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].

Within-host epidemiological and evolutionary dynamics of malaria

PhD project

Context : Malaria in humans results from infection by various species of Plasmodium such as *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. Although *P. falciparum* and *P. vivax* are the most common, *P. falciparum* is responsible for the most severe form of the disease, resulting in almost all deaths, while *P. vivax* is generally considered less severe. The malaria parasite has a complex life cycle, involving sexual reproduction in the insect vector and two stages of infection in the human (or animal) host: a hepatic stage[1] and a blood stage[2]. This blood stage can be either asexual or sexual (the only infectious stage for the vector). Different species of *Plasmodium* show specific preferences for red blood cells of different ages[3]. Several empirical pieces of evidence show that hosts can be co-infected by multiple species of *Plasmodium*.

Objectives : This PhD project aims to: (i) Characterize the competitive advantage of a specific Plasmodium species within mixed malaria infections in the infected host. (ii) Identify the preferential strategy of infecting red blood cells of different ages which is favored by natural selection within mixed Plasmodium infections. (iii) Precisely describe the evolution of gametocyte production, which is essential for host-vector transmission.

Methods : The proposed approach involves age-structured mathematical models within hosts, taking into account the heterogeneity of red blood cell maturation stages (*eg*., reticulocytes, mature red blood cells, and senescent red blood cells), as well as competition between different genotypes within the infected host. Furthermore, the age of red blood cell infection will be considered in the parasitic phase. Here, age is a continuous variable representing the time elapsed since the infection of the respective red blood cell. Such a continuous age structure, based on partial differential equations, allows for tracking the development of parasitized red blood cell maturation. Additionally, such a structural variable yields a precise description of the rupture of these parasitized red blood cells and the phenomenon of merozoite release (extracellular forms of malaria parasites)[4,5], as well as parasite sexual commitment.

Expected results : This project will contribute to deepening the epidemiological and evolutionary understanding of parasite multiplication within the host of *Plasmodium* species. This improved understanding of the evolutionary coexistence of *Plasmodium* species within the same host has significant clinical and public health implications for therapeutic decision-making. Furthermore, this PhD project will address fundamental questions in both ecology and evolution. From an ecological perspective: What is the effect of erythrocytic environment heterogeneity (or different stages of red blood cell maturation) on species coexistence within an infected individual? In an evolutionary context: What is the impact of the abundance of red blood cell maturation stages on the parasite's preferential choice of an evolutionarily stable maturation age? What is the effect of variable (or fluctuating) reticulocyte production over time by the bone marrow on these evolutionary attractors? Is it possible to evolve towards synchrony in parasite

generation time? What would be a relevant fitness measure for a better understanding of gametocyte production evolution?

Feasability: The advisory team specializes in evolutionary ecology, epidemiology, structured models, dynamical systems, and adaptive dynamics. This team, which has previously collaborated on topics related to structured models in population dynamics[6,7], provides a conducive working environment for the doctoral candidate, in addition to the entire consortium of this NEXUS project.

Keywords: Age-structured models (PDE); adaptive dynamics; epidemiology; evolution; malaria.

References [in bold, people involved in this NEXUS project]: *[1]Frevert (2004) Sneaking in through the back entrance: The biology of malaria liver stages. Trends in Parasitology. [2] Bannister and Mitchell. (2003) The ins, outs and roundabouts of malaria. Trends in Parasitology. [3] Paul, Ariey, and Robert (2003) The evolutionary ecology of Plasmodium. Ecology Letters. [4]* ***Djidjou-Demasse*** *et alli. (2022) Understanding dynamics of Plasmodium falciparum gametocytes production: Insights from an age-structured model. Journal of Theoretical Biology. [5]* ***Djidjou-Demasse*** *et alli (2022) Differential preferences for RBCs is key for Plasmodium species evolutionary diversity within human host. Studies in Applied Mathematics. [6]* ***Richard****, Choisy, Lefèvre &* ***Djidjou-Demasse*** *(2021) Human-vector malaria transmission model structured by age, time since infection and waning immunity. Nonlinear analysis: real world applications. [7] Fabre, Burie, Ducrot,* ***Lion****,* ***Richard****, and* ***Djidjou-Demasse*** *(2022) An epi-evolutionary model for predicting the adaptation of spore-producing pathogens to quantitative resistance in heterogeneous environments. Evolutionary Applications.*

Supervision : Ramsès Djidjou-Demasse (CRCN HDR MIVEGEC & EPT; advisor), Sylvain Gandon (DR CEFE; co-advisor), Quentin Richard (MCU, IMAG ; co-advisor).

Host laboratory : UMR MIVEGEC (IRD 224-CNRS 5290-UM), France et EPT, Sénégal.

Application procedure

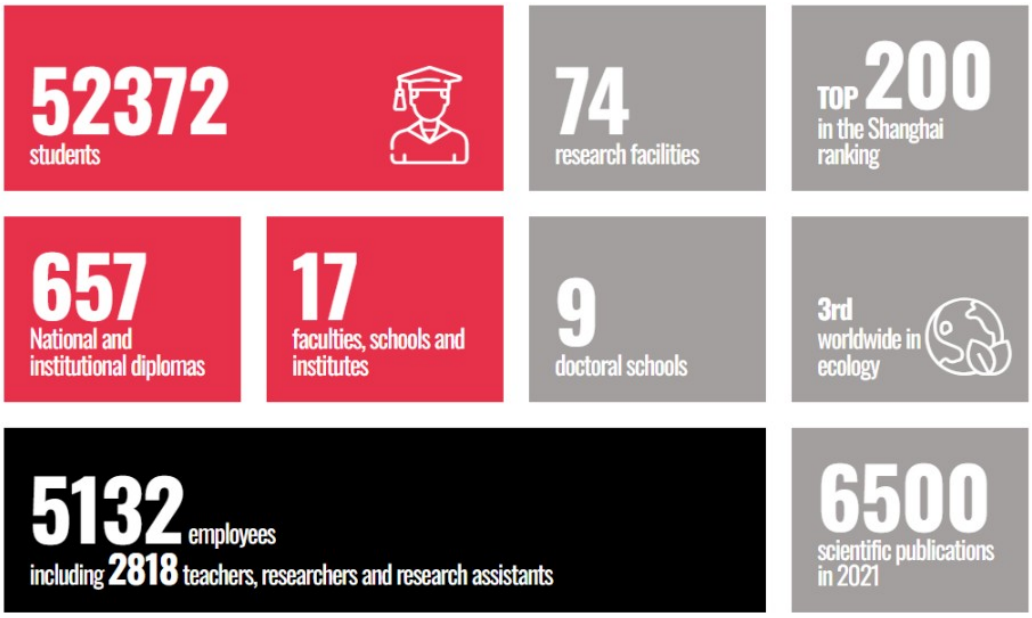
The application must include the following

- a CV
- a letter of motivation
- a copy of the degree required for registration
- any additional specific information requested by the doctoral school I2S (https://adum.fr/as/ed/I2S/home.pl).

If you would like to apply for this position, please send an e-mail to Demasse (ramses.djidjoudemasse@ird.fr), Sylvain Gandon (sylvain.gandon@cefe.cnrs.fr), Quentin Richard (quentin.richard@umontpellier.fr), with CC to Sébastien Lion (sebastien.lion@cefe.cnrs.f r) and exposum-aap@umontpellier.fr to inform them of your interest.

Before Sunday 21 April, 8pm CET

KEY FIGURES



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