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.

Keywords: Molecular Communications, Targeted Drug Delivery, Least Effective Concentration, Sustained Drug Release, Rate Optimization

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 [18]. 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 [7, 16, 17] while in the local case the drug molecules are delivered locally to the target site as presented in [4]- [6], [8]. 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 [14]. 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 the 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. limited energy and reservoir [5]. 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) [10]. 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 with N3Sim to specify the values of simulation parameters including the location of transmitter and receiver. 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 of single releasing transmitter is presented in Section 5, while multiple transmitter scenario is investigated in Section 6. Simulation results with N3Sim are presented in sections 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 [22] 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 [23], relaying [24, 25], inter symbol interference [26, 27] and detection [28]. Other researches in upper layers include addressing [29], distance measurement [30, 31] and scheduling [32, 33] in link layer as well as routing [34]-[37] in network layer. Flow control and congestion control issues in transport layer are investigated in [4, 5, 8] 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 [5], 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 [6] 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 [8] 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 in the blood network. A drug propagation model of cardiovascular system is presented in [7]. 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 targeted drug delivery is presented in [16] in the context of diffusion based molecular communication. In [17], 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 [8], which in steady state and with assumption of no absorption, produces the concentration $c(r)$ given by [9]:

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

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 $R = \{r_1, ..., r_N\}$. Provided that the diffusion channel is an LTI system [12], 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:

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

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 transmitter the second constraint needs to be verified just at the tumor boundary as the following:

$$T = \{(x, y) \in \mathbb{R}^2 : (x - x_c)^2 + (y - y_c)^2 = R^2\} \tag{6}$$

Figure 1 shows how the total optimal rate of released molecules changes with increasing the number of activated transmitters. It is derived for a circular tumor of radius 2.5 cm located randomly in a square grid of transmitters of density λ=0.26 cm^{-2}. A drug molar concentration of 10 mol/m^3 which equals 6.022×10^{18} molecules/cm^3 is proved to produce significant apoptosis [15] and is considered as the threshold value C_{th}. The total optimal rate is then derived once the first, second and ultimately 10th nearest transmitter to the tumor is activated. The average value is calculated for 200 random locations of tumor.
As shown in Figure 1, the total optimal rate is decreased as we activate more transmitters. Therefore, in the following sections we consider two different modes: a simple mode in which a single closest transmitter is activated and a complex mode in which multiple transmitters emit drug molecules simultaneously. Note that in both cases if a nanomachine runs out of the drug, the next nearest transmitter could be activated to maintain the desired concentration.

5. Single Transmitter Drug Delivery System

Once a tumor is diagnosed, we can activate one single nearest transmitter for simplicity. In this scenario, a single transmitter allocates its molecule rate to guarantee enough release at the furthest point of the tumor. Therefore, the transmitter with minimum distance to the center of the tumor is selected. In the case of circular tumor, the distance from a point to the furthest point of a circle equals distance to the center plus radius.
Suppose we want to guarantee the minimum concentration of C_{th} at the furthest point of the circular tumor to make sure we have enough concentration

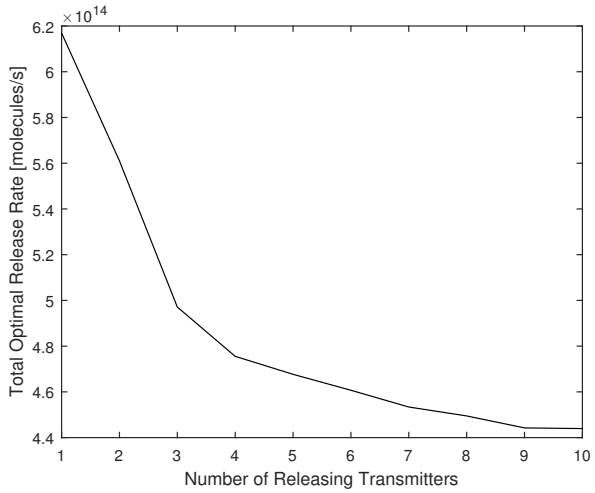

Figure 1: Optimal total number of released molecules in a multiple transmitter drug delivery scenario for $C_{th} = 6.022 \times 10^{18}$ molecules/cm^3, λ=0.26 cm^{-2} and R=2.5 cm

in the other parts of the tumor. The distance from the nearest transmitter to the furthest point is shown with d_{min}. Using (1) the optimal rate of released molecules can be obtained as the following:

$$Q_{opt} = 2\pi D C_{th} d_{min} \tag{7}$$

Distance from nearest transmitter to the furthest point of circular tumor d_{min} can be defined as distance to the center d_c plus the radius R. This is shown in Figure 2.

