Reaction-diffusion model for the understanding of tuberculosis dynamics at the scale of a secondary pulmonary lobule

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Tuberculosis (TB) is still one of the major humankind threats, being one of the 3 main causes of death by an infectious disease worldwide. TB is a communicable chronic infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). An infection with *Mtb* often causes no symptoms, remaining controlled as a non-contagious latent tuberculosis infection, but a 10% of infected people will develop the contagious active disease (i.e., a TB) even several years after the infection. An 85% of the TB cases correspond to a pulmonary disease, while the rest are extrapulmonary [1]. Despite the global efforts to fight the disease, its incidence is still stable, being the infectious disease that has killed most people in history. European cities today face a significant challenge to control TB infection and spread. The End TB Strategy by the World Health Organization [2] identifies the Latent Tuberculosis Infection as one of the challenges to overcome in order to accomplish the stated objective.

Mathematical and computational models may be used for making progress on the understanding and control of the latent infection.

We built a reaction diffusion model to reproduce tuberculosis infection in a secondary lobule. This model is formed by 10 elements: b_i (intracellular bacilli, bacilli contained inside macrophages), b_e (extracellular bacilli, bacilli outside macrophages), m_u (uninfected macrophages, macrophages with no bacilli inside), m_i (infected macrophages, macrophages with bacilli inside), m_a (activated macrophages, macrophages that are activated and can kill bacilli), n (neutrophils), T (T-cells), f (fibroblasts), s (inflammatory response signal) and V_nc (necrotic volume, volume occupied by dead cells).

The model consists of 10 partial differential equations that determine the evolution of each element from an initial state. Elements interact with each other and diffuse to the nearest alevoli.

All these elements and reactions are considered to occur inside each alveolus. The size of a secondary pulmonary lobule is around 1 cm^3 and contains around 10^5 alveoli. In our model it was implemented as a $52 \times 52 \times 52$ alevoli grid.

In Fig. 1 the results of the evolution of an initial infected macrophage with one bacillus are shown. During the first lysis cycle extracellular bacilli are more than intracellular ones. When immune response is activated the number of bacilli is reduced and number of uninfected macrophages are dominant. This results and the numbers obtained reproduce biological data [3]. Lesions encapsulation success depended on fibroblast diffusion coefficient. If fibroblast molecules did not diffuse rapidly enough the infection was out of control. Immune system induced a faster control of the lesions, which were smaller and easier to encapsulate. In Fig. 2 the encapsulation process of a lesion in a host where immune system is properly activated. It can be seen that when the lesion reached the septum it is surrounded by fibroblasts.

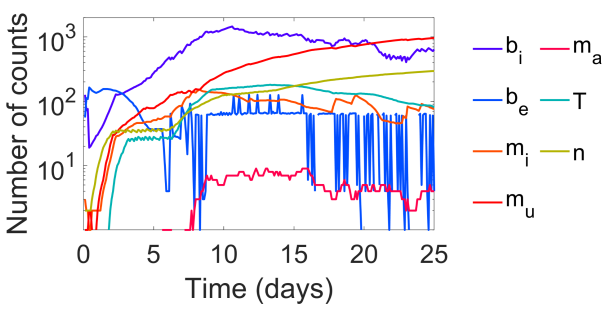

Fig. 1. Number of counts of the different elements of the model at the alveolus where infection starts. The elements are intracellular bacilli b_i, extracellular bacilli b_e, uninfected macrophages m_u, infected macrophages m_i, activated macrophages m_a, neutrophils n, and T-cells T.

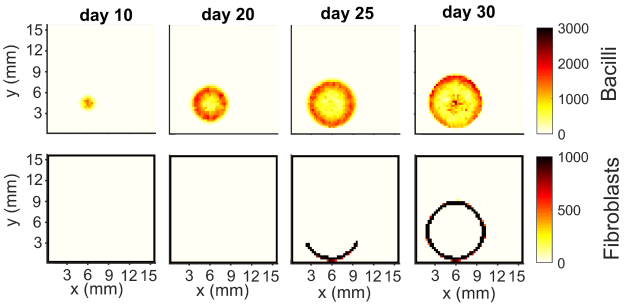

Fig. 2. Number of bacilli and fibroblasts observed in a secondary lobule at different times. Fibroblast encapsulate the lesion when the septum is reached.

[1] World Health Organization, *Global Tuberculosis Report 2017* (World Health Organization, Geneva, 2017).

[2] World Health Organization, *The End TB Strategy* (World Health Organization, Geneva, 2014).

[3] P.-J. Cardona, Patogénesis de la tuberculosis y otras micobacteriosis, Enferm. Infec. Microbiol. Clin. **36**, 38-46 (2018).