Optimization Course Project

An Optimum Drug Delivery Algorithm: Dynamic Programming Approach

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Abstract

One of the most challenging issues in pharmacology is to effectively distribute particular drugs in specific quantities within different parts of an organism without affecting the healthy parts. An effective drug delivery system (DDS) should be capable of controlling the release rate of drugs, while simultaneously minimizing the side effects at non-targeted sites. This is similar to a communication system wherein signals are reliably transmitted at a given rate to a desired receiver while the induced interference to non-targeted receivers is minimized. This paper proposes a new optimization technique based on dynamic programming to improve the performance of the DDS. The proposed DDS inspired by an On-Off Keying (OOK) communication system uses molecular communication (MC) as an abstraction of the propagation of drug particles in the body. MC enables to analyze and design efficient DDS based on communication theory. In this paper, the DDS objective is to minimize the total amount of absorbed drug particles at a healthy organ while at the same time at least a minimum level of drug particles is continuously received by the tumor. To achieve the objective, the optimum coding sequence is obtained by the proposed algorithm for a simple DDS model based on On-Off Keying method in a diffusion-based homogenous environment. Numerical results indicate that the proposed dynamic programming based drug delivery algorithm improves the performance of the delivery system.

I. Introduction

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Nowadays targeted drug delivery systems (DDSs) are increasingly attracting the interest of research communities in nanotechnology since they are at the cutting edge of modern medical therapeutics [1-2]. An effective DDS should be capable of controlling the release rate of drugs within different parts of an organism while simultaneously minimizing the side effects at non-targeted sites.

The transportation of drug particles in the human body is similar to a communication system. In a communication system, signals are reliably transmitted at a given rate to a desired receiver while the induced interference to non-targeted receivers is minimized. Molecular Communication (MC) is a new communication paradigm where information is conveyed through the propagation of molecules [3]. MC is a new paradigm that has been developed by nature for communication among living organisms, such as cells for intracellular and intercellular signaling. One of the most general and common types of MC is the diffusion-based communication which refers to the situation where molecules propagate only through spontaneous diffusion in a fluidic medium. The study of diffusion-based MC has the potential to benefit from the observation of nature for the design of bio-inspired and bio-compatible solutions especially for medical applications [4], [5].

The targeted DDS has been envisioned as one of the most important applications of the MC paradigm enabling to analyze and design efficient drug delivery systems based on communication theory [4],[6]-[9]. Similar to a communication system, in MC, the transmitter is the drug injector, the receiver is the organ under treatment, and the channel is the transportation media of drug particles. Publications in this area over the past few years show a promising future for this interdisciplinary research field. The feasibility of applying MC to drug delivery systems is demonstrated through a cooperative nanoparticle system for tumor targeting [6]. Furthermore, modeling methods for an effective and less invasive drug delivery have been proposed for cancer treatments in [3] and [7].

In this paper, we propose an efficient DDS, developed based on dynamic programming as an optimization technique. The objective of drug delivery is to minimize the total absorbed drug by the healthy organ during delivery time subject to continuously receiving at least a specific minimum level of drug by the tumor in order that the treatment to be effective. Inspired by On-Off Keying (OOK) communication system, an optimum coding sequence is designed based on the proposed delivery algorithm which is adopted at the transmitter for injecting drug. According to this method, when an injection occurs a number of drug particles are released in a fixed period of time and when no injection occurs no drug particles are emitted. The proposed delivery algorithm is evaluated by computer simulations for the DDS model that consists of (i) an injector

(e.g. transmitter), (ii) a diffusion-based homogenous medium (iii) a tumor and a healthy organ (e.g. receivers). Numerical results indicate that the developed drug delivery algorithm is an efficient method.

The rest of the paper is organized as follows. In Section II, we introduce the model of the DDS for a diffusion-based homogenous media. In section III, we formulate a drug delivery system according to a new approach based on dynamic programming. The delivery algorithm is derived to minimize the total amount of absorbed drug particles at a healthy organ while at the same time at least a minimum level of drug particles is continuously received by the tumor. Section IV presents the numerical results. Finally, conclusions are given in section V.

II. Drug Delivery System Model

The Drug Delivery System (DDS) model considered in this paper is shown in Fig. 1. It includes one injector (transmitter), a diffusion-based homogenous media, the healthy organ and tumor (two receivers).

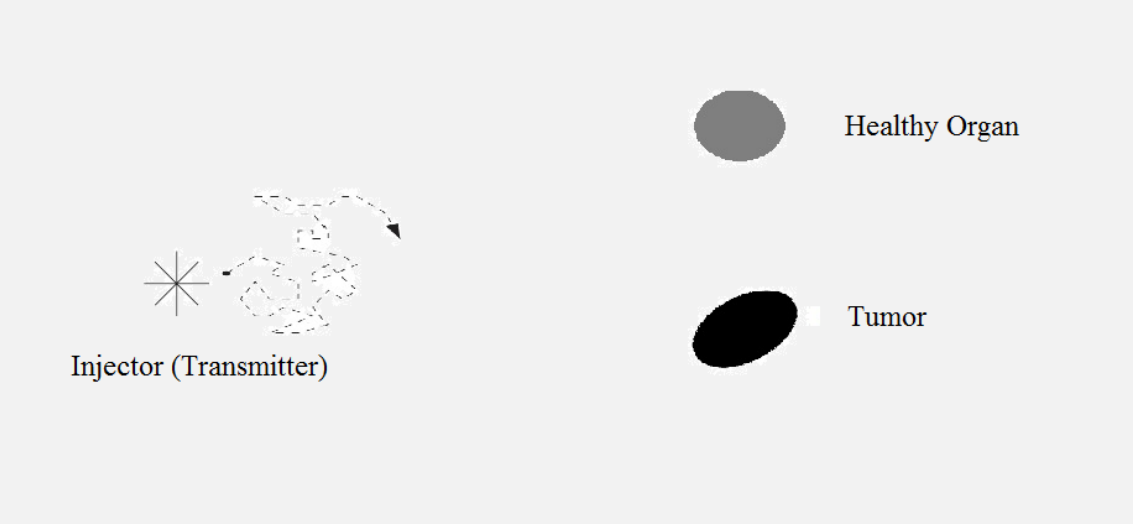

Fig. 1 DDS model

The transmitter which is located at $\tilde{x}_I = (0 \quad 0 \quad 0)$ is responsible for injecting drug particles into the space as a function of time through an On-Off Keying method. According to this method when an injection occurs, the transmitter releases M molecules in a period of time T and when no injection occurs no drug particles are released in the environment. If the operation time of the DDS model is considered $L = NT$, the transmitted signal $s(t)$ can be expressed as follows:

$$s(t) = \sum_{k=1}^{N} MX_k[u(t-kT) - u(t-(k-1)T)] \quad (1)$$

Where $u(t)$ is the unit step function and X_k is defined as:

$$X_k = \begin{cases} 1 & \text{when injection occures} \\ 0 & \text{when no injection occures} \end{cases} \equiv s(t) = \begin{cases} M & (k-1)T \le t < kT \\ 0 & (k-1)T \le t < kT \end{cases}$$

It is assumed that the injected particles are identical and undistinguishable between each other.

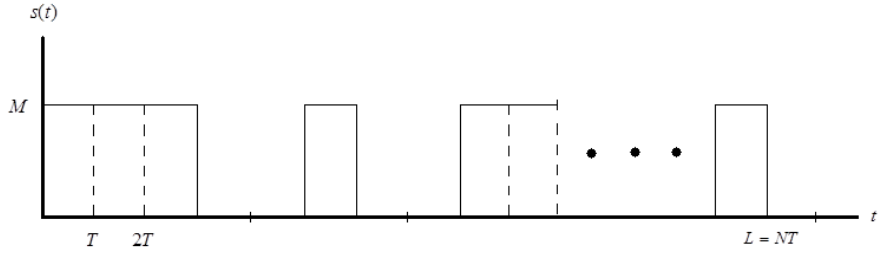

Fig. 2 Transmitted signal

Fig. 2 depicts a simple example for the transmitted signal $s(t)$.

The DDS model includes a Diffusion-based homogenous media that is based on the free diffusion of molecules between the transmitter and the receiver. Once injected, every drug particle moves independently according to its Brownian motion in a medium. Fick's second law of diffusion [10] predicts how the concentration function changes with time:

$$\frac{\partial C(x,y,z,t)}{\partial t} = D\nabla^2 C(x,y,z,t) \quad (2)$$

Eq.(2) is known as the DIFFUSION equation in the three dimensional space. It can be shown that the solution to (2) with an instantaneous point source release at $t = 0$ at any location $(x \quad y \quad z)$ is of the form [10]:

$$C(x,y,z,t) = \frac{M}{(4\pi Dt)^{3/2}} \exp\left(-\frac{x^2+y^2+z^2}{4Dt}\right) \quad (3)$$

where D is the diffusion coefficient that is considered to be a constant parameter in here. M denotes the number of molecules emitted at the transmitter. Eq.(3) is the solution to an instant

release of molecules, in other words the input signal to the diffusion channel is a Dirac delta function.

However, we are aiming to release M drug particles continuously during a time period of T. The solution to the diffusion equation for a constant and continuous release is obtained by the time-integration of the solution for an instantaneous release. If the injection duration is T; the general form of the solution is [11]:

$$C(x,y,z,t)=\frac{\partial R/\partial t}{(4\pi D)^{3/2}}\int_0^{t_1}\frac{1}{(t-\tau)^{3/2}}\exp(-\frac{x^2+y^2+z^2}{4D(t-\tau)})d\tau \qquad (4)$$

where $\frac{\partial R}{\partial t}$ is the time rate of drug injection which is considered to be a constant and equal to M drug particles.

For computing (4) at a known location $(x_1 \quad y_1 \quad z_1)$ there are two cases:

In the first case we consider a continuous injection from time $t=0$ to the current time $t \le T$, while the second case is the solution for times greater than T (i.e. after injection stops). The solution can be expressed as follows [11]:

$$C(t)=\begin{cases} \frac{M}{4\pi D d_1}\operatorname{erf}(\sqrt{\frac{d_1^2}{4Dt}}) & t \le T \\ \frac{M}{4\pi D d_1}\left\{\operatorname{erf}(\sqrt{\frac{d_1^2}{4D(t-T)}})-\operatorname{erf}(\sqrt{\frac{d_1^2}{4Dt}})\right\} & t > T \end{cases} \qquad (5)$$

where $\operatorname{erf}(.)$ denotes the error function.

$$\operatorname{erf}(u)=\frac{2}{\pi^{1/2}}\int_0^u \exp(-z^2)dz$$

Here $d_1=\sqrt{x_1^2+y_1^2+z_1^2}$ is the distance between the transmitter and the receiver.

The DDS model includes two receivers whose tasks are to absorb the incoming concentration of the drug particles. The first receiver is the healthy organ which is located at $\tilde{x}_O=(x_O \quad y_O \quad z_O)$. The second receiver is the tumor under treatment that is located at $\tilde{x}_T=(x_T \quad y_T \quad z_T)$.

III. Dynamic Programming-Based Drug Delivery Algorithm

The goal is to find the optimum sequence of $\{X_k\}_{k=1}^{N}$ that will lead to a minimum dosage of the total drug level at the organ; while the drug level at each time kT is greater than a certain dose at the tumor site. We assume that the location of the organ and the tumor are known at the transmitter.

Therefore the optimization problem can be formulated as follows:

$$\begin{aligned} obj: \quad & \min_{\{X_k\}} \left\{ \sum_{k=1}^{N} C_O(k) \right\} \\ s.t. \quad & C_T(k) \geq Q \\ & X_k \in \{0,1\} \quad k = 1,2,...,N. \end{aligned} \tag{6}$$

where $C_O(k)$ is the drug level at time kT in the organ and $C_T(k)$ is the drug level at time kT in the tumor. Here Q is the minimum concentration of drug particles that is required to be absorbed at each time kT by the tumor in order to have an effective treatment.