$$d_{min} = d_c + R \tag{8}$$

Therefore, the expected number of released molecules to satisfy C_{th} can be expressed as:

$$E[Q_{opt}] = 2\pi D C_{th} E[d_c + R] \tag{9}$$

In single receiver scenario, the vector form optimization variable of optimization problem $Q = [Q_1, ..., Q_N]$, is reduced to a single optimization variable of Q_{opt}. We consider two extreme cases in which we have a high or low density of transmitters compared to the size of the tumor. In the following subsections we focus on two extreme particular cases, such that we can derive closed form expressions.

5.1. High Density

If we have a large density of deployed transmitters, the minimum distance transmitter would be located at the center of the tumor and we have $d_{min} = r$. Therefore:

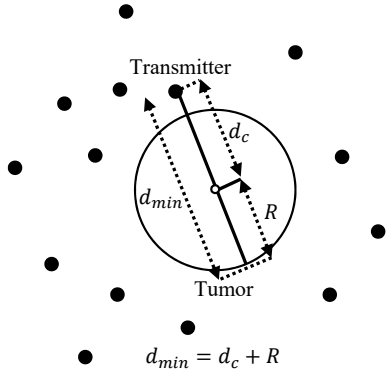

Figure 2: Illustration of randomly deployed transmitter nanomachines around the tumor

$$E[Q_{opt}] = 2\pi DC_{th}R \tag{10}$$

In this case, the size of tumor has a significant effect on the expected number of released molecules. This expected value is increased linearly with the tumor radius. As we see, the average Q is not dependent on the density of transmitters in this region. It means that after a given point increasing the density has no benefit in terms of saving drug molecules.

5.2. Low Density

In the second particular case, we have a low density of deployed transmitters. In this case, the nearest transmitter would be located very far from the tumor center and thus d_{min} can be approximated by d_c. Thus:

$$E\left[Q_{opt}\right] = 2\pi DC_{th}E\left[d_c\right], \tag{11}$$

where $E\left[Q_{opt}\right]$ has the following form in terms of the density of transmitters denoted by λ:

$$E\left[Q_{opt}\right] = \frac{K}{\sqrt{\lambda}}, \tag{12}$$

in which K is dependent on the distribution of the transmitters and has the following general form:

$$K = 2\pi DC_{th}E\left[d_c\right]\sqrt{\lambda} \tag{13}$$

As we see, the size of the tumor does not affect the average number of required molecules in this case. But increasing density has the benefit of saving drug resources. The distribution of transmitters also plays an important role. We consider Poisson distribution, as well as regular grid and regular hexagonal.

5.2.1. Poisson Distribution

Considering the low density case and assuming a Poisson process with density of λ the probability density function from an arbitrary point to nth nearest point of Poisson process is given by:

$$f(d_c, n) = \frac{2(\pi\lambda)^n}{(n-1)!} d_c^{2n-1} e^{-\pi\lambda d_c^2} dd_c \tag{14}$$

Setting $x = 2\pi\lambda d_c^2$ and substituting into above equation results in chi-square distribution with $2n$ degrees of freedom:

$$f(x, n) = \frac{x^{n-1}}{2^{n-1}(n-1)!} e^{-\frac{x}{2}} dx \tag{15}$$

If x is a Chi-squared random variable with $2n$ degrees of freedom then$\sqrt{x}$ is a Chi distribution variable with $2n$ degrees of freedom, thus:

$$d_c \sim \frac{1}{\sqrt{2\pi\lambda}} \chi_{2n} \tag{16}$$

Then the expected value of distance from center and $K_{Poisson}$ are defined as follows:

$$E[d_c] = \frac{1}{2\sqrt{\lambda}} \tag{17}$$

$$K_{Poisson} = \pi DC_{th} \tag{18}$$

5.2.2. Regular Grid

In the case of regular square partitioning consider a square with side length of A. The average distance from the center of the square to a point selected uniformly over the area of rectangle is:

$$E[d_c] = \frac{A}{6}(\sqrt{2} + \ln(1+\sqrt{2})) \tag{19}$$

If the density of transmitters in the regular square grid is defined as the number of transmitters per unit area, K_{sq} becomes:

