Postdoc modelling and measurement of resistance evolution in E.coli : antibiotics and bacteriophages. (M/F)

Workplace : Montpellier, FRANCE

Type of Contract : FTC Scientist

Contract Period : 24 months

Expected date of employment : between March and December 2020

Proportion of work : Full time

Remuneration : net salary per month: 2449 € for < 2 years post PhD and 3381 € for > 2 years post PhD.

Desired level of education : PhD

Experience required : Maximum 7 years post PhD

Missions:

Scientific context:

Resistance evolution in microbes (to antibiotics and other forms of therapy) is both a major issue in medicine and agronomy and a central challenge in theoretical population biology (mixing evolution and demography, out of equilibrium). On the other hand, the subject can be tackled by various theoretical tools (microbial growth models, theory of mutation and evolutionary rescue) and a diversity of techniques from experimental microbiology (disk diffusion, fluctuation tests, automated methods to measure bacterial growth). Yet, there is no general and empirically validated theory on the probability of emergence of resistance, or on how each factors determine it (drug dose and effect, population sizes, mutation rate etc.). Because of this, most dosage regimens are prescribed based on case-specific empirical observation, rather than on theory – based optimization a priori. The study of resistance evolution is also a means to test more general theories on mutation selection and stochasticity, in changing environments, with applications well beyond the treatment of infectious diseases.

Aims and missions:

The goal of this project is to empirically test various models of evolutionary rescue. The recruit will perform real-time measurements of demographic dynamics in the bacterium Escherichia coli, facing lethal stresses. We routinely use several strains of E.coli B transformed with a fluorescent marker (YFP or CFP) and a lux operon (for live cells), both constitutive and chromosomic, and a fluorescent dead cell stain. The dynamics of live and dead cells and of total biomass will be monitored by fluoroluminometry (LEHTINEN et al. 2003), which allows an automated measurement at fine timescale in many replicates: typically of the order of a thousand populations for every single experiment of a few days duration. We will study abiotic stresses (single antibiotics or combinations) and biotic stresses (single or cocktails of bacteriophages) and their interactions. The postdoc will empirically study the effect of the nature and dosage of the stress and of the strain of origin, on (i) the probability of resistance

emergence, (ii) its dynamics (early or late, from de novo or preexisting variation) and the type of resistant mutant selected (reduction in death rate, increase in birth rate, single or multiple mutations).

The postdoc will analyze the data obtained using models, partly already developed by the host team, that include the dynamics of the stress (pharmacodynamics/pharmacodynamics of the drug in vitro, epidemiology of the bacteriophage) and the evolution of resistance (evolutionary rescue theory (MARTIN et al. 2013)). Last we will try to test more complex but more general models, based on adaptive landscape theory (e.g. ANCIAUX et al. 2018).

References :

Anciaux, Y., L.-M. Chevin, O. Ronce and G. Martin, 2018 Evolutionary Rescue over a Fitness Landscape. Genetics 209: 265.

Lehtinen, J., M. Virta and E. M. Lilius, 2003 Fluoro-luminometric real-time measurement of bacterial viability and killing. Journal of Microbiological Methods 55: 173-186.

Martin, G., R. Aguilee, J. Ramsayer, O. Kaltz and O. Ronce, 2013 The probability of evolutionary rescue: towards a quantitative comparison between theory and evolution experiments. Philos Trans R Soc Lond B Biol Sci 368: 20120088.

Activities:

- Set up and run experiments of fluoroluminometry to monitor bacterial dynamics (pipeting, programming microplate reader, data extraction). Main task, training by researchers G. Martin, R. Froissart, technical help (M.A. Devillez).

- Develop models (systems of ordinary differential equations) to describe the observed dynamics. Main task, training with G. Martin.

- Fit the models on the observed dynamics and estimate relevant (pharmacokinetics, epidemiologic and evolutionary) parameters. Main task, jointly with G.Martin.

- Test alternative evolutionary rescue models on these data from various adaptive landscape models. Secondary task, with G. Martin.

- Develop alternative home-made microplates and/or mini-chemostats to mimic more complex pharmacokinetics. Secondary task, with G. Martin.

Skills : This is a quantitative, theory-oriented experimental project. Previous experience in at least one of the 3 central skills below is required, experience in more than one of them is a plus but not a necessity:

- Basic microbiology (pipeting, plating, CFU counting etc.), which can be acquired early on during the postdoc. Previous experience in microbial experimental evolution and/or demography will be a plus.

- Modelling by differential equations. Basic knowledge in models of demography and population genetics is required. Further experience in stochastic processes and systems dynamics will be a plus.

- Time-series data analysis by nonlinear regression and GLMs. Previous experience in the fitting of dynamical models is a plus.

- Motivation to perform both (simple automated) experiments and model development and test is critical.

- Ease to write articles in English is necessary.

Work Context: The postdoc will work in the Institut des Sciences de l'Evolution de Montpellier (ISEM) in the team 'evolution and demography', under the direction of Guillaume Martin, webpage:

http://www.isem.univ-montp2.fr/fr/personnel/equipes/metapopulations/martin-guillaume.index/

The ISEM lab is on the Triolet campus of the Montpellier University, France. Montpellier is an important site, at worldwide level, in ecology/evolution, e.g. it hosted the last joint meetings from the European and American Evolution societies (Evolution 2018). There are many researchers in the domain (both local and visitors) and various weekly seminars in ecology and evolution, in several sites in the city.

The postdoc will be hired via the ANR project RESISTE (https://informatique-mia.inra.fr/resiste/) whom PI is G. Martin (theoretical biology, developed the fluoroluminometry system in the lab). This project will benefit from the expertise of various partners in ANR RESISTE:

- In Avignon : Mathematics and statistical analysis of dynamical systems (e.g. Lionel Roques, from INRA BioSP, co PI of the RESISTE project).

- In Montpellier : R. Froissart, M. Fronhoeffer et O. Kaltz (specialized in microbial experimental evolution, on bacteria and phages) and O. Ronce (Modelling of evolutionary rescue).

The postdoc will work in a dedicated L2 level bacteriology lab, equipped with an Easy Spiral Pro + Scan 500 + dataLink (Interscience) for automated colony counting on petri dishes, a microplate dispenser (Multidrop, Thermofisher) and a multimode plate reader (Clariostar BMG Labtech) equipped with two injectors, and a stacker (reading up to 50 microplates), and several microplate agitator and incubators.