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Releasing rate optimization in a single and multiple transmitter local drug delivery system with limited resources

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ABSTRACT

Drug delivery is one of the most important applications of molecular communication. Drug transmitters have limited resources in terms of energy and reservoir and these limitations should be taken into consideration when designing a drug delivery system. Drug molecules may also be expensive and releasing a large amount of them can have harmful effects on the healthy parts of the body. In this paper, we consider a multiple transmitter local drug delivery system in which the nearest transmitters to a randomly located tumor are activated to release drug molecules and guarantee the Least Effective Concentration (LEC) in every part of the tumor. We propose two different scenarios: a single transmitter drug delivery system for which the optimal rate of the transmitting nanomachine and the optimal density of deployed nanomachines are derived through formulations and simulations. Poisson distributed as well as regular square and hexagon grid deployments are investigated. We then extend it to a multiple transmitter drug delivery system for which the optimal allocated rate to each releasing transmitter is derived in order to minimize the total rate of release and maintain LEC in every part of the tumor. It is shown that activating multiple transmitters leads to a reduction in the total optimal release rate of drug molecules as well as improving the time duration between consecutive administrations.

1. Introduction

Molecular communication is the transmission and reception of chemical signals or molecules. It is a multidisciplinary field between nanotechnology, biology and communications. This kind of communication is inspired from communication among living organisms and is considered as a promising approach in the health related applications due to bio-compatibility [1–4].

Targeted drug delivery (TDD) is one of the most important applications of molecular communications. It is recently under intensive research and is at the cutting edge of modern medical therapeutics [5]. The aim of drug delivery is to deliver drug at the target site with a rate dictated by the needs of the body over the period of the treatment. The drug delivery can be systemic or local. In the systemic drug delivery, drug is injected into the circulatory system as in [6–8], while in the local case the drug molecules are delivered locally to the target site as presented in [4,9–11]. In this paper, we are focusing on a local drug delivery system.

When the drug delivery system is localized to its site, such as a solid tumor, the drug needs to be released at a suitable rate to maintain drug level in the therapeutic range for the whole treatment period [12]. In sustained drug release systems, nano-transmitters release medication over an extended period of time to ensure prolonged treatment of the diseased area. In this regimen, the drug concentration needs to be maintained between a minimum referred to as Least Effective Concentration (LEC), below which the drug does not provide sufficient therapeutic effect, and a maximum referred to as Maximum Tolerated Concentration (MTC), above which the drug results in harmful effect for the rest of the body [13].

In this paper, we address the transmission rate control issue in a multiple transmitter local drug delivery system. The objective is to minimize the total release rate of the transmitter nanomachines while maintaining the minimum effective concentration at the target site. Optimal release rate of drug molecules is necessary in order to avoid toxicity in healthy parts of the body as well as dealing with limitations of nanomachines e.g. their limited energy

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and reservoir [9]. To this end, we propose a simple drug delivery system which consists of a single releasing transmitter. In this case, we find the optimal rate and density of deployed transmitter nanomachine through formulations and simulations. We extend this scenario to a multiple transmitter drug delivery system. The optimal allocated rate for each transmitter is calculated to ensure the minimum total rate of release.

In order to verify our design-oriented analytic results we use N3Sim, a well known simulation framework in Java for diffusion-based molecular communication (DMC) [14]. In DMC, transmitters encode information by releasing molecules into the medium, thus varying their local concentration. N3Sim is a Java package that models the movement of these molecules according to Brownian dynamics in a 2-D or 3-D environments. We also use MATLAB as an interface to specify the values of simulation parameters including the location of transmitter and receiver in N3Sim. This allows user to run multiple simulations automatically on a single configuration file. We use MATLAB as well for integrating, processing and representing the results.

This paper is organized as follows: Section 2 reviews the related works. In Section 3, we describe the system model. In Section 4, we talk about single and multiple transmitter drug delivery scenarios. Simple mode including a single releasing transmitter is presented in Section 5, while multiple transmitter scenario is investigated in Section 6. Simulation results with N3Sim are presented in Section 7. We talk about nanomachine placement and release trigger mechanisms in Section 8. Section 9 concludes this paper.