$$\lambda = \frac{1}{A^2} \tag{20}$$

$$K_{sq} = \frac{\pi}{3} DC_{th}(\sqrt{2} + \ln(1+\sqrt{2})) \tag{21}$$

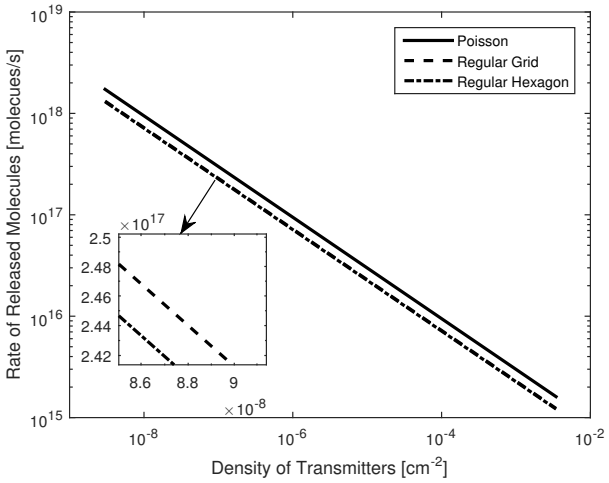

Figure 3: Impact of transmitters distribution type on the optimal release rate in the low density case

5.2.3. Hexagonal Grid

Now let us assume the hexagon partitioning which is a well known way of congruent partitioning also used in cellular mobile phone networks. The hexagons is supposed to have the side length and circum-radius of R. The average distance from hexagon center to a point uniformly selected over hexagon $E[d_c]$ is given by

$$E\left[d_c\right] = R(\frac{1}{3} + \frac{\ln(3)}{4}), \tag{22}$$

in which λ has the following with R:

$$\lambda = \frac{1}{\frac{3\sqrt{3}R^2}{2}} \tag{23}$$

Then:

$$K_{hex} = \frac{2\pi DC_{th}\sqrt{2}}{3^{\frac{3}{4}}}(\frac{1}{3} + \frac{\ln(3)}{4}) \tag{24}$$

In the low density case, distribution type manifests itself in the y-intercept of logarithmic rate-density curve and does not affect the slope at which the rate is decreased. This is shown in Figure 3.

5.3. Overall Behavior

The expected optimal rate (molecules/s) of the releasing transmitter is plotted in Figure 4 for both low and high density values, when the transmitters have deterministic placement in a regular grid. The cross validation of asymptotic bounds is carried out with simulations. As we see the simulation results matches

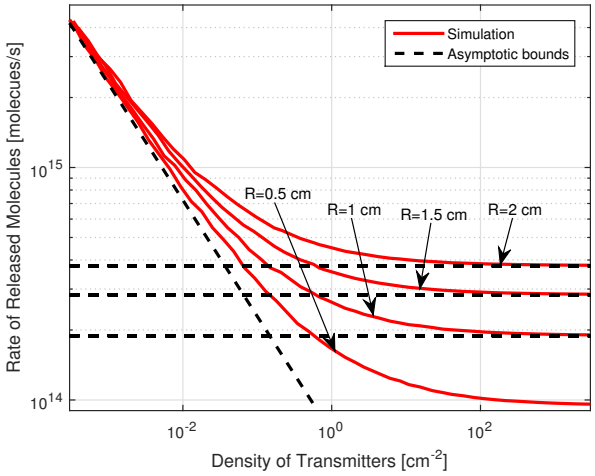

Figure 4: Optimal release rate of a single transmitter drug delivery scenario for regular grid deployment

well with the closed form expressions. Similar results are achieved in the case of other distributions.

The intersection of asymptotic bounds in low and high density regions can give us the optimal density of required transmitters for any given size of the circular tumor. This optimal value for Poisson, grid and hexagonal distribution is shown in equations(25)-(27) respectively. As we see, the optimal density is inversely related to the tumor area.

$$\lambda_{opt,Poisson} = (\frac{1}{2R})^2 \tag{25}$$

$$\lambda_{opt,square} = [\frac{\sqrt{2} + \ln(1+\sqrt{2})}{6R}]^2 \tag{26}$$

$$\lambda_{opt,hex} = \frac{2}{\sqrt{27}}(\frac{\frac{1}{3} + \frac{\ln(3)}{4}}{R})^2 \tag{27}$$

We show in Figure 5 the optimal density of transmitters for a circular tumor of a given radius. As we see the optimal density is decreased as the tumor size is increased. Deterministic deployments outperform the Poisson distribution. It is also evident that the regular hexagonal distribution works slightly better than regular square distribution.

