What is the ExposUM Doctoral Nexus?

The Doctoral Nexus proposed by the ExposUM Institute are networks of 3 to 4 PhD students from different disciplines and affiliated to at least two different research units.

Compared with a traditional PhD, taking part in a Doctoral Nexus will encourage the ability to work in a team and to design projects in a transdisciplinary way while deepening one's own field of expertise.

A specific teaching programme will be offered and the doctoral students concerned will also have the opportunity to organise a seminar within the Nexus network.

Theses are funded from the outset for 4 years, including the PhD student's salary and an environmental allowance.

Summary of the overall project

The epidemiological and evolutionary dynamics of infectious diseases are affected by many environmental, ecological and social factors. In order to understand and anticipate the public health consequences of an epidemic, and the evolution of the pathogen, we need to precisely model the pathogen's environment. In this project, we plan to study a specific aspect of this environment, which is age structure. Motivated by the realisation, during the COVID-19 pandemic, that age structure was a crucial modelling ingredient to make public health predictions (hostpitalisation peak, vaccination), anticipate viral evolution (variant dynamics) or understand physiopathology (intra-host kinetics).

The EMIPSA project brings together biologists, mathematicians, statisticians and medical doctors who propose to use age-structured models to analyse the epidemiological (change in the number of cases) and evolutionary (change in variant frequencies) dynamics of pathogens. Our Nexus project will allow interactions between 4 distinct PhD projects on (1) the evolution of pathogen life-history strategies, particularly respiratory viruses, in population structured by infection age and vaccination status [evolutionary ecology], (2) the rigorous mathematical justification of the structured models used in evolutionary epidemiology [mathematics and modelling], (3) modelling intra-host evolutionary dynamics in malaria, taking into account the age structure of red cells [mathematics and modelling], and (4) the anticipation of the impact of epidemics on the French critical care system, taking into account the dynamics of the distribution of risk factors, and more specifically age [public health].

Evolution of pathogen life-history strategies: infection age, heterogeneity and plasticity

PhD project

Context : Pathogen adaptation to their environment depends on many phenotypes which are expressed at different steps of the life cycle : infection of a new host, intra-host pathogen growth, production of transmissible propagules. These various phenotypes are often summarised using a reduced number of traits : virulence α, transmission rate β, recovery rate γ. These phenotypes can evolve due to direct, or indirect, selection pressuresmodulées **[1]**. The succession of variants during the COVID-19 pandemic has demonstrated the importance of understanding and predicting the factors that govern this evolutionary dynamics. However, classical adaptation models assume that traits are constant during the infection, which implies that infection times are exponentially distributed and that the transmissibility of a host is independent of the time since the beginning of the infection (i.e. infection age). These constraints do not match empirical estimates of pathogen generation times **[2].** Although some models have taken infection-age structure into account **[3],** they often consider simplified epidemiological scenarios and cannot describe transient evolutionary dynamics in a heterogeneous host population, where the number of contacts or immunity status is variable among hosts. It is therefore important to develop a new theoretical framework to describe pathogen adaptation in more realistic scenarios. Such a framework will be most useful to understand the phenotypic evolution of SARS-CoV-2 and other pathogens.

Objectives : This PhD project aims at modelling the evolution of pathogen strategies of host exploitation when they can be affected by the infection-age distribution of the host population, the heterogeneity of the host population, and the ability of pathogens to modulate their strategy as a function of the time elapsed since the start of the infection (which is known as plastic strategies). The models will rely on a mechanistic description of intra-host pathogen growth, in order to characterise the selection gradients on the traits that govern pathogen replication. This analysis will be used to understand short- and long-term evolution of pathogen life history traits (transmission, virulence…). We'll analyse three epidemiological scenarios.

- *Evolution in a homogeneous host population. We will analyse the evolution of pathogen phenotypes when hosts are all identical, in various epidemiological scenarios (exponential growth, endemic equilibrium, seasonal fluctuations).*
- *Evolution in a heterogeneous host population. We will then take into account age-dependent variations in behaviour or morbidity. For instance, older individuals have often less contacts than young adults, but are more at risk, as observed for SARS-CoV-2. How does this heterogeneity affect the evolution of pathogen strategies ?*
- *Pathogen adaptation to vaccination :* Vaccination introduces another form of heterogeneity in the host population. Pathogens can adapt to vaccines **[4]** through

immune escape strategies but also specific age-dependent exploitation strategies. We will analyse the joint evolution of these different strategies.

Methods : The PhD candidate will combine (1) compartmental epidemiological models taking into account host status (infection, vaccination, age) , (2) infection-age-structured models (partial differential equations), and (3) models of intra-host pathogen growth during acute infections.

Expected results : The model will be used to quantify the selective advantage of a phenotypic variation in traits expressed at different times during an infection and in different epidemiological scenarios. This will allow us to characterise both transient and long-term pathogen adaptation.

