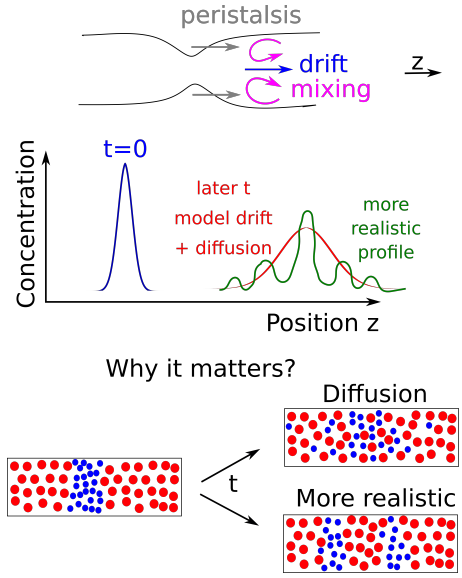
Physical modeling of the gut microbiota

In a human body, bacteria have been estimated to be in approximately equal number as human cells, 99% of them in the digestive tract [1]. A question that has just started being addressed is how the physical environment may explain the organization of the microbiota in the gut. Besides the flow in the gut, there are also biotic factors, which mechanism of action may actually be physical. The main effector of the adaptive immune response in the gut is a type of antibodies, which mainly protect the host by binding bacteria together, as we contributed to show [2]. Our aim is to develop a more comprehensive model of the physical and mechanical environment in the gut and its consequences for microbiota, to distinguish which aspects can be interpreted with physical arguments. Two main ingredients are missing in the existing models: a more realistic modeling of transport, and antibody-mediated bacterial clustering. Described in an effective way, these aspects will be integrated to a comprehensive model of the physical environment of the gut microbiota, which will be used to study the microbiota spatial structure, and the microbiota evolution, and used to interpret data, in collaboration with immunologist Emma Slack (ETH Zürich).

The internship will be located in Laboratoire Jean Perrin, Sorbonne Université, Jussieu, Paris. The advisor will be Claude Loverdo. The internship can be followed by a PhD, but we have no specific funding for a PhD student. There are two possible directions for the internship:

A more realistic transport



One of the challenges is to model the flow in the digestive system. Muscles around the digestive tract contract, performing what is called peristalsis. This has two functions: to move the digesta forward; and to mix it, such that the nutrients are sufficiently close to the epithelial cells to be effectively transported via diffusion and passed to the blood and lymph. A classic way to model effectively such a transport is a combination of drift and diffusion. But in an in vitro set-up reproducing peristalsis [3], as well as in vivo, detailed measures show that, if we start with a delta of concentration, there is indeed a widening of the distribution, but by packets, not continuously (see schematic). For certain observables, such as the mean square displacement corrected for the drift, a diffusive description is good enough. But, for instance when modeling bacteria that interact by direct contact, daughter bacteria will remain closer to each other than what would be the case for diffusion with the same mean square displacement.

The intern will first use existing results in the literature to rebuild a numerical simulation that will be used first for heuristics. It will then be used to test analytical approximations to develop.

Antibody-mediated bacterial clustering

The only strong handle the host has to control its microbiota at the species level is its adaptive immune system. Its main effector released in the gut lumen is secretory immunoglobulin A (sIgA), a type of antibody. Many studies have focused on the complex molecular and cellular pathways that trigger its secretion, but little had been done to decipher how it really acts after secretion. Mice vaccinated with inactivated salmonella produce specific sIgA and as a consequence are not sick when fed with live salmonella. But sIgA neither kills salmonella nor prevents them from reproducing. A classic idea in immunology is that as one antibody has several binding sites, antibodies aggregate bacteria when they collide into each other. However, this effect would be negligible at realistic bacterial concentrations in the digestive system, simply due to the very long typical time for bacteria recognized by the same sIgA encountering one another. We contributed to show that the main protective effect is actually the following: upon replication, daughter bacteria remain attached to one-another by sIgA, driving the formation of clumps derived from a single infecting bacterium [2]. Clustering has physical consequences: the produced clusters do not come physically close to the epithelial cells. And as interaction with the epithelial cells is essential for salmonella virulence, this is sufficient to explain the observed protective effect. This "enchained growth" is effective at any bacterial concentration.

Thus the main protective effect of sIgA is due to binding bacteria together, which can be studied with simple mechanical models. As a stepping stone, we showed that since sIgA-mediated links between bacteria may break, their breaking may interact with bacterial replication, and may lead to fast-replicating bacteria being more likely to be trapped into clusters by sIgA. Thus, the immune system could simply produce sIgA against all the bacteria it encounters, instead of having to make complex decisions about which bacteria are good and which are bad, and only fast-replicating bacteria, the most likely to do harm, or at least to destabilize the microbiota, would be affected [4]. The intern will extend this model for different geometries of the bacteria, and different geometries of the links between bacteria.

For more information

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