We use dynamic programming to solve the above optimization problem [12]. The dynamic programming technique computes the optimal solution based on the principle of optimality.

Principle of Optimality: A problem is said to satisfy the Principle of Optimality if the sub-solutions of an optimal solution of the problem are themselves optimal solutions for their sub-problems. For example in shortest path problem as shown in Fig. 3, if P_{AB} is the shortest path in a graph between "A" node and "B" node, then any portion of this path such as P_{AC} is also the shortest path between "A" node and "C" node and also the P_{CB} is the shortest path between "C" node and "B". Thus in order to find the shortest path between "A" node and "B" node, the path from "A" node to each middle node such as "C" should be also the shortest one.

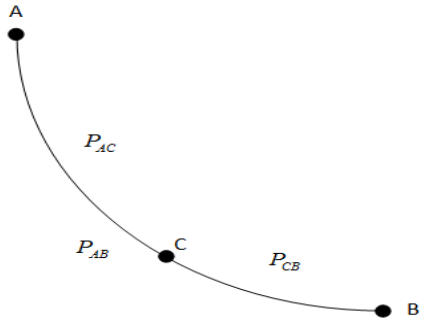

Fig. 3 A simple illustration for Principal of Optimality

To achieve the objective of the optimization in (6), based on the principle of optimality, each sub-solution before $k < N$ should be also optimal. Therefore, for all $N_1 \le N$ the following objective should be satisfied as well.

$$\begin{aligned} obj: \quad & \min_{\{X_k\}} \left\{ \sum_{k=1}^{N_1} C_O(k) \right\} \\ s.t. \quad & C_T(k) \ge Q \\ & X_k \in \{0,1\} \quad k = 1,2,...,N_1. \end{aligned} \tag{7}$$

Note that the optimal detection method is used in communication theory named Viterbi algorithm which is developed based on dynamic programming as well [13].

A) Trellis diagram of the DDS model

The DDS model has two states: (1) The "injection" state and (2) the "stop injection" state.

In each period of time, depending on what the previous state is the system chooses the current state. In each state, the model solves the optimization problem and then the best sequence that satisfies the constraints at time kT is selected. As an example, if the previous state (at time $(k-1)T$) is the "injection" state, depending on the best optimum solution the system can either choose the "injection" state or the "stop injection" state at time kT. Fig. 4 presents a simple explanation of how the system works in both states.

In Fig. 4 $B_{ij}(k)$ is the branch metric from "*i*" state to "*j*" state at time kT for $i, j = \{1,2\}$.
This metric is defined as:

$$B_{ij}(k) = \begin{bmatrix} B_O^{ij}(k) \\ B_T^{ij}(k) \end{bmatrix} \tag{8}$$

where $B_O^{ij}(k)$ is the drug level in organ point at time kT from "*i*" state to "*j*" state and $B_T^{ij}(k)$ is the drug level in the tumor point at time kT from "*i*" state to "*j*" state. Depending on the drug levels at the receivers, the transmitter will inject or stop injecting during the current period.

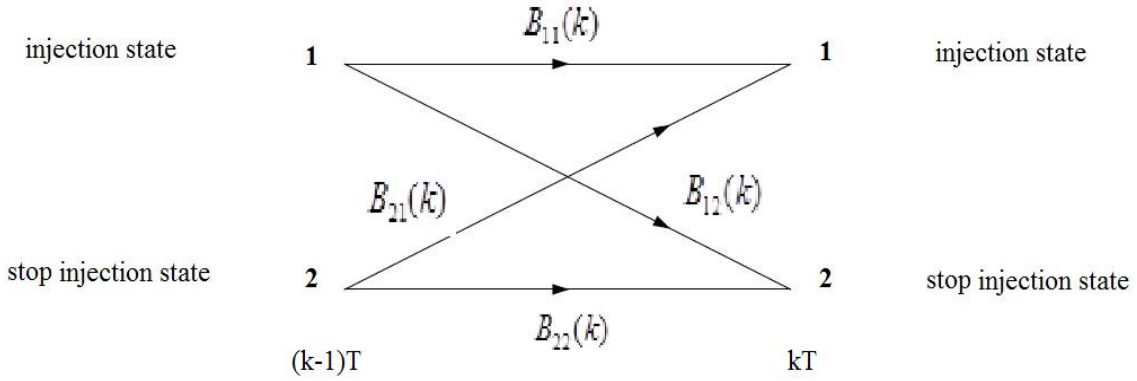

Fig.4 $B_{11}(k)$ is the branch metric from "injection" state to "injection", $B_{12}(k)$ is the branch metric from "injection" state to "stop injection", $B_{21}(k)$ is the branch metric from "stop injection" state to "injection" and $B_{22}(k)$ is the branch metric from "stop injection" state to "stop injection".

B) Calculations of branch metrics $B_O^{ij}(k)$, $B_T^{ij}(k)$

Let $X^{(1)}(k-1)=\left\{x_1^{(1)}, x_2^{(1)}, ..., x_{k-1}^{(1)}\right\}$ be the survival path at time $(k-1)T$ for "injection" state and $X^{(2)}(k-1)=\left\{x_1^{(2)}, x_2^{(2)}, ..., x_{k-1}^{(2)}\right\}$ be the survival path at time $(k-1)T$ for "stop injection" state:

(1) When the state changes from "injection" to "injection", a candidate survival path for calculating $B_O^{11}(k)$ and $B_T^{11}(k)$ at time kT can be expressed as:

$$X_{11}(k)=\left\{X^{(1)}(k-1),1\right\}=\left\{x_1^{(1)}, x_2^{(1)}, ..., x_{k-1}^{(1)}, 1\right\}$$

(2) When the state changes from "stop injection" to "injection", another candidate survival path for obtaining $B_O^{21}(k)$ and $B_T^{21}(k)$ is:

$$X_{21}(k)=\left\{X^{(2)}(k-1),1\right\}=\left\{x_1^{(2)}, x_2^{(2)}, ..., x_{k-1}^{(2)}, 1\right\}$$