2. Related works on molecular communication and molecular communication based drug delivery

A layered architecture of molecular communication is proposed in [15] in order to decompose the complex functionality of molecular communication into several manageable layers. The major part of literature in molecular communication is devoted to physical layer issues such as modulation techniques [16], relaying [17,18], inter symbol interference [19,20] and detection [21]. Other researches in upper layers include addressing [22], distance measurement [23,24] and scheduling [25,26] in link layer as well as routing [27–30] in network layer. Flow control and congestion control issues in transport layer are investigated in [4,9,11] respectively.

In the field of drug delivery, some models bypass the injection through cardiovascular system and suppose the transmitters nanomachines are located close to the target site e.g. tumor. In [9], a transmission rate optimization problem is formulated to maximize throughput and efficiency. In this work, all transmitters are located at the same location for simplicity. Thus, the spatial distribution of transmitters is not discussed but mentioned as a future work. In [4], a TCP like protocol is presented to find the suitable releasing rate between the transmitter and receiver and avoid congestion. A multiple transmitter drug delivery system is formulated in [10] as an image processing problem to confine drug in irregular shapes of diseased tissue, as well as distributing the released rate among transmitters. An initial definition of congestion in diffusion-based molecular communication is introduced in [11] and the congestion control issue is investigated in a drug delivery scenario by proposing a reception model consisting of a set of pure loss queuing systems.

On the other hand, some literature investigate the drug delivery scenario in a systemic manner in which the drug is injected into the blood network. A drug propagation model of cardiovascular system is presented in [6]. This model allows the analytical expression of the drug delivery rate at the targeted site given the drug injection rate. A model of enzyme-catalyzed TDD is presented in [7] in the context of DMC. In [8], a molecular communication model is presented for systemic drug delivery at multiple diseased sites. The main focus of this paper is to ensure drug release at the target sites where may not express significant trigger stimuli.

3. System description

We consider a previously deployed network of transmitters all over the body. The transmitters can be located in a random fashion in which the uncertainty in transmitters locations can be represented by Poisson point process (PPP) or they can be arranged deterministically in a regular grid or a regular hexagonal distribution. Transmitters can work in two modes of operation, either active or inactive.

We assume that nano-transmitters, release molecules in a duty cycled manner. This has been demonstrated to approach a constant release rate of molecules [11], which in steady state and with assumption of no absorption, produces the concentration $c(r)$ given by [31]:

$$c(r) = \frac{Q}{2\pi Dr}, \tag{1}$$

where $c(r)$ is the concentration at distance r from the transmitter located at the origin, Q is the rate of released molecules and D is the diffusion coefficient.

Now, let us consider a multiple transmitter local drug delivery scenario in which N denotes the number of activated transmitters and Q_i is the release rate of each one. The set of transmitter locations is denoted by $R = \{r_1, \ldots, r_N\}$. Provided that the diffusion channel is an LTI system [32], the drug concentration at each point can be calculated as the superposition of concentrations produced by each transmitter at that point and is given by:

$$c(r) = \frac{1}{2\pi D} \sum_{i=1}^{N} \frac{Q_i}{\|r - r_i\|_2} \tag{2}$$

c is the number concentration which is defined as the number of entities of a constituent N divided by the volume V:

$$c = \frac{N}{V}. \tag{3}$$

The tumor is considered circular and the distance from a transmitter to the tumor is defined as the distance from the transmitter to the center of that tumor.

4. Optimal rate allocation in single and multiple transmitter drug delivery system

We are interested to find the optimum rate of each transmitter, so that the total number of drug molecules released during the treatment period is minimized while keeping the concentration at tumor location above the effective concentration. This is important because nanomachines come with limited reservoir and energy. This leads us to the following linear programming (LP) optimization problem which is formulated as:

$$\begin{aligned} \text{minimize} \quad & \sum_{i=1}^{N} Q_i, \\ \text{subject to} \quad & Q_i \geq 0, \ i = 1, \ldots, N, \\ & \frac{1}{2\pi D} \sum_{i=1}^{N} \frac{Q_i}{\|r - r_i\|_2} \geq C_{th}, \ \forall r \in T, \end{aligned} \tag{4}$$

where the first constraint forces all Q_is to be non-negative, while the second constraint guarantees that the drug concentration inside the tumor area is above the threshold value of C_{th}. The circular tumor is represented with the following set of points:

$$T = \{(x, y) \in \mathbb{R}^2 : (x - x_c)^2 + (y - y_c)^2 \leq R^2\} \tag{5}$$

where the center of tumor is specified with x_c and y_c and the tumor radius is R. It can be shown that for a single releasing