Pneumo-gaming: Computer game based on multi-level mathematical modelling and simulation used to investigate early-phase bacterial lung infection.

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***Abstract*— Pneumococcal infection is the most frequent cause of pneumonia, and one of the most prevalent and dangerous diseases. The risk groups for the disease namely, infants elderly and immunosuppressed people, are more exposed and vulnerable because vaccines are not efficient in them, and when the symptoms appear the risk of death is high. Instead, preventing the alveolar infection would be a promising strategy in this group. A multilevel mathematical model converted into a game is proposed to understand the biological mechanism of the prevention of the disease through the gaming experience of the users.**

Here we propose to create a game out of a mathematical model that contains the main interactions during the early steps of pneumonia infection. The game can be used as a educative resource as an interphase between the user and the knowledge about pneumonia.

Keywords*— *Streptococcus pneumoniae; pneumonia; alveolar infection; biofilm; multilevel mathematical model; gamification

I. Introduction

Lung infectious diseases like pneumonia are prevalent worldwide diseases and they pose a serious threat to the health of risk groups like children, elderly and immunosuppressed patients. On average, every 20 seconds one child dies due to pneumonia worldwide, especially in third-world countries. In addition to this tragedy, infections like pneumonia are a serious economic burden for the healthcare system. In 2011 and only in the US, pneumonia was responsible for 1.1 million hospitalizations with a total cost of $ 7 billion [1].

One of the critical issues to improve prevention and treatment of lung infections is to foster our understanding of the physiological interactions between the pathogens, bacteria and viruses, and the patient’s immune system. Interestingly, a number of physiological barriers try to stop the establishment of the infection in the lung alveoli. The failure of some these physiological barriers are within the known weaknesses of the immune response in vulnerable people, including infants, elderly and immunocompromised people like those with organ transplantation [2]. Consequently, it might be beneficial to identify and understand these potential weaknesses to find new therapeutic strategies for improving the current prevention and treatment of these infections. We think that computer modelling and simulation can foster the discovery of the key features responsible for the successful establishment of bacterial lung infections.

II. BACTERIAL PNEUMONIA

A. *A primer on pneumonia at the physiological and molecular level*

At the very early phase of the bacterial invasion, physiological barriers play a crucial role in the quick resolution of the infection and the prevention of the disease. Moreover, the damage inflicted in the infected tissue poses a further risk factor and increases the possibility of other pathogens to attack this part of the lung [3]. Thus, a strategy to reduce the overall infection risk is to handle the pathogen infection before entering and damaging healthy tissue.

One example for a physiological barrier in the lung is the epithelial cell barrier of the alveoli; there we can find alveolar macrophages and a thin layer of liquid attached to the surface of the epithelial cells. This liquid layer is continuously produced and generates a flow which clears the alveoli from bacteria, which otherwise would grow in the external surface of the lung alveoli using as nurture proteins in the tissue debris. The epithelial cells that make up the alveoli impede the bacteria from entering the bloodstream, but also react to their presence by producing chemicals that attract to the point of the infection the first line defense immune cells, the macrophages [4]. All these processes take place within the first 24 hours after the arrival of the bacteria to the alveoli. After this period, many other types of immune cells like neutrophils are recruited to the alveoli, starting a hard fight with the bacteria which often generates tissue damage. The focus of our model-based game is to understand the role of this early phase physiological barriers in preventing the infection.

B. *Aim of the initiative*

The role played by the alveolar physiological barriers within the first 24 hours after infection is virtually impossible to investigate *in vivo* with the current technologies. Instead, we propose that it is possible to build a mathematical model that predicts the interaction of these elements and the pathogens in a single alveolus. The difficult part of this strategy is to make an efficient use of the modelling and simulation to determine the key physiologic and bacterial parameters determining the shift between a successful infection and a rapidly cleared one. To this end, one strategy could be to launch a random, massive amount of computer simulations and use unsupervised machine learning methods to statistically analyze the output of these simulations. However, this strategy is computationally and statistically exhausting.

Interestingly, in other biological complex problems with similar computational requirements like the elucidation of protein folding, gaming approaches has been explored to make use of the ability of players to digitally interact with the biological problem, learn within the game experience and propose alternative solutions, for example, the best folding structure for given proteins (see for example, the game Foldit: https://fold.it/portal/). In Foldit, it has been shown that, trained gamers can solve biological problems more efficiently and closer to the reality than dedicated computers.

Inspired by this gaming strategy, we propose to create a game based on computer model and simulation that:

1. Increase the awareness of the general public on the risk for the health associated to lung infectious diseases.

2. Educate the general public, especially youngsters, on the basis of the interaction between the human immune system and the pathogens.