(3) Shifting from "injection" to "stop injection", a candidate survival path for calculating $B_O^{12}(k)$ and $B_T^{12}(k)$ will be:

$$X_{12}(k)=\left\{X^{(1)}(k-1),0\right\}=\left\{x_1^{(1)}, x_2^{(1)}, ..., x_{k-1}^{(1)}, 0\right\}$$

(4) For going from "stop injection" state to "stop injection" state, another candidate survival path for $B_O^{22}(k)$ and $B_T^{22}(k)$ is:

$$X_{22}(k) = \left\{ X^{(2)}(k-1), 0 \right\} = \left\{ x_1^{(2)}, x_2^{(2)}, ..., x_{k-1}^{(2)}, 0 \right\}$$

Note that one of these survival paths will be chosen as the final survival path which will represent the best solution for our optimization problem.

Based on the previous definitions, $B_O^{ij}(k)$ and $B_T^{ij}(k)$ are computed by:

$$\begin{aligned} B_O^{ij}(k) &= \sum_{l=1}^{k} y_O^l(k) \qquad \text{for all possible } X_{ij}(k) \\ B_T^{ij}(k) &= \sum_{l=1}^{k} y_T^l(k) \qquad \text{for all possible } X_{ij}(k) \end{aligned} \tag{9}$$

According to (5), $y_O^1(k)$ and $y_T^1(k)$ are given as

$$y_O^l(k) = \begin{cases} x_l \dfrac{M}{4\pi D d_O} \operatorname{erf}\left(\sqrt{\dfrac{d_O^{\,2}}{4DT}}\right) & l = k \\ x_l \dfrac{M}{4\pi D d_O} \left\{ \operatorname{erf}\left(\sqrt{\dfrac{d_O^{\,2}}{4D(k-l)T}}\right) - \operatorname{erf}\left(\sqrt{\dfrac{d_O^{\,2}}{4D(k+1-l)T}}\right) \right\} & l < k \end{cases} \tag{10}$$

$$y_T^l(k) = \begin{cases} x_l \dfrac{M}{4\pi D d_T} \operatorname{erf}\left(\sqrt{\dfrac{d_T^{\,2}}{4DT}}\right) & l = k \\ x_l \dfrac{M}{4\pi D d_T} \left\{ \operatorname{erf}\left(\sqrt{\dfrac{d_T^{\,2}}{4D(k-l)T}}\right) - \operatorname{erf}\left(\sqrt{\dfrac{d_T^{\,2}}{4D(k+1-l)T}}\right) \right\} & l < k \end{cases} \tag{11}$$

where x_l is the l-th element of $X(k)$. $B_O^{ij}(k)$ and $B_T^{ij}(k)$ are calculated when $X(k) = X_{ij}(k)$ for $i = 1, 2$ and $j = 1, 2$. Here d_O denotes the distance between the injector and the organ and d_T is the distance between the injector and the tumor.

Furthermore, we define a weight vector $w_1(k)$ for "injection" state and $w_2(k)$ for "stop injection" state at time kT which are defined as:

$$w_1(k)=\begin{bmatrix} w_{O1}(k) \\ w_{T1}(k) \end{bmatrix} \Rightarrow \begin{cases} w_{O1}(k)=\sum_{l=1}^{k} C_O^1(l) \\ w_{T1}(k)=C_T^1(k) \end{cases} \Rightarrow \text{"injection" state}$$

$$w_2(k)=\begin{bmatrix} w_{O2}(k) \\ w_{T2}(k) \end{bmatrix} \Rightarrow \begin{cases} w_{O2}(k)=\sum_{l=1}^{k} C_O^2(l) \\ w_{T2}(k)=C_T^2(k) \end{cases} \Rightarrow \text{"stop injection" state} \qquad (12)$$

where $w_{O1}(k)$ denotes the total minimum of the drug absorbed by the organ till time kT in the "injection" state, while $w_{T1}(k)$ is the drug level in the tumor site at time kT in the "injection" state. Similarly, $w_{O2}(k)$ is the total minimum of the drug absorbed by the organ till time kT in the "stop injection" state, while $w_{T2}(k)$ is the drug level in the tumor site at time kT in the "stop injection" state.

We define $w_{ij}(k)$ for all *i* and *j* as follows:

$$\begin{aligned} w_{11}(k) &= w_{O1}(k-1)+B_O^{11}(k) \quad \text{when } X(k)=X_{11}(k) \\ w_{12}(k) &= w_{O1}(k-1)+B_O^{12}(k) \quad \text{when } X(k)=X_{12}(k) \\ w_{21}(k) &= w_{O2}(k-1)+B_O^{21}(k) \quad \text{when } X(k)=X_{21}(k) \\ w_{22}(k) &= w_{O2}(k-1)+B_O^{22}(k) \quad \text{when } X(k)=X_{22}(k) \end{aligned} \qquad (13)$$

The objective is to find the optimum sequence in order to inject a minimum amount of drug as possible to cure the tumor and at the same time have the lowest effect on the healthy organ. Therefore, when the "injection" state is considered at time kT; $w_{O1}(k)$ and $X^{(1)}(k)$ are selected based on satisfying the optimization criterion at this time as indicate follows:

For **"injection"** state:

if $w_{11}(k) < w_{21}(k)$ and $B_O^{11}(k) \geq Q \rightarrow w_{O1}(k)=w_{11}(k)$; $w_{T1}(k)=B_O^{11}(k)$; $X^{(1)}(k)=X_{11}(k)$

if $w_{11}(k) > w_{21}(k)$ and $B_O^{21}(k) \geq Q \rightarrow w_{O1}(k)=w_{21}(k)$; $w_{T1}(k)=B_O^{21}(k)$; $X^{(1)}(k)=X_{21}(k)$

In the same way, when the "stop injection" state is considered at time kT; $w_{O2}(k)$ and $X^{(2)}(k)$ are selected based on satisfying the optimization criterion at this time as indicate follows:

For **"stop Injection"** state:

if $w_{12}(k) < w_{22}(k)$ and $B_O^{12}(k) \geq Q \rightarrow w_{O2}(k)=w_{12}(k)$; $w_{T2}(k)=B_O^{12}(k)$; $X^{(2)}(k)=X_{12}(k)$

if $w_{12}(k) > w_{22}(k)$ and $B_O^{22}(k) \geq Q \rightarrow w_{O2}(k)=w_{22}(k)$; $w_{T2}(k)=B_O^{22}(k)$; $X^{(2)}(k)=X_{22}(k)$

Where $X^{(1)}(k)$ and $X^{(2)}(k)$ are the survival paths of "injection" and "stop injection" states up to time kT, respectively.

