Cystic Fibrosis Lung Microbiota: An Example of Predator-Prey Ecology.

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The lower respiratory system has been classically considered as a sterile organ, although the molecular tools demonstrated the existence of a lung microbiota even tough in a healthy status. The Cystic Fibrosis (CF) lungs have a pathogenic bacterial colonisation that started after the birth, determining the clinical status of the patient and the disease progression. The application of the next-generation sequencing techniques to CF-respiratory samples has allowed us to expand our knowledge to this complex microbiota, focusing in other fastidious or uncultured microorganisms that we never have considered as real pathogens. Recent works demonstrated that the lung microbiota of the CF-patients with worst lung function is characterised by a low diversity and complexity with the enrichment of the typical CF-pathogens.

Presence of the predator species *Bdellovibrio bacteriovorus* in healthy and CF human gut microbiota has been recently described, as well as the ability to attack the classical CF-pathogens as *Pseudomonas aeruginosa* or *Staphylococcus aureus* [1]. The introduction of these predators has been suggested to control the gut microbiota disbiosis [2], but the consequences of these strategy is not enough supported by scientific data.

The aim of the present work was describe a mathematical model to elucidate the ecological repercussion of the prey-predator interaction in the CF lung. Fifteen CF-adults regularly attended in Ramn y Cajal Hospital were recruited and each one contributed with 3-4 induced sputum samples during a follow-up period of a year. The induced sputum samples were separate in two aliquots; one process as routinely for classical microbiology culture and the other was frozen at $-80C$ immediately and reserved for next-generation sequencing experiments. DNA samples were sent to FISABIO (Valencia, Spain) for massive 16S rDNA amplicon sequencing in Hi-Seq Illumina platform and bioinformatic analysis.

We use a computational agent based of multiple predator-prey model to simulate the behaviour of bacteria inside the lung. This type of models allows us to combine several features that seem interesting to simulate the ecology of bacteria: the bacteria are discretely defined, are spatially distributed, and can be born and die during simulation. In our simulations we introduce 5000 agents initially 5 different types of agents with two defines roles: 3 agents with the role of preys and 2 agents with the role of predators, as a simple ecosystem. These agents are dispersed spatially randomly with different initial proportions. The various initial proportions are defined from the experimental data from sputa. The initial proportions of all types of agents were defined according with the real data observed in the lung microbiota of CF-patients.

The rules for defining how agents behave on their own and with each other are: for prey agents, each individual agent reproduces at a given reproduction rate. To avoid an exponential growth apply a logistic-type growth constrain. In the meantime, if a prey agent meets a predator agent, it dies with some probability because predation. For predator agents, the rules are somewhat the opposite. If a predator cannot find any prey spatially nearby, it dies with some probability. But if the predator can feed on prey, it can also reproduce at a certain growth rate. Both types of agents diffuse in space by random walk.

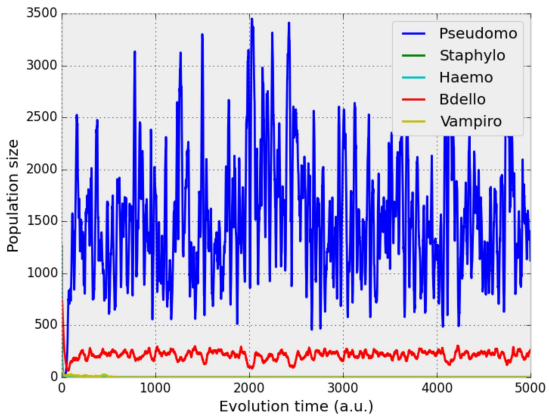

Figure 1: Time evolution bacteria populations.

Fig.1 shows a typical result for our simulations. We have 3 types of preys (*Pseudomonas*, *Staphylococcus*, *Haemophilus*) and 2 types of predators (*Bdellovibrio*, *Vampirovibrio*). In this figure we can observe as populations survive only one type predator and one prey type, disappearing the other types of agents. This behaviour, where all populations least two, with predator and prey roles, disappear produces classical oscillatory solution of the Lotka-Volterra equations. The rest of populations disappear. This result is obtained with the initial condition, 40% and 40% of initial number of agents of populations of bacteria *Pseudomonas* and of *Staphylococcus*, respectively, but in this case the prey, which survives, can be either higher initial population. Finally, if we increase the initial population of predators (Vampiro and Bdello), about 15%, we can make disappear all populations.

These preliminary results show these type of Agent Based Models like a useful tool to understand possibles medical actions to improve CF patients.

[1] V. Iebba et al. Front Microbiol. **5**, 280 (2014).

[2] A. Mosca, M. Leclerc, J.P. Hugot, Front Microbiol. **7**, 455 (2016).