6. Multiple Transmitter Drug Delivery System

It was shown in Figure 1 that the total optimal released rate of molecules can be decreased once multiple transmitters are activated. Therefore, we can save

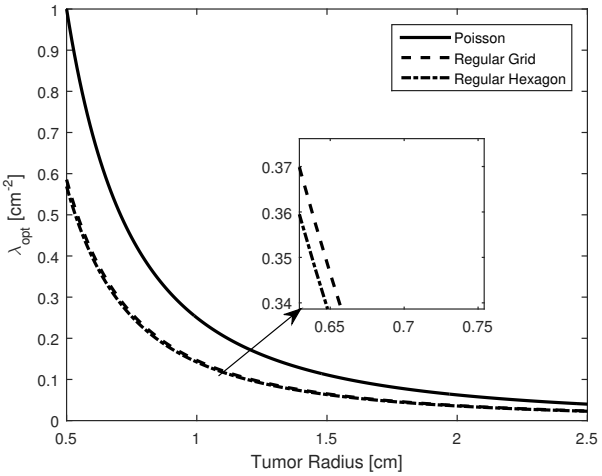

Figure 5: Optimal density of transmitters for a given tumor radius

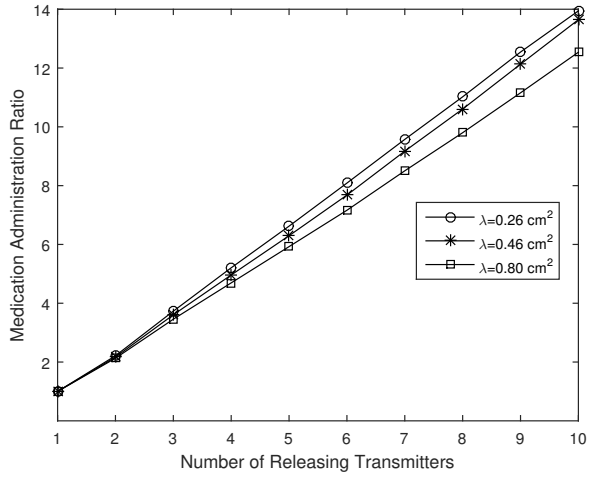

Figure 6: Time duration ratio between consequent administrations

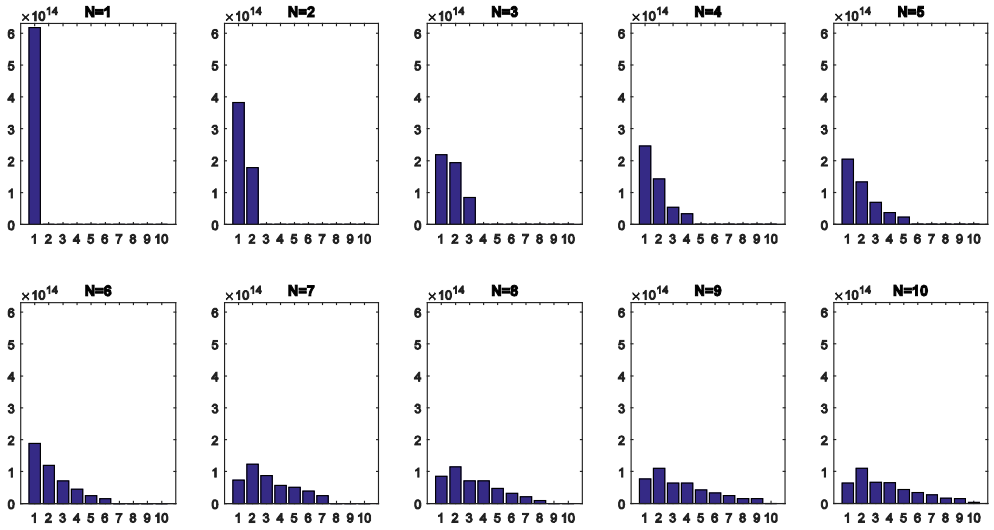

Figure 7: Optimal allocated rate for R=2.5 cm and $\lambda = 0.26$ cm^{-2}

molecules by activating multiple transmitters. Although this reduction may not seem very large at the first glance, it has significant role in our prolonged treatment scenario in which the molecules are to be released for a long time e.g. several hours [14].