Note that for "injection" state, if the constraint isn't satisfied by both $B_T^{11}(k)$ and $B_T^{21}(k)$ (that may be happened at the beginning due to not enough released drug), the maximum of $\left\{B_T^{11}(k), B_T^{21}(k)\right\}$ will be selected as the drug level in the tumor along with its corresponding $w_{O1}(k)$ and $X^{(1)}(k)$. The algorithm does the same for "stop injection" state when the constraint isn't satisfied by both $B_T^{12}(k)$ and $B_T^{22}(k)$ as well.

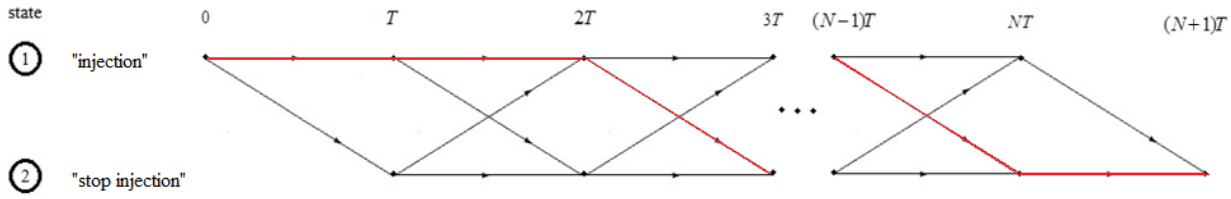

Fig. 5 Possible paths between "injection" and "stop injection" state

Fig. 5 illustrates the possible paths between the "injection" and "stop injection" state. Note that the transmitter is in the "injecting" state at the beginning of the process and it must stay in this state until the drug level at the tumor site reaches to a minimum of Q particles. Afterwards the state can change according to our objective. At the end when $k = N$, the task must end in "stop injection" state.

At the final step when $k=N$, the final survival path is selected between "injection" and "stop-injection" states in order to satisfy the objection.

$$if \quad w_{O1}(N) < w_{O2}(N) \text{ and } w_{T1}(N) \geq Q \quad \rightarrow \quad X(N) = X^{(1)}(N)$$
$$if \quad w_{O1}(N) > w_{O2}(N) \text{ and } w_{T2}(N) \geq Q \quad \rightarrow \quad X(N) = X^{(2)}(N)$$

Note that at the final step $\min\left(w_{O1}(N), w_{O2}(N)\right) = \min\limits_{\{X_k\}} \left\{\sum_{k=1}^{N} C_O(k)\right\}$ and $X_k = X(N)$ according to (6).

IV. Numerical Results

In this section we present numerical results for applying the proposed delivery algorithm based on dynamic programming to the DDS model. The numerical results conclude that applying optimization techniques improve the performance of the DDS system.

In simulations, we set $D = 0.43$ cm^2/min , $M = 10^6$ and $Q = 2\times10^4$. Since we have considered a time slotted system, we set $N = 25$ time slots, that each have a duration of $T = 1$ min. Therefore the delivery time of the system is 25 minutes. Moreover, the distance between the injector and organ is considered $d_O = 2$ cm , and the distance between the injector and tumor is $d_T = 1$ cm.

Fig. 6 shows the total amount of drug particles absorbed at the healthy organ during delivery time. As seen in Fig. 6, the amount of drug particles that are absorbed by the organ increases by passing time; however the amount that has been absorbed at the end is approximately 10.86×10^5 that is almost equal to the amount of drug that is injected in one period of "injection" state.

Fig. 7 illustrates the number of drug particles that are continuously received at the tumor when the system is operating. Note that at the first time slot, the number of drug particles received at the tumor is high because the system is in the "injection" state. As seen In Fig. 7, at least a minimum level of $Q = 2\times10^4$ drug particles are continuously received by tumor at each time, which satisfies the constraint of objection. This result denotes that the proposed algorithm works well and the injector is controlling the release rate of drugs needed to cure the tumor according to the constraint.

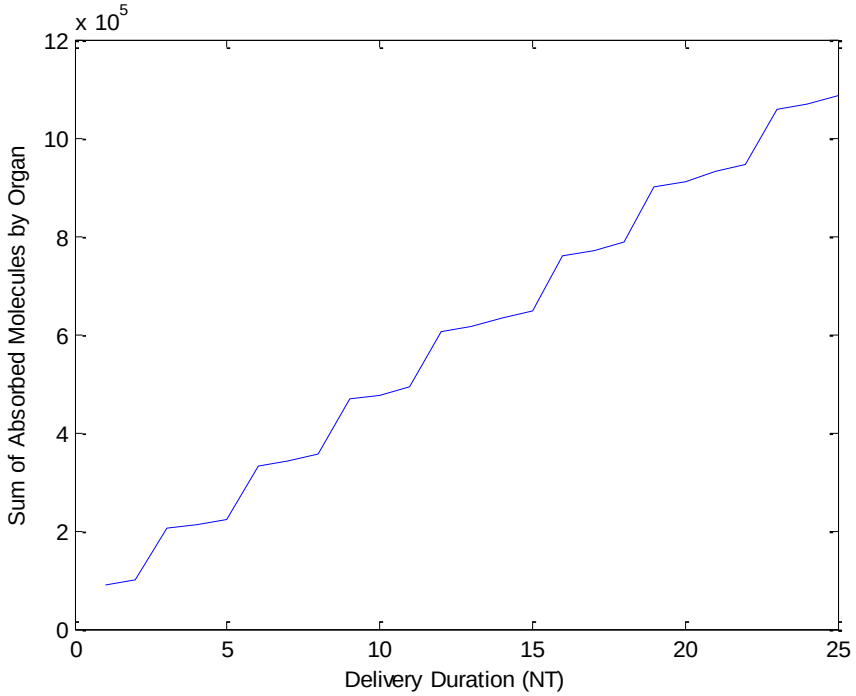

Fig. 6 The total amount of drug particles absorbed at the organ site in the delivery duration

