Modelling biofilm growth subject to local antibiotic delivery

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Introduction

Implant infection is a serious clinical problem, with treatment usually involving systemic delivery of antibiotics. However, due to the ability of bacteria within biofilms to survive antibiotic dosages that would ordinarily kill free-swimming proliferative bacteria, biofilm infections are extremely difficult to eradicate. Antibiotic resistance and tolerance confound the problem, often associated with nutrient insufficiency, hypoxia in the deeper layers of biofilm and antibiotic concentration at levels above the Minimum Inhibitory Concentration (MIC) [1]. An alternative approach is to delivery antibiotics locally in a sustained manner. In this study, we present a mathematical model of biofilm growth subject to antibiotic delivery, with the aim of understanding how the biofilm growth and composition depends on the drug dose and release rate.

Methods

We have formulated a 1D biofilm growth model in which we introduce controlled antibiotic release directly from the implant. If the release is inadequate to prevent bacterial growth, then infection can take hold, however if drug release is excessive then this may impair the recovery of healthy tissue around the implant. This represents a delicate balance, amenable to exploration and optimization through mathematical modelling.

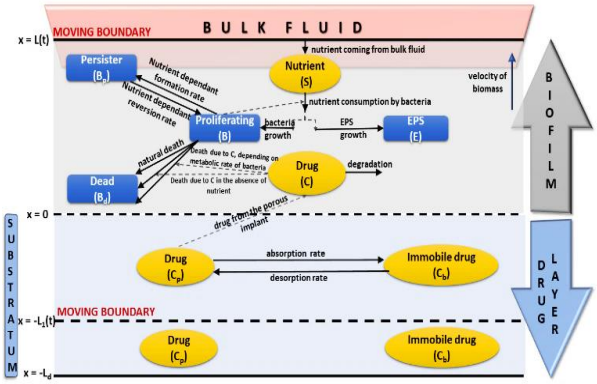

Figure 1: Schematic of the bacterial species, nutrient and antibiotic interaction in our latest model.

The approach of modelling biofilm growth while optimizing antibiotic dose and release rate simultaneously may result in a more efficient biofilm prevention strategy. The model consists of different bacterial phenotypes, self-produced extra cellular polymeric substance (EPS), nutrient concentration, water volume fraction in the biofilm pores, growth of the biofilm and a porous implant filled with antibiotic (see Fig.1) [2]. We have simulated how different model parameters, including nutrient concentration, influence the growth of different bacterial phenotypes. We also simulated how different antibiotic-release strategies from a nano-porous implant impact on the time-course of biofilm growth and its constitution [3]. In this model, antibiotic-induced death of active bacteria along with natural death are considered.

Results

As expected, the density of proliferative bacteria increases moving away from the implant, where antibiotic is being delivered from and decreases with increasing antibiotic dose. However, the persister bacteria, one of the main reasons for antibiotic resilience, increases with increasing antibiotic dose since the proliferative bacteria transforms into the persister phenotype in order to survive the antibiotic dosage.

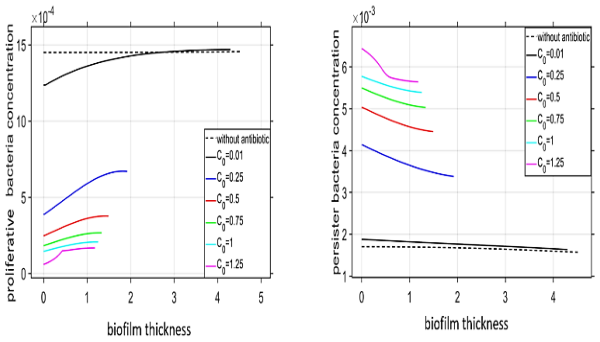

Figure 2: Plot for proliferative and persister bacteria vs biofilm thickness at final time for different levels of antibiotic eluting from the implant.

Conclusions

Our model suggests that careful tailoring of antibiotic release could help prevent implant-associated infection as biofilm thickness and proliferative bacteria cells decrease with increasing antibiotic dosage. The model is able to capture experimentally observed resilience to antibiotic shown by persister cells. Our immediate next steps would be to find the optimal antibiotic delivery configuration such that the infection gets eradicated along with persister cells which will result in no further infections on the implant.

References

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