Faisability: The theoretical framework to analyse these models exists, based on models already developed by S. Lion and S. Gandon **[5]**. O. Ronce will bring her unique expertise of life-history evolution in age-structured demographic models **[6]**. A challenge of this project will be to jointly take into account infection-age structure and epidemiological dynamics. Because this challenge is shared by the various PhD projects of the Nexus project, the PhD candidate will greatly benefit from the expertise and progress of the whole consortium.

Keywords: epidemiology, virulence, viral evolution, age structure, vaccination, intra-host dynamics

Références [en gras, personnes impliquées dans le projet NEXUS]: [1] Day & **Gandon** (2007) Applying population-genetic models in theoretical evolutionary epidemiology. *Ecology Lett.* **[2]** Blanquart et al (2022) Selection for infectivity profiles in slow and fast epidemics, and the rise of SARS-CoV-2 variants. *Elife*. **[3]** Foutel-Rodier et al (2022) From individual-based epidemic models to McKendrick-von Foerster PDEs: A guide to modeling and inferring COVID-19 dynamics. *J. math. Biol.* **[4] Gandon** & Day (2007) The evolutionary epidemiology of vaccination. *J. R. Soc. Interface.* **[5] Gandon** & **Lion** (2022) Targeted vaccination and the speed of SARS-CoV-2adaptation. *PNAS*. **[6]** Cotto, Olivieri & **Ronce** (2013). Optimal life-history schedule in a metapopulation with juvenile dispersal. *J. evol. Biol.*

Supervision : Sébastien Lion (DR CNRS, CEFE Montpellier ; advisor), Sylvain Gandon (DR CNRS, CEFE, Montpellier; co-advisor), Ophélie Ronce (DR CNRS, ISEM, Montpellier; co-advisor).

Host laboratory : Centre d'Écologie Fonctionnelle et Évolutive (CEFE), 1919, route de Mende, 34293 Montpellier Cedex 5. (https://www.cefe.cnrs.fr)

Application procedure

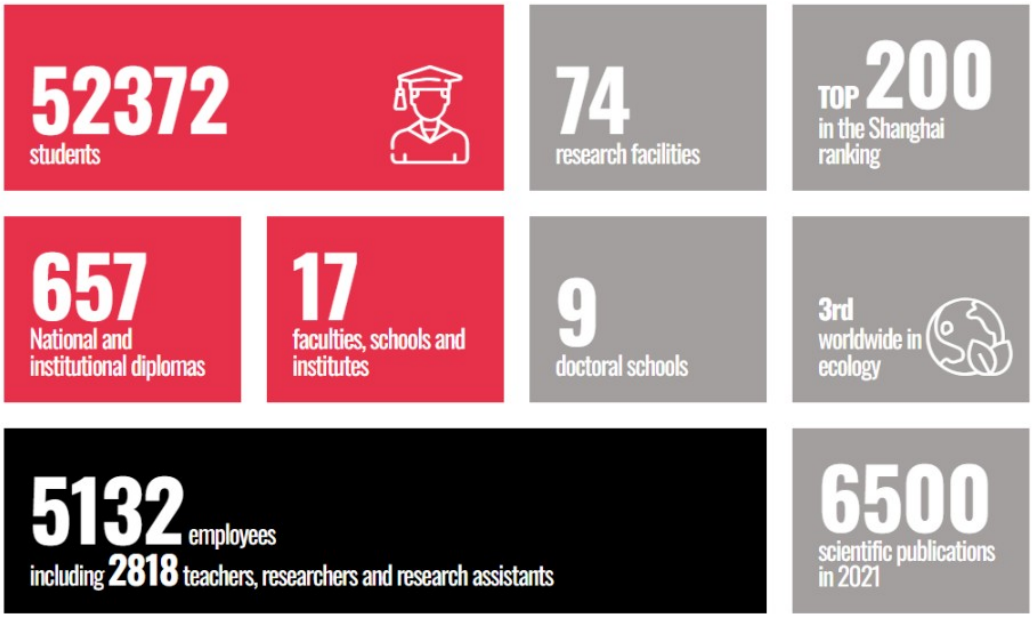
The application must include the following

- a CV
- a letter of motivation
- a copy of the degree required for registration
- any additional specific information requested by the doctoral school **GAIA** (https://adum.fr/as/ed/gaia/index.pl).

If you would like to apply for this position, please send an e-mail to Sébastien Lion (sebastien.lion@cefe.cnrs.fr), Sylvain Gandon (sylvain.gandon@cefe.cnrs.fr), and Ophélie Ronce (ophelie.ronce@umontpellier.fr), with a CC to exposum-aap@umontpellier.fr to inform them of your interest.

Before Sunday 21 April, 8pm CET

KEY FIGURES



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