2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

An Optimal Strategy for Individualized Drug Delivery Therapy: A Molecular Communication Inspired Waveform Design Perspective

Dongze Wang, Yue Sun*, *Member, IEEE*, Yue Xiao, and Yifan Chen, *Senior Member, IEEE*

***Abstract*—To enhance the drug delivery therapy efficacy and reduce the adverse effects on patients, we propose a molecular communication (MC) inspired optimization strategy to maintain the locoregional concentration of drug within a therapeutic window, the safe drug concentration range for individualized therapy. Observing the parallels between the propagation of information molecules and the delivery of drugs, MC, as a new paradigm, has drawn devised to overcome the challenges of the drug delivery system. The drug delivery is mapping to the transmission process of information molecules from the transmitter to the receiver. In addition, the locoregional concentration-time profile of the administered drug particles corresponds to the signalling waveform. Different from conventional drug delivery strategy, this work focuses on locoregional concentration instead of plasma concentration. Furthermore, with sustained-release preparations schemes, we also propose an algorithm to obtain the optimal administration time. The simulation results demonstrate that this strategy effectively maintains the relative steady-state drug concentration.**

***Index Terms*—Molecular communication, sustained-release preparations, locoregional drug concentration, therapeutic window, optimal administration time.**

I. Introduction

Drug delivery therapy promise to deliver drugs to the precise lesion locations at a controlled dosage and rate while minimizing the adverse effects on the healthy parts of the body. Currently, the major challenge is the low efficacy, resulting in only 0.7% of the administered dose reaching target diseased tissues, since reliance on systemic blood circulation [1]. Molecular communication (MC) is a new paradigm inspired by the biological system in nature, which exchanges information molecules between the biological nanomachines within a fluid environment [2]. Owing to the similarities between the delivery of drugs and the propagation of information molecules, the drug delivery process can be mapped into the MC model by the principles of pharmacokinetic and fluid dynamic [3][4]. MC-inspired drug delivery system reveals how the drug particles propagate in the vessels and the evolution of their distribution over time, which is vital to control the locoregional concentration of the drug. Consequently, MC-based Blood-mediated drug delivery is a new and growing field to enhance the locoregional therapeutics and diagnostics of the tumour.

Individualized drug delivery regimes aim to provide patients with the most suitable type and dose of medicine at the optimal time. In drug therapy, the pharmacological effect depends on the plasma concentration and the locoregional concentration. The relationship between plasma concentration and efficacy is not simply proportional, and an arbitrary increase in dose often can not achieve the desired effect [5]. Thus, it is critical to maintaining the locoregional drug concentration within a reasonable range, sustaining pesticide effects, and reducing adverse effects and drug resistance. However, much of the research up to now has been descriptive from the perspective of drug dosage concerning plasma concentration [6][7]. To design the drug concentration signaling pulse from a waveform design perspective, we propose an optimal strategy for individualized drug delivery inspired by MC.

The rest of this paper is organized as follows. Section II introduces the mapping of the drug delivery process and the components of an MC system. Section III illustrates the methodology of obtaining the optimal administration time. Section IV presents the parameters setting and analyzes the simulation results. Finally, Section V concludes the paper.

II. Drug Delivery System Model Based on MC

The role of sustained-release agents $in\ vivo$ in the delivery process is illustrated in Fig. 1. The drug particles are the information molecules; the release rate of drug particles corresponds to the input pulse $x_{Ti}(t)$; the locoregional drug concentration at the lesion corresponds to the received signal $y_{Ri}(t)$.

A. Sustained-release Model

In the conventional therapy of oral or injection drugs, it is inconvenient to administer drugs several times a day, which will cause a dramatic fluctuation of plasma concentration. In addition, the use of conventional agents will lead to the "crest-to-trough" phenomenon and adverse reactions such as toxicity, drug resistance and low efficacy. Consequently, the sustained-release agents were born, which can control the release rate of drug particles, improve the compliance of patients, reduce the excessive fluctuation of plasma concentration and drug administration times [8].

*Corresponding author: Yue Sun (sunyuestc90@126.com).

D. Wang, Y. Sun, and Y. Xiao are with the School of Information Science and Technology, Chengdu University of Technology, Chengdu 610059, China.