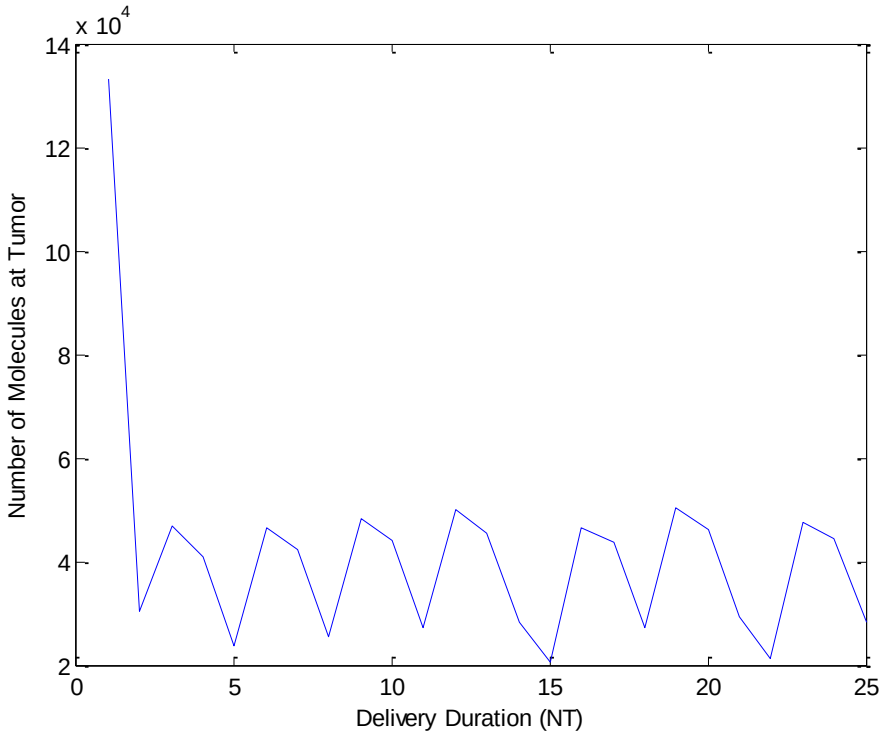

Fig. 7 The number of drug particles continuously received at the tumor site in the delivery duration

Fig. 8 shows the optimum coding sequence for the injector that is obtained based on the proposed delivery algorithm. According to Fig. 8 the final surviving path that is selected as the

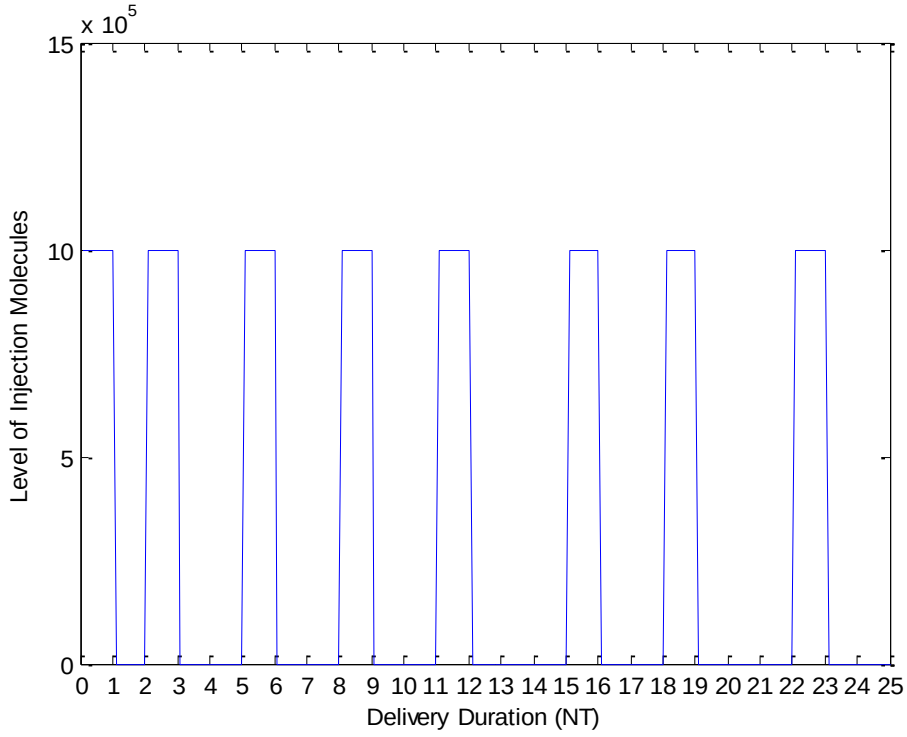

Fig. 8 The optimum coding sequence for the injector, obtained based on the proposed delivery algorithm

optimum coding sequence is $X \in \{1,0,1,0,0,1,0,0,1,0,0,1,0,0,0,1,0,0,1,0,0,0,1,0,0\}$. This result shows that the transmitter has been in the "injection" state in a total number of 8 times through the delivery duration.

Fig. 9 is considering the results for the total amount of drug particles absorbed at the organ when the delivery algorithm isn't applied to the system and the transmitter is injecting drugs, continuously. Note that the total amount of drug particles are increasing as the time is passing. This concludes that if optimization techniques are not applied the high amount of drug dosage can seriously damage the healthy organ.