Employing several transmitters has also the benefit of extending the time duration between consequent administrations. If the comparison criterion is the inverse average rate ratio, the result is shown in Figure 6. Increasing the the number of activated transmitters from one to two nearly doubles the the time duration between consequent administrations. The impact of density of deployed transmitters on time duration between consequent administrations is also shown in Figure 6. It is shown that increasing density reduces the time duration for any given number of transmitters.

A typical profile of the optimal allocated rate is shown in Figure 7 for a medium density deployment. The tumor radius is 2.5 cm and the number of activated transmitters is increased from 1 to 10. As indicated in Figure 7, the total rate is distributed among several transmitters.

Figure 8 shows the total optimal release rate for different sizes of tumor. Increasing the tumor size leads to an increase in the total optimal rate in order to maintain LEC inside the tumor. The trend of reduction is similar for different sizes of tumor.

The relationship between the total optimal rate and number of activated transmitters is shown in Figure 9 for several transmitter densities. For larger densities, we have a lower optimal rate since the transmitters are more probable to be located near the tumor.

Similar to single transmitter case, we consider two extreme particular cases

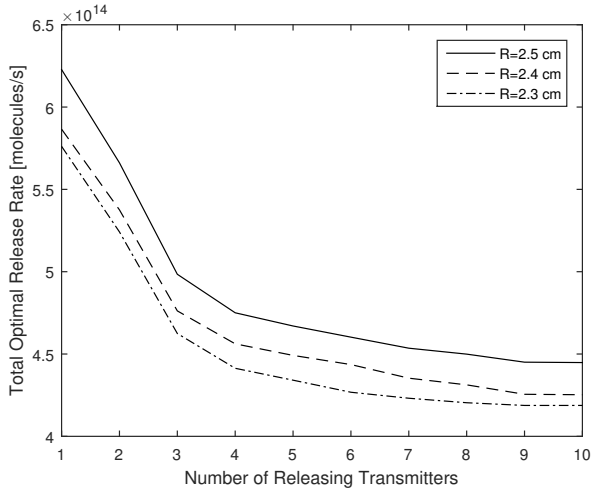

Figure 8: Total optimal release rate for different tumor sizes located in a square grid with λ=0.26 cm^{-2}

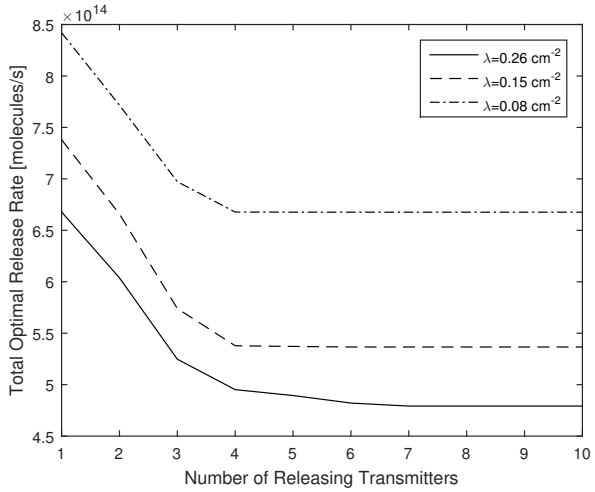

Figure 9: Total optimal release rate for $R = 2.5$ cm located in a square grid

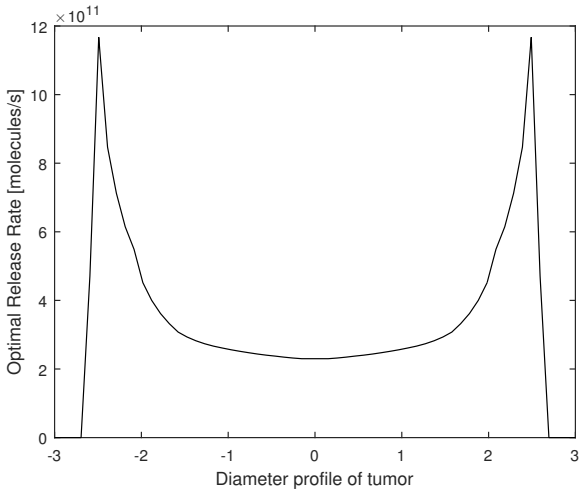

Figure 10: Rate distribution in a diameter profile of tumor

in the following subsections:

