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Synchronization among tumour-like cell aggregations coupled by quorum sensing: A theoretical study

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Abstract

In this paper we examine the synchronization of a collection of repressilators in tumour-like cell aggregations coupled using quorum sensing. The force of diffusion that exists between neighbouring cells on the surface of the tumour has been paid due consideration. The study reveals that such a coupled system would show synchronization. Our computational results further show that such a prediction holds not only for individual tumours but also for multiple tumours coupled together. The degree of synchronization is found to be dependent on the strength of coupling, which is in turn determined by the cell density.

Keywords: Repressilator; Synchronization; Quorum sensing; Cell aggregation; Genetic oscillators

1. Introduction

Medical researchers today are quite concerned about different issues related to the synchronization of biological oscillators and the mechanisms by which this is achieved. The said phenomenon is of utmost importance in many physiological conditions. For instance, the human heart functions via alternate contractions and relaxations of its chambers, the auricles and the ventricles, set off by signals from the sino-atrial node, also known as the pacemaker. This tissue consists of a collection of myocytes that synchronously generate electrical impulses to trigger the contractions of the heart. However, several important questions regarding synchronization are yet to be explored.

Of grave concern in health sciences today is the manifestation of the deadly disease cancer, and its treatment modalities. Sometimes the occurrence of tumours can lead to carcinogenesis. Analytical studies of tumours can be broadly classified into three parts based on the particular stage in the life cycle of a tumour they examine: *avascular tumour growth*, *tumour-induced angiogenesis* and *metastasis*. The first approach models the incipient stages of the tumour that results in a benign growth. The tumour is localized and sufficiently small. The latter two approaches model the malignant stages of the tumour when the tumour obtains its own blood supply (angiogenesis) and can use it to be transported to different parts of the body (metastasis). While these approaches are more relevant to cancer cure, they entail a prohibitively complex model without sufficient experimental data for verification.

One cannot ignore the importance of such a study, although it involves a large amount of complexities. Indeed any theoretical approach requires experimental data in order to quantify its predictions. However, we can make educated

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guesses regarding the situations that are likely to appear *in vivo* before proceeding towards experimental analysis — a feasible approach in many cases where a direct experiment can be difficult or even impossible. Investigations on tumours fall into such a category. We are unable to simulate, with a significant degree of authenticity, the cellular conditions under which a tumour initiates and propagates in the human body. In the present day and age, one cannot conduct clinical trials on human subjects in order to verify the accuracy of the predictions made. Moreover, experimental data obtained from tests on sub-human primates are not directly applicable to humans. This necessitates the modelling of theoretical constructs that approximate the changes taking place at a microscopic level inside human tissue.

Biological oscillators are quite common in nature. They are extremely wide in their scope, occurring in several phenomena such as circadian rhythms and in specialized systems like the endocrine system. Organisms are continuously subjected to dynamic changes enforced by the external environment and also by the cyclic behaviour induced by internal cellular clocks. Instances of the latter include the cardiac pacemaker which is found at the sino-atrial node in the human heart and the suprachiasmatic nuclei (SCN) located in the human hypothalamus that is responsible for endogenous 'circadian rhythms'. These oscillators are specialized structures composed of thousands of inherently diverse clock cells that still manage to oscillate in unison. The mechanism behind such collective behaviour remains as one of the nature's abiding mysteries.

Clock cells operate via biochemical networks that consist of numerous intertwined regulatory feedback loops. The sheer complexity of these networks serves as a deterrent for the understanding of underlying mechanisms behind their function. Synthetic genetic networks bypass this problem, doing away with the overwhelming complexity of such systems while maintaining certain levels of control that enable us to examine their functions in detail. The synthetic biological oscillator, called the "repressilator", was developed in *Escherichia coli* with this very purpose in mind. It consists of a network of three transcriptional genes that inhibit each other in a cyclic manner. Individual cells in the culture were found to oscillate spontaneously.

As a logical step forward, a mode of inter-cell coupling was introduced that would improve the oscillatory response in a systemic manner. Quorum sensing as a means for population control and synchronization has been studied in recent times. Hahnfeldt et al. [1] gave a dynamical theory to explain the growth, treatment response and postvascular dormancy of tumour. In a recent communication, McMillen et al. [2] have demonstrated theoretically that a population of identical genetic oscillators can be synchronized using quorum sensing. Garcia-Ojalvo et al. [3] have also shown quorum sensing as a means to induce synchronization in an array of noisy coupled repressilators. Several attempts to model the tumour growth have been made in recent years by different researchers [4–7].

For the purpose of our study, we will use cells that are structurally identical to those used in [3].

The present investigation is primarily based on the introduction of cellular aggregations into the said problem. While in the studies referred to above, the researchers had considered single cells in solution coupled by quorum sensing, we develop here a new mathematical model, incorporating the level of complexities that arise due to the coupling of each cell to its neighbours via diffusion. Such a situation is prevalent in a 'tumour-like' mass that consists of several layers of cells. However, in such a structure only the outermost layer of cells are in direct contact with the external solution and hence only these are coupled by quorum sensing.

The continuum hypothesis of tumour structure assumes that there is an absence of well-defined layers in a tumour. There is a gradual drop in cell density from the surface of the tumour to the interior. We adopt this hypothesis in our study. Moreover, Ward and King [4] have modelled avascular tumour growth and found that the live cell density falls quite sharply from the outer surface of the tumour to the interior. Hence, it is reasonable to assume that the outermost layer is the only one where we find live cells. Besides, on the surface of a tumour a cell can be in physical contact, and hence capable of exchanging products via diffusion, with several cells. In our model, we have incorporated such an exchange between a cell and two of its neighbours.

In the following sections, we have first examined the case of a single cell aggregation (which for our purposes we call a 'tumour') in isolation. We consider a single tumour and check whether its own cells synchronize under quorum sensing. Subsequently we move on to a population of 'tumours' coupled by quorum sensing and find that they synchronize globally when we increase the strength of the coupling.

2. The proposed model

The repressilator consists of three genes combined together in a pathway. The products of each inhibit the transcription of the others in a cyclic manner [3]. The relationship is shown in the diagram (see Fig. 2.1). The gene lacI