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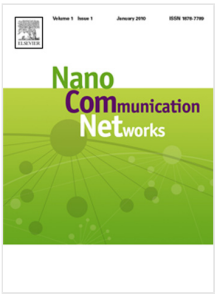

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Chieh Lo, Kartikeya Bhardwaj, Radu Marculescu

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Towards Cell-based Therapeutics: A Bio-inspired Autonomous Drug Delivery System

Chieh Lo[a,*], Kartikeya Bhardwaj[a], Radu Marculescu[a]

[a]*Department of Electrical and Computer Engineering, Carnegie Mellon University, 5000 Forbes Ave, Pittsburgh, PA, 15213*

Abstract

Traditional drug delivery systems are often inefficient and imprecise as they mainly rely on diffusion processes. For example, the blood circulation system is often used to transport and deliver drugs throughout the body; due to the randomness involved in molecular diffusion, this approach can cause inefficient and imprecise delivery of drugs. To address this problem, we propose an autonomous and adaptive bacteria-based drug delivery system that integrates bacterial chemotaxis and quorum sensing in order to deliver drugs efficiently and precisely at various location in the human body. More specifically, we design a synthetic AND gate that enables bacteria to detect molecules produced by tumors and release the appropriate drugs in a coordinated manner; the system can also dynamically adjust the amount of drugs released based on tumor size and activity level. Our experimental results show that the proposed system can be effectively used for cell-based therapeutics while preventing drug overuse and multi-drug resistance.

Keywords: Drug delivery, Cell-to-cell communication, Molecular communication

1. Introduction

Traditional drug delivery systems like injecting drugs into blood vessels are often inefficient as they rely on diffusion processes to deliver drugs. Indeed, diffusion makes these systems imprecise spatially (i.e., with respect to a target location) and in terms of dosage [1]; this can lead to drug overuse and multi-drug resistance [2, 3]. To address both problems, targeted cell-based therapies have gained significant attention recently [4]. This type of treatment interferes directly with specific cell molecules required for tumor growth, rather than indiscriminately targeting malignant and nonmalignant cells as is the case in traditional chemotherapy [5]. For instance, Alexander-Bryant *et al.* introduce strategies for designing targeted cancer therapies in [6]. More precisely, they propose to deliver a high dose of anticancer drugs directly to the cancer tumor, while minimizing the drug uptake by nonmalignant cells. However, the problem of how to efficiently deliver the drugs to the target location remains unsolved.

In recent years, targeted drug delivery has been actively studied and a number of mathematical models have been already proposed. For instance, in [7], the authors propose to design micro-robots with a rotating helical tail in order to prevent invasive drug delivery when swimming in a viscous fluid. However, a more bio-compatible approach is to use bacteria as bio-robots designed to perform pre-determined tasks. A model of using bacterial network to move bacteria toward the target locations has been proposed in [8]; the authors also provide some statistical analysis to quantify the performance of the drug delivery process. Therefore, bacteria-based drug delivery can be a perfect candidate because bacteria can be engineered to navigate to the target location. However, to the best of our knowledge, a mechanism by which bacteria can be engineered to collectively release a precise amount of drugs at the target location, in an adaptive manner has not been developed yet [9]. Consequently, as one of our main contributions, we propose a genetic circuitry that can sense the tumor related signals and then release drugs precisely to the target in an adaptive and coordinated manner.

Getting now into more details, one of the advantages of using bacteria as a drug delivery vehicle is that bacteria can sense multiple types of signals and make decisions through complex regulatory pathways. One such instance is the regulation of bacterial movement known as chemotaxis [10]. In a heterogeneous environment,

*Corresponding author

Email addresses: chiehl@andrew.cmu.edu (Chieh Lo), kbhardwa@andrew.cmu.edu (Kartikeya Bhardwaj), radum@cmu.edu (Radu Marculescu)