6.1. High Density

In the limit case of very high densities, the optimization problem (4) will be converted to the following problem:

$$\begin{aligned} &\text{minimize} \quad \int_r Q(r)dr, \\ &\text{subject to} \quad Q(r) \geq 0\ , \\ &\qquad\qquad \frac{1}{2\pi D}\int_r \frac{Q(r)}{\|x-r\|_2} \geq C_{th},\ \forall x \in T, \end{aligned} \tag{28}$$

where $Q(r)$ is the rate function in terms of r which is a continuous variable showing the location of transmitters. The rate distribution for a high density case is shown in Figure 10 for a diameter profile of tumor. It is shown that the highest rate is allocated to the ones near the boundary and there is a rate reduction as we get near to the center. The rate allocated to the ones outside is zero.

6.2. Low Density

Checking the distribution profile for several deployment densities indicates that in very low densities, the total optimal rate is assigned solely to the first nearest transmitter. Once the density is increased, tier one transmitters will be activated.

7. Simulation Results with N3Sim

Cross-validation and reproducibility is a challenge in the area of molecular communication [11]. In this paper, we use N3Sim in order to have a blind simulation. N3Sim is a well-known simulation framework for diffusion-based molecular communications. It allows the automation of multiple simulations through scripts. When using the key word *param* as value for any of the parameters in the configuration file, the program will read its value from the parameters list of the execution command (in the same order that they appear at the configuration file). In the current simulation, we give the value *param* to the variables outPath (so that each simulation has a different folder), space size as well as transmitter and receiver location. We use MATLAB as an interface to communicate with N3Sim. Then, an script will execute all the required simulations automatically. After carrying out the actual diffusion simulation, the N3Sim output is read, integrated and processed with another script. Scripts for executing simulations automatically and reading the N3Sim outputs as well as the simulator configuration file can be found in our webpage[1].
For each density of transmitters, the location of tumor is defined randomly in the script. According to this location, the nearest transmitter and the furthest receiver locations are specified in the script and the average steady state concentration is calculated for 200 random locations of tumor. A typical down-scaled configuration of a regular grid deployment in N3Sim including a tumor of an arbitrary size is shown in Figure 11. The interpolation of the average steady state concentration at receivers locations gives an estimation of synthesized concentration. This is shown in Figure 12.
For 3-dimensional simulations, we consider an unbounded simulation space while having no collisions among the emitted particles. The transmitters are punctual and release molecules every 2000 ns. The tumor radius is considered 0.5 cm without loss of generality. Receiver has a radius of 100 nm. The time step needs to be considered with caution. This is because time step should satisfy equation (29) in order to get reasonable results from the simulator.

$$timeStep \leq \frac{(0.25d)^2}{2D} \tag{29}$$

where d is the distance between the transmitter and receiver and D is the diffusion coefficient. The results from N3Sim is shown in Figure 13. We see that there is a good matching between the simulation results.

8. Nanomachine Placement and Release Trigger Mechanisms

Drug delivery systems offer localized release of therapeutics that systemically delivered agents do not introduce. By selectively placing a drug delivery adjacent to diseased tissue, the release of the drug leads to high bioavailability