Similarly, Fig. 10 considers the results for the number of drug particles continuously received at the tumor when the delivery algorithm isn't applied to the system. It is obvious that in this case the number of drug particles increases as the time passes. Fig. 10 depicts that without optimization, injection occurs in a high rate which may not only lead to damaging the healthy organ, but consuming high dosage of drugs that will not be even necessary for curing the tumor.

Note that the MATLAB codes for the delivery algorithm are given in Appendix A.

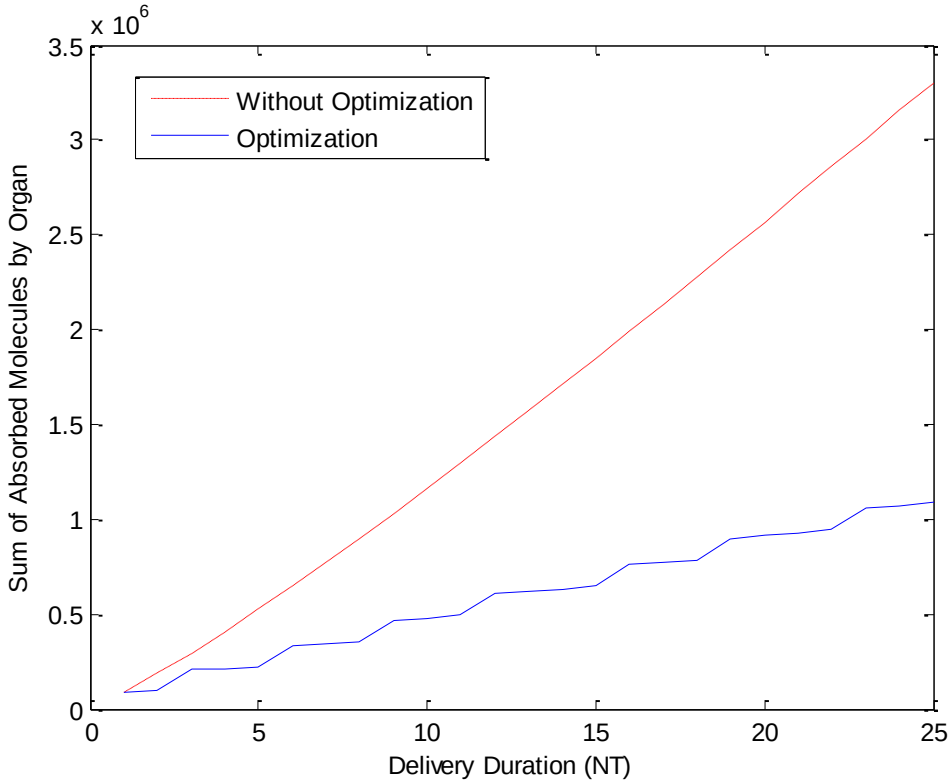

Fig. 9 Comparing the total amount of drug particles absorbed at the organ with and without applying optimization technique.

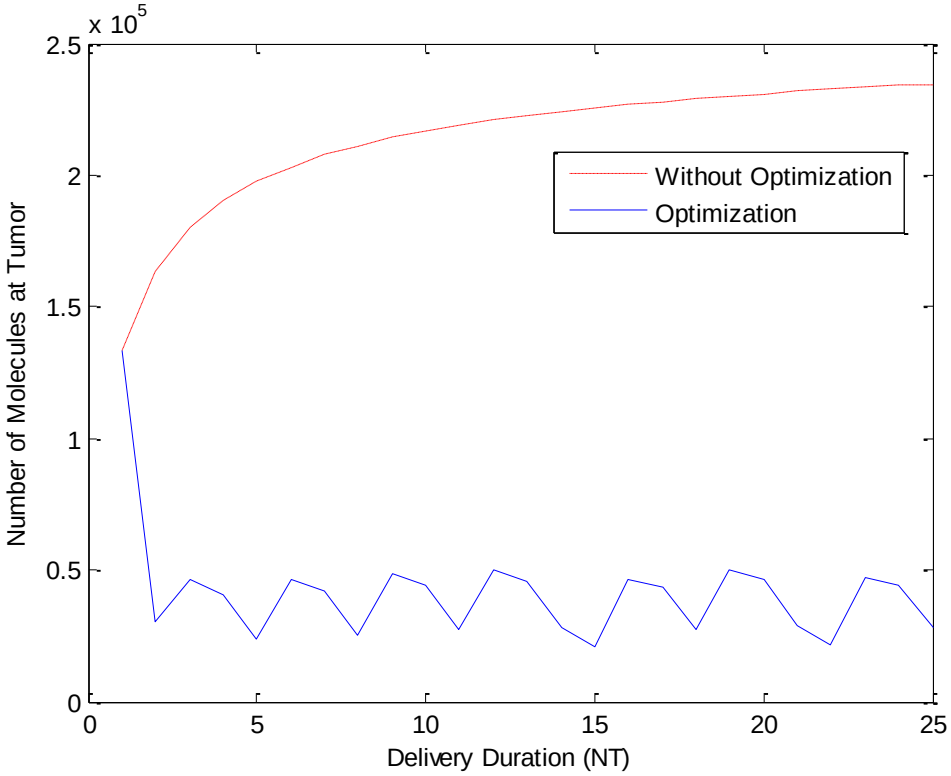

Fig. 10 Comparing the number of drug particles continuously received at the tumor with and without applying optimization technique.

V. Conclusion

In this paper, we have proposed a new optimization technique based on dynamic programming for an efficient drug delivery system (DDS). At the transmitter, we have considered an On-Off keying method for the delivery of drugs in a diffusion-based homogenous media. The objective surveys to minimize the total absorbed drug by the healthy organ during delivery time subject to continuously receiving at least a specific minimum level of drug by the tumor in order that the treatment to be effective. In this regard, an optimum coding sequence, which is adopted at the transmitter for injecting drugs, has been presented based on the proposed delivery algorithm in order to achieve the objective. Numerical results indicate that the proposed dynamic programming based drug delivery algorithm improves the performance of the delivery system.