3. Exploit the knowledge generated by experienced gamers to elucidate the key physiological and bacterial factors deciding between a successful infection and a rapidly cleared one.

The starting point of the initiative is a multi-level mathematical model developed by the Laboratory of Systems Tumor Immunology (FAU Erlangen-Nürnberg) in collaboration with clinical and experimental researchers from Marburg and Berlin-Charité. The model can simulate the early phases of the pneumococcal infection in a single alveolus. It accounts for the macrophages moving on surface of the lung alveoli, the reactivity of the epithelial cell layer, the growing and moving bacteria, as well as the role of the liquid layer flowing on the epithelial cells and the diffusion of chemicals attracting macrophages in response to bacteria.

The mathematical model is implemented in Matlab R2015b combining agent based modelling and ordinary differential equation modelling. To translate the model into a game it is used the language of Unity to make it friendly playable.

III. THE GAME

A. Definition of the game

Alveolar infection is a process that involves many elements at different time and space scales. In order to simplify the problem the focus of the will be in the first 24 hours of infection, in which cytokines from alveolar macrophages and cell recruitment has not yet began to be relevant. Also, the model focuses in a single alveolus, composed by 11x11 epithelial cells. In the model we consider three interconnected processes occurring at different scales: the lining fluid dynamics of the alveolus and bacterial growth, the macrophage movement and the signaling pathway inside epithelial cells of the alveolus. Figure 1 displays these scales graphically.

Purple layer represents the epithelial cells that protect the alveolus. These cells produce a gradient of chemicals (cytokines in red) that diffuse through the lining liquid of the alveolus (light blue in Figure 1) in response to bacteria (red-orange oval). The gradient is felt and followed by the macrophages (gray structure) to eat the bacteria.

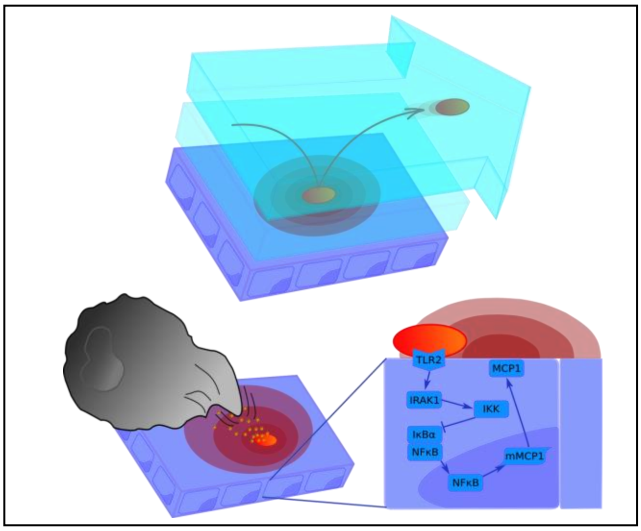

Fig. 1. Scheme of the game

B. Game captions

Figure 2 shows a caption of the game after being run during 15 hours. Bacteria (in red) growth on the epithelial cell layer (background). Macrophages (light blue) follow the cytokine gradient (orange colors) to find and eat bacteria. The game is defined stochastic so different launches can produce different outcomes. The gamer should be able to modify the parameters of the bacteria and the macrophages in a way that the game will produce an outcome in which it won't be any bacteria after 24 hours.

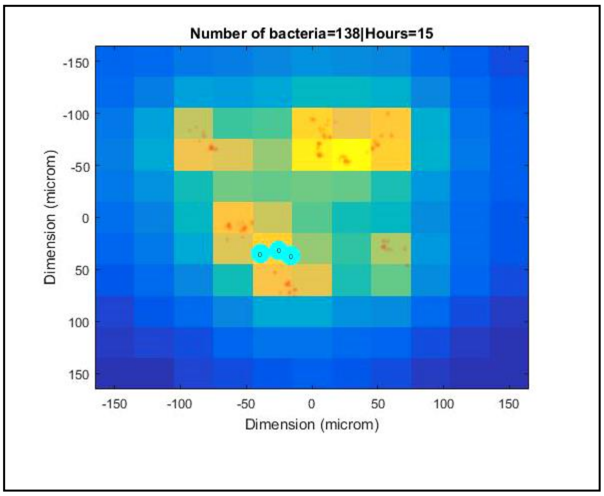

Fig. 2. Caption of the game

IV. CONCLUSIONS

The game is able to generate biologically feasible simulations of the early steps of pneumonia infection. The game will let the user to play with these simulations to understand the interactions occurring during the lung infection. It can be used as an educative resource that helps to visualize in real time the biological interactions and also it can be used to obtain useful information from the players to improve the knowledge of the biological processes.

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