[1] `https://www.dropbox.com/s/4ohucs7ottc92a2/Suplemantary%20material.pdf?dl=0`

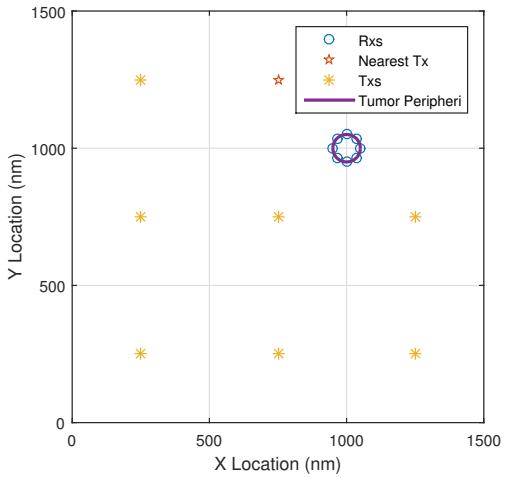

Figure 11: Transmitters and receivers configuration in N3Sim environment

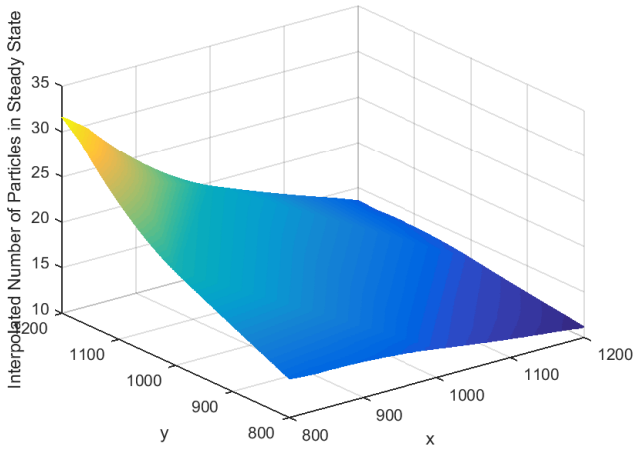

Figure 12: Interpolated concentration across tumor

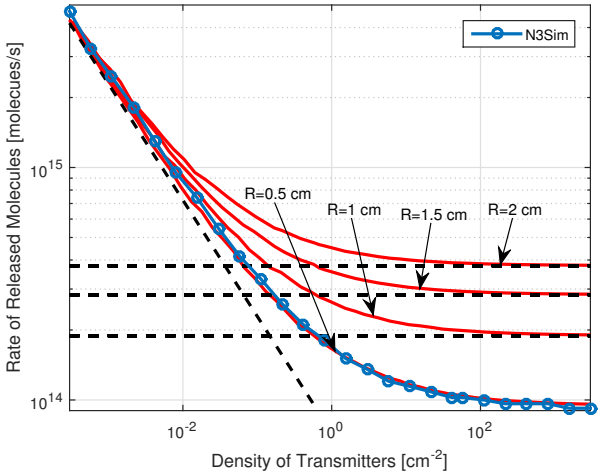

Figure 13: Verification with N3Sim

at the site of action, with low therapeutic levels in other sensitive regions of the body. Alternatively, drug delivery systems or bare drugs injected intravascularly can be rapidly sequestered by clearance organs, which can lead to an unsafe exposure of healthy tissue to toxic drug levels [21]. Several studies on intratumoral approaches and adjacent therapeutic release has been carried out for melanoma [38, 39] and bladder cancer [40] treatment.

Controlled delivery systems provide an alternative approach to regulating the bioavailability of therapeutic agents. In controlled drug delivery systems, an active therapeutic is incorporated into a polymeric network structure called hydrogels in such a way that the drug is released from the material in a predefined manner [19, 20]. Depending on the drug delivery formulation and the application, the drug release time may be anywhere from a few hours to a month to several years [21]. These bio-nanomachines may also be engineered to release molecules at the optimal release rate [5]. Chitosan-based hydrogels are among the best candidates since they do not induce an immune response. Release of loaded therapeutics from a hydrogel can occur by one of three different modes: diffusion, chemical/environmental stimulation, and enzyme-specific stimulation. Diffusion is regulated by movement through the polymer matrix or by bulk erosion of the hydrogel as it breaks down in vivo. Environmentally responsive hydrogels gels that swell in response to external cues like pH and temperature effectively open their pores for enhanced diffusion of the entrapped therapeutic under predetermined conditions. This type of controlled release can be used to limit drug release outside of the effective range of the diseased tissue. Better specificity can be obtained by using the recent mechanisms of local enzymatic cues.

9. Conclusion

Molecular communications can help drug delivery systems for accurate delivery of drug molecules to the tumor site as well as saving the scarce resources like energy and reservoir capacity. In this paper, we proposed a multiple transmitter drug delivery system which releases drug molecules at an optimal rate to maintain the minimum effective concentration inside the tumor. Both single and multiple transmitter scenarios are investigated. For the first scenario, the optimal rate of releasing transmitter as well as optimal density of deployed transmitters are derived for a given tumor size through formulations and the results are verified with simulations. The simulation is also carried out with the help of N3Sim which is a well known simulator in the area of molecular communication. We have used MATLAB as an interface to execute N3Sim simulations with appropriate parameters in an automated manner as well as Analyzing the results. In the latter case of multiple transmitters, the optimal allocated rate of each transmitter is calculated to achieve the minimum total release rate. The impact of tumor size and density of deployed transmitters are also investigated.

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