It should be note that the proposed methodology can be applied for different drug delivery scenarios as well. Furthermore, the proposed algorithm can be extended for more realistic issues in pharmacology such as heterogeneous environment that is our undergoing research.

Appendix A: MATLAB Codes

The MATLAB codes are written as follows.

```
clear all
D=0.43;            % Diffussion coefficient
M=10^6;            % Drug rate
T=1;
N=25;              % Number of periods
do=2;              % distance between injector and organ
dt=1;              % distance between injector and tumor
Q=20000;           % thershould


% Calaulate yo and yt for the input as a one step

yo=zeros(1,N);
yt=zeros(1,N);

yo(1)=(M/(4*pi*D*do))*erf(sqrt(do^2/(4*D*T)));
yt(1)=(M/(4*pi*D*dt))*erf(sqrt(dt^2/(4*D*T)));

for m=2:N

    yo(m)=(M/(4*pi*D*do))*(erf(sqrt(do^2/(4*D*(m-1)*T))-
     erf(sqrt(do^2/(4*D*m*T))));

    yt(m)=(M/(4*pi*D*dt))*(erf(sqrt(dt^2/(4*D*(m-1)*T)))-
     erf(sqrt(dt^2/(4*D*m*T))));

end

% Intialization: k=1

WO1(1)=yo(1);
WT1(1)=yt(1);
WO2(1)=yo(1);
WT2(1)=yt(1);
X1(1)=1;
X2(1)=1;

% After k>1

for k=2:N

    X11=[X1,1];
    X12=[X1,0];
    X21=[X2,1];
    X22=[X2,0];

    BO11=0;
    BO12=0;
    BO21=0;
```

```
BO22=0;
BT11=0;
BT12=0;
BT21=0;
BT22=0;

% Calculate branch metrics

for m=1:k

    BO11=BO11+X11(m)*yo(k+1-m);
    BO12=BO12+X12(m)*yo(k+1-m);
    BO21=BO21+X21(m)*yo(k+1-m);
    BO22=BO22+X22(m)*yo(k+1-m);

    BT11=BT11+X11(m)*yt(k+1-m);
    BT12=BT12+X12(m)*yt(k+1-m);
    BT21=BT21+X21(m)*yt(k+1-m);
    BT22=BT22+X22(m)*yt(k+1-m);

end

% Calculate transition weight

W11=WO1(k-1)+BO11;
W12=WO1(k-1)+BO12;
W21=WO2(k-1)+BO21;
W22=WO2(k-1)+BO22;

% Select survival paths

% Survival path for "Injection" state or state "1"

if  W21<W11

    if  BT21>=Q
        X1=X21;
        WO1(k)=W21;
        WT1(k)=BT21;

    elseif BT11>=Q
        X1=X11;
        WO1(k)=W11;
        WT1(k)=BT11;

    elseif BT11>BT21
        X1=X11;
        WO1(k)=W11;
        WT1(k)=BT11;

    else
        X1=X21;
        WO1(k)=W21;
        WT1(k)=BT21;
```

```
    end

else

    if BT11>=Q
        X1=X11;
        WO1(k)=W11;
        WT1(k)=BT11;

    elseif BT21>=Q
        X1=X21;
        WO1(k)=W21;
        WT1(k)=BT21;

    elseif BT11>BT21
        X1=X11;
        WO1(k)=W11;
        WT1(k)=BT11;

    else
        X1=X21;
        WO1(k)=W21;
        WT1(k)=BT21;
    end

end


% Survival path for "Stop-Injection" state or state "2"

 if W22<W12

    if BT22>=Q
        X2=X22;
        WO2(k)=W22;
        WT2(k)=BT22;

    elseif BT12>=Q
        X2=X12;
        WO2(k)=W12;
        WT2(k)=BT12;

    elseif BT12>BT22
        X2=X12;
        WO2(k)=W12;
        WT2(k)=BT12;

    else
        X2=X22;
        WO2(k)=W22;
        WT2(k)=BT22;
    end

else
```

```
        if BT12>=Q
            X2=X12;
            WO2(k)=W12;
            WT2(k)=BT12;

        elseif BT22>=Q
            X2=X22;
            WO2(k)=W22;
            WT2(k)=BT22;

        elseif BT12>BT22
            X2=X12;
            WO2(k)=W12;
            WT2(k)=BT12;

        else
            X2=X22;
            WO2(k)=W22;
            WT2(k)=BT22;
        end

    end

end

% Final decision

if WO1(N)<WO2(N)

    if WT1(N)>=Q
        X=X1;
        WO=WO1;
        WT=WT1;

    elseif WT2(N)>=Q
        X=X2;
        WO=WO2;
        WT=WT2;

    elseif WT1(N)>WT2(N)
        X=X1;
        WO=WO1;
        WT=WT1;

    else
        X=X2;
        WO=WO2;
        WT=WT2;
    end

else

    if WT2(N)>=Q
```

```
        X=X2;
        WO=WO2;
        WT=WT2;

    elseif WT1(N)>=Q
        X=X1;
        WO=WO1;
        WT=WT1;

    elseif WT1(N)>WT2(N)
        X=X1;
        WO=WO1;
        WT=WT1;

    else
        X=X2;
        WO=WO2;
        WT=WT2;
    end

end

n=1:N;
plot(n,WO,'b')
xlabel('Delivery Duration (NT)'); ylabel('Sum of Absorbed Molecules by
Organ');
hold on
figure
plot(n,WT,'b')
xlabel('Delivery Duration (NT)'); ylabel('Number of Molecules at Tumor');
hold on
figure

for m=1:N

    for i=1:10
        XX((m-1)*10+i)=M*X(m);
    end

end

m=1:10*N;
plot(m,XX,'b')
xlabel('Delivery Duration (NT)'); ylabel('Level of Injection Molecules ');
```

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