur increases exponentially with the number of variates. Many multi-variate motif search algorithms make simplifying assumptions, such as searching for motifs acrossall variates, assuming that the motifs are of the same length or that they occur on a fixed subset of variates.

In this presentation, we will address a relatively broad form of multi-variate motif detection, which seeks frequently occurring patterns (of possibly differing lengths) in sub-spaces of a multi-variate time series. In particular, we aim to
(a) allow for significant variations in temporal length as well as in the sub-space of variates,
(b) leverage contextual information to help select contextually-distinct patterns,
(c) identify most frequent such patterns among all.

Based on these goals, we first formally define the frequent, contextually-distinct, multi-variate motif discovery problem and then propose a salient multi-variate motif (SMM) algorithm that, unlike existing methods, is able to seek a broad range of patterns in multi-variate time series

Tomas Revilla

Title: Plant coexistence under adaptive exploitation and mutualism

Abstract: We consider the coexistence between species that affect one another indirectly via shared exploiters and mutualists, a common situation in plant communities interacting with generalist herbivores and pollinators. Previous works studied these indirect effects, as "apparent competition" in the case of shared exploitation, or "indirect facilitation" in the case of shared mutualisms, by considering feedbacks between resource (e.g., plants) and consumer (e.g., herbivores and pollinators) population dynamics. Here instead, we consider feedbacks between plant population densities and adaptive preferences of their exploiters and mutualists, which have fixed population densities. A model for two competing plants predicts transitions between single and multiple states of coexistence, as interactions with two animals varies between both animals being exploiters, one exploiter and the other mutualist, and both being mutualists. Overall, we conclude that combined adaptive preferences of exploiters and mutualists can make plant coexistence more likely, at least locally (i.e., dependent on initial conditions), by enabling alternative stable states.

Monica Salvioli

Title: A Stackelberg Approach To Cancer Treatment

Abstract: Standard cancer therapy conventionally applies chemotherapy at the maximum tolerated dose.The underlying idea is that killing the maximum number of cancer cells will result in the best outcome for the patient. However, though this approach is usually able to kill the majority of malignant cells, it often spares a small number of them, which evolve resistance to treatment leading to its failure. We develop a game theoretical model of cancer treatment to compare the standard treatment protocols with a dynamic therapy that takes into account the evolutionary dynamics of resistance. We show how a Stackelberg approach could remarkably improve the outcome for the oncologist (and the patient), compared to the current standard of care, thus contributing to the on-going discussion on the importance of personalized therapies and on the need to change targets for cancer treatment.

Matteo Sereno

Title: Energy Efficiency & Game Theory: Applications to Network Management Policies

Abstract: In this talk I will present some of my research efforts on energy efficient (network) management policies. In particular, I will discuss the application of energy-aware cooperative management of cellular access networks. In this setting I will briefly describe the investigated system/systems and the addressed problems. Later on, I will discuss the application of the same type of theoretical framework to cooperative energy efficient management policies for Internet data centers.

Karl Sigmund

Title: Outbreaks of Corruption - an evolutionary perspective

Abstract: Cooperation can be sustained by institutions that punish free-riders. Such institutions, however, tend be subverted by corruption if they are not closely watched. This monitoring can uphold a regime of honesty and cooperation, but it comes at a price. The temptation to reduce the monitoring costs leads regularly to outbreaks of corruption and breakdown of cooperation. We model the corresponding cycle by means of evolutionary game theory, using analytical methods and numerical simulations.

Anthony Sun

Title: A social-ecological model for lake pollution dynamics

Abstract: Classical ecological models often don't see human influence as a dynamical variable. In the context of eutrophication in shallow lakes, we use a game theoretical approach to represent how the anthropogenic discharge of pollution changes to compare and interpret results obtained with the replicator dynamics and with the logit best-response dynamics.
Although the two can be seen as contradictory, they can give rise to qualitatively similar results regarding the location, resistance and existence of stable equilibria in complex cases.

Yannick Viossat

Title: Modeling adaptive therapy

Abstract: Adaptive therapy is a new kind of cancer therapy. Instead of attempting to eradicate the tumor, it tries to manage it optimally, and in particular to delay the emergence of resistance to treatment. One way is to give smaller treatment doses in order to maintain a population of sensitive tumor cells. The competition with these sensitive cells may slow down the growth of resistant cells. A few mathematical models of adaptive therapy are available, with often markedly distinct assumptions and conclusions. We will review some of these models and discuss possible directions for future modeling efforts.

Fei Xu

Title: Sexual predation preference in a predator-prey system

Abstract: In this talk, we consider the interaction between a predator species and a prey species, in which the prey species has sexual dimorphism and predator species preys sex-selectively. The male and female prey species may have different appearance, size and behavior, and these differences significantly influence the payoff of the predator. On the other hand, predators often adjust their sex bias to maximize their per capita population growth rate. We construct mathematical models by incorporating a game theory-based sex-selective predation strategy into the predator-prey system to investigate the interplay between the predator species and the prey species. Our investigation reveals the effects that such game-theoretic behaviors of predators have on the long-term behavior of the system.

Zhijun Wu

Title: Equilibrium Distributions of Populations of Biological Species on Networks of Social Sites

Abstract: We discuss the problem of how a population of biological species would distribute over a given network of social sites so that their social contacts through the connected sites can be maximized (or minimized).
This problem has applications in modeling the behaviors of social (or solitary) species such as the development of social groups in human society and the spread of solitary animals in distant habitats. We show that this problem can be formulated as an evolutionary game, with the equilibrium state of the game corresponding to a strategy for choosing the residing sites, each with a certain probability, or equivalently, to a distribution of the population on these sites. The game has a symmetric payoff matrix, and can therefore be analyzed via the solution of a corresponding quadratic program. With a goal to maximize the social contacts, the species tend to spread on network sites where there are dense connections such as a complete subnetwork or in other words, a network clique. We show that at equilibrium, the population may or may not distribute on a network clique, but the stability of the equilibrium state does depend on the structure of the selected subnetwork. In particular, we show that the distribution of the population on a maximal network clique is evolutionarily stable unless the clique is ``attached" to another clique of the same or larger size, when the population may be able to switch or expand to the neighboring clique to increase or at least maintain its total amount of contacts. However, the

distribution of the population on a non-clique subnetwork is always evolutionarily unstable or weakly evolutionarily stable at the very best, for the population can always move away from its current distribution without decreasing its total amount of contacts. We conclude that the strategies to spread on maximal network cliques are not only equilibrium strategies but also evolutionarily more stable than those on non-clique subnetworks, thus theoretically justifying the evolutionary advantages of joining social cliques in social networks for social species, as we often observe in real world.
This is joint work with former students Min Wang and Wen Zhou.


Li You

Title: Including blood vessel in a game theoretical model of cancer dynamics

Abstract: Blood vessels are an important factor for the growth of a tumor, as they provide it nutritionist and possibilities to metastasize. Implementation of blood vessels can help us analyze the (eco-evolutionary) dynamics of real tumors. In this work we include the dynamics of blood vessels, the angiogenesis, in a spatial game-theoretical model, where three different types of cancer cells are included: (i) those dependent on exogenous testosterone (T+), (ii) those that produce testosterone and provide it as a public good to their environment (TP), and (iii) those that are independent of testosterone (T-). All these cells engage in pairwise interactions to proliferate and survive, while their proliferation rate also depends on cells' distance from blood vessels. We study frequency dynamics of our model under different scenarios of blood vessel dynamics. The proposed model is a great tool for modeling real tumors as it incorporates different hypotheses regarding both angiogenesis and tumorigenesis, giving opportunities for treatment implementation.