Cystic fibrosis lung microbiota: Coexistence of prey and predators

R. Vida[1], J. de D. Caballero[2,3], L. García-Regueiro[1], R. del Campo[2,3], and J. Galeano[1]
[1]Grupo de Sistemas Complejos, Universidad Politécnica de Madrid, 28040 Madrid, Spain
[2]Servicio de Microbiología, Hospital Ramón y Cajal, 28034 Madrid, Spain
[3]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), 28034 Madrid, Spain

Cystic fibrosis (CF) is a genetic disorder that affects mostly the lungs. It is caused by the occurrence of mutations in a particular gene. The natural evolution of CF pulmonary disease consists in a progressive decline in lung function caused by a vicious circle of inflammation and tissue destruction that is triggered and maintained by chronic bacterial colonisation of the lower respiratory tract. The main pathogen detected in the CF airway by conventional culture techniques is *Pseudomonas aeruginosa*, which has a major influence on patients survival and their quality of life.

The application of the recent molecular techniques based on massive nucleotide sequencing for the study of the composition of the lung microbiota has allowed us to discover a completely unknown ecosystem.

In the present work was to monitor the lung microbiota composition of 15 CF patients during a year in relation to their clinical data and antibiotic consumption. The fifteen CF-adults contributed with 3-4 induced sputum samples during a follow-up period of a year. Samples were processed for classical microbiology cultures and also submitted to massive sequenciation by bioinformatic analysis to determine the lung microbiota composition. A new computational model based was design to predict the ecological interactions of CF-pathogens and prey-predator bacteria along time. For this model we used as prey bacteria *Pseudomonas, Staphylococcus* and *Haemophilus* whereas the predator species were *Vampirovibrio* and *Bdellovibrio*.

The microbiological cultures of the 56 sputum samples recruited demonstrated chronic lung colonisation by *P. aeruginosa* (11 patients), *S. aureus* (11 patients), *Burkholderia* (1 patient) and *Pandoreae* (1 patient). *P. aeruginosa* and *S. aureus* co-colonisation was observed in the 8 patients with lowest lung function.

Considering all samples, 156 bacterial species were detected, corresponding 90% the classical cultivable CF-pathogens. Unexpectedly, the recognise predators *Vampirovibrio* (17 samples, 12 patients, 0.003%) and *Bdellovibrio* (6 samples, 3 patients, 0.002%) were detected. Computational model results were consistent with the extinction of all populations except one predator and one prey that finally coexist. Finally, introducing a high initial population of predators (0.15% instead 0.03%) all populations disappear.

Thanks to these results, we present an agent based model designed to simulate the Predator-Prey ecological interrelation-ships that could be present in the lung microbiota. For this purpose, and considering the real proportions observed in our sputum samples, the bacteria selected as preys were *P. aeruginosa* and *Staphylococcus*, whereas

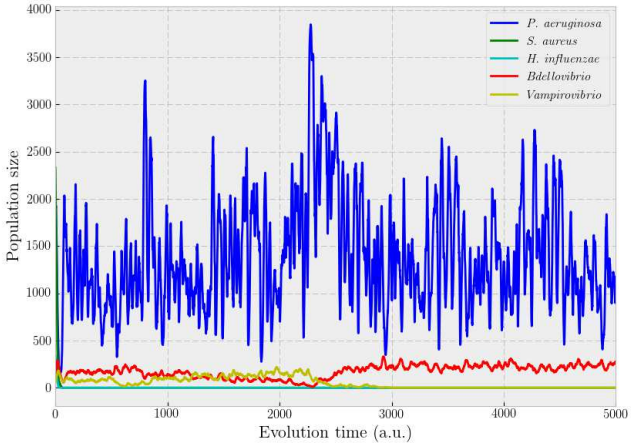

Fig. 1. Temporal evolution of bacterial population size. Initial distribution: 2000 *Pseudomonas*, 2000 *Staphylococcus*, 250 *Haemophilus*, 500 *Bdellovibrio*, and 250 *SPP bacteria*.

Bdellovibrio was considered a predator. Because of uncertainty about the role of *Vampirovibrio*, we decided to introduce as a second putative predator (SPP) [1].

The model analyse the behaviour of the agents, including the spatial distribution and the overall results obtained at the arbitrary time points reproduce the classical oscillatory solution of the Lotka-Volterra equations and were consistent with the extinction of all populations except one predator and one prey, which ultimately coexist in equilibrium. To understand the influence of the initial populations of predators, there were performed a great number of simulations, studying whether populations survive or die by using the survival rate. A threshold appears in the simulations, and it becomes relevant if the objective is changing the final state of equilibrium. The newly designed computational model allows us to hypothesise that inoculation of predators into the lung microbioma could eradicate CF pathogens in early stages of the process.

In conclusion, the presence of predator bacteria was described for first time in the lung microbiota of CF-patients. The computational model could help us to understand the bacterial ecology linked to CF-environment.

[1] J. de D. Caballero, R. Vida, M. Cobo, L. Máiz, L. Suárez, J. Galeano, F. Baquero, R. Cantón, and R. del Campo, Individual patterns of complexity in cystic fibrosis lung microbiota, including predator bacteria, over a 1-year period, mBio **8**, e00959–17 (2017).