Estudio de las fases del proceso de infeccin del intestino grueso por *Clostridiodies difficile* mediante el simulador de modelos basados en agentes, *gro*

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Clostridiodies difficile is an anaerobic gram-positive toxigenic bacterium that causes a severe infectious diarrhoea and pseudomembranous colitis. The large intestine of humans and mammals is protected by the gut microbiome, composed of approximately 400 bacterial species. Supply of broad-spectrum antibiotics in hospitals leads to disruption of the gut symbiosis, resulting in the emergence of niches that can be colonised by various pathogens such as *C. difficile*.

The first step against *C. difficile* infection is to stop giving broad-spectrum antibiotics, followed by providing certain antibiotics that have specific activity against *C. difficile* such as vancomycin. Nevertheless, in the last decade in about 20% of the cases conventional therapies are useless, because *C. difficile* has developed resistance and new virulent strains. Faecal microbiota transference is a novel approach to this complex problem, which is an experimental method with between 80% and 90% successful recovery rate. The via of administration of the transference and the bacterial composition of the donor faecal sample do not seem to be relevant, it is sufficient to restore a healthy and diverse gut microbiota.

The aim of this work is to study the *C. difficile* infection process and its treatment using the individual-based modelling programme *gro*, which is an open-source biological simulator created by Eric Klavins research group at the University of Washington. Specifically, I have used the version from Alfonso Patn's Artificial Intelligence Laboratory at the Polytechnic University of Madrid.

The results obtained agreed with real patient data, allowing the visualisation of the complete process of the 3 most abundant intestinal bacterial populations (*Enterobacterales*, *Lactobacillales* and *Fusobacteriales*) together with *C. difficile*. Bacterial growth was analysed in a state of symbiosis, followed by a state of dysbiosis in which *C. difficile* thrives, and finally, after the faecal microbiota transference, leading to the recovery of intestinal bacterial diversity.

In the first simulation of a healthy individual, bacteria grew exponentially according to their growth rate and the percentage of *C. difficile* population was low, as it could not thrive due to its condition as a bad competitor specie. In the second simulation, the supply of a generic antibiotic affected most bacterial populations but not *C. difficile*, leading to a decrease in intestinal bacterial diversity and, consequently, an increase in the *C. difficile* population. It is at this point that *C. difficile* begins to synthesise toxins and symptoms of infection may become visible. In the last simulation, the donor bacteria were added to the patient, restoring intestinal bacterial diversity, and thus decreasing the *C. difficile* population. Figure 1 shows the percentage of each bacterial population throughout the simulation after a faecal microbiota transference.

C. difficile infection is an evolving global health problem, there are on average 7 cases for every 10,000 overnight patients stays in European hospitals. The incidence in the US is similar, it is the main cause of hospital associated infection, with an estimated 14,000 deaths each year. For these reasons, the search for a treatment for this disease is a necessity, being focused on the faecal microbiota transference. However, in spite of the proven effectiveness of the faecal microbiota transference and an intuitive reasoning of its function, there are many important questions about the exact procedures and key molecules involve in the metabolic pathways of a faecal microbiota transference.

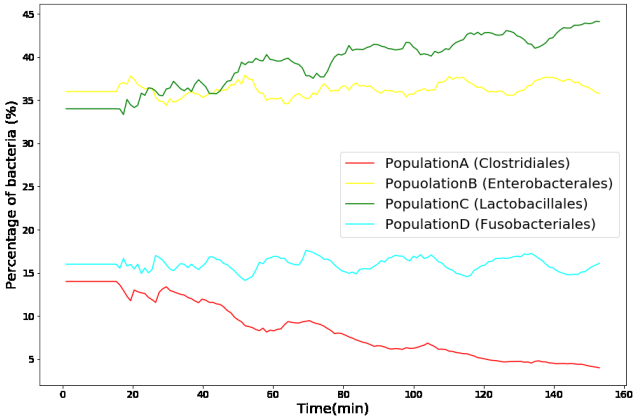

Fig. 1. Percentage of bacteria per population over time in a bacterial growth simulation of a faecal microbiota transference.

[1] S.S. Jang, K.T. Oishi, R. G. Egbert and E. Klavins *Specification and simulation of synthetic multicelled behaviors*, ACS Synthetic Biology **8**, 365-374 (2012).

[2] M. Gutierrez, P. Gregorio-Godoy, G. Prez del Pulgar, L.E.. Muoz, S. Sez and A. Rodrguez-Patn *A new improved and extended version of the multicell bacterial simulator gro*, ACS Synthetic Biology **8**, 1496-1508 (2017).

[3] "https://github.com/olgahs/" Clostridium-difficile-infection

[4] "https://www.youtube.com/" "playlist?list=PLjLAYk-Cbhr-3gYw-yvHSmS5z3UDDCGSd"