Y. Chen is with the School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 611731, China.

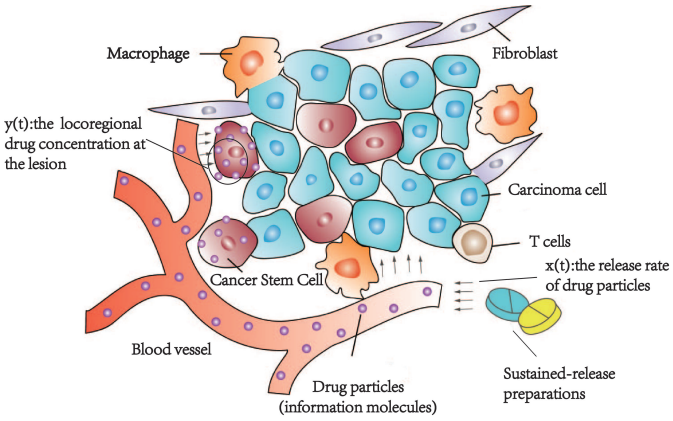

Fig. 1. The delivery process of sustained-release agents

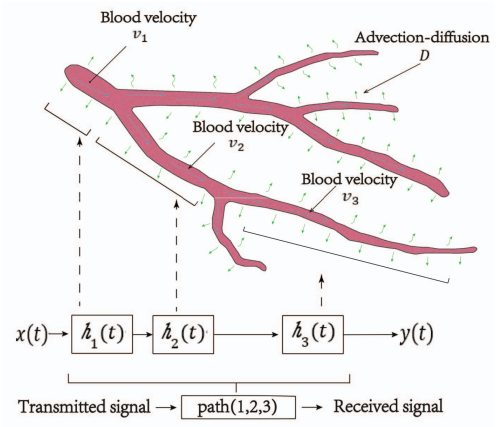

Fig. 2. The vascular network model based on molecular communication

From the MC perspective, the pharmacokinetic model of cylindrical and degradable sustained-release agents is illustrated as the release process of communication, denoted as the input pluse $x_{Ti}(t)$ of the i_{th} administration [9]:

$$x_{Ti}(t) = 2\pi C_0 hB\left(r - B\left(t - T_i\right)\right) \quad i = 1, 2, 3, \ldots \tag{1}$$

where C_0 is the dosage per unit area, h and r are the height and radius of the cylindrical troche, respectively. B indicates the surface degradation rate of the agent. Q_i represents the drug dosage carried by a sustained-release tablet, which is given as:

$$Q_i = \int_{T_i}^{T_i + T_{slot}} x_{Ti}(t)\, dt \tag{2}$$

where T_i is the time of i_{th} administration and T_{slot} is the duration of drug release.

B. Vascular Network Model

The channel model corresponds to the vascular network with advection, which is depicted by the advection-diffusion equation [10]:

$$\frac{\partial c}{\partial t} + \nabla \cdot (vc) = D\nabla^2 c \tag{3}$$

where v denotes the velocity vector, D denotes the diffusion coefficient. The vascular network has several bifurcation nodes as shown in Fig. 2. When the drug particles pass through a node, they enter another path of the channel network which is characterized by the Channel Impulse Response (CIR). As a result, the CIR of blood vessels at different stages are described as $h_j(t)$ [10]:

$$h_j(t) = \frac{1}{\sqrt{4\pi Dt}} e^{\frac{-(d_j - v_j t)^2}{4Dt}} \quad j = 1, 2, 3, \ldots \tag{4}$$

where d_j and v_j are the length and advection velocity of j_{th} stage of blood vessel, respectively.

According to the analysis of pharmacokinetic data, the half-life of drugs is an essential reference factor for rational drug use, which has a great correlation with the elimination function of the liver and kidney [11]. Hence, the CIR is further given as (5):

$$H_j(t) = h_j(t) e^{-kt} \quad j = 1, 2, 3, \ldots \tag{5}$$

where k denotes the drug clearance rate. In a specific MC system, the clearance rate is assumed as a constant.

C. Drug Particles Reception Model

The reception model describes the evolution of the locoregional drug concentration at the lesion, taking the effects of the channel and the degradation of the therapeutic agent into account. According to the MC channel model above and the drug release rate $x_{Ti}(t)$, the drug concentration at the first-order bifurcation node of the vascular network can be described as:

$$g_i(t) = \int_{\tau} x_{Ti}(\tau) H_1(t - \tau) d\tau \quad i = 1, 2, 3, \ldots \tag{6}$$

Similarly, $y_{Ri}(t)$ is the locoregional drug concentration at the lesion:

$$y_{Ri}(t) = g_i(t) \otimes H_2(t) \otimes H_3(t) \tag{7}$$

The cumulative locoregional drug concentration-time profile at the lesion $y_R(t)$ is given as:

$$y_R(t) = \sum_i y_{Ri}(t) \quad i = 1, 2, 3, \ldots \tag{8}$$

III. Methodology

In clinical therapy, the optimal therapeutic effect is achieved within a specific range of locoregional drug concentration, which is called the therapeutic window or the safety window [12]. The upper limit of the therapeutic window denotes the minimum toxic concentration (MTC). Similarly, the lower limit represents the minimum effective concentration (MEC). The drug concentration above MTC may cause adverse effects, While the drug concentration below MEC could hardly produce therapeutic effects. In addition, unreasonable drug concentration may increase the possibility of patients developing drug resistance [13].

An algorithm is proposed to explore the optimal administration time T_i for efficient individualized therapy. The locoregional drug concentration-time profile at the lesion has the following two phases, ascending phase and maintaining phase,

1) Ascending phase, the locoregional drug concentration at the lesion rises during the first few doses until reaching the expected value. To emphasize the effect of the administration time, we assume that the drug dosage is constant for each administration:

$$Q_i = C \quad i = 1, 2, 3, \ldots \tag{9}$$

2) Maintaining phase, when the locoregional drug concentration reaches the expected value, the subsequent administration aims to maintain it in a safe range.

The peak point of the concentration-time profile after i_{th} dose is (t_i, y_{Rmax}). When $t > t_i$, the drug concentration will decline until $(i+1)_{th}$ administration arrives. Once $(i+1)_{th}$ administration reaches at time T_{i+1}, the drug concentration will keep decreasing from T_{i+1} to $T_{i+1} + \Delta t$ because of the rate of consumption of drug particles is greater than the rate of compensation. Conversely, due to the compensation rate of the drug particles is greater than the consumption rate, the drug concentration rises continuously during $T_{i+1} + \Delta t$ and t_{i+1} until it returns to y_{Rmax}. As a result, the locoregional drug concentration is maintained around the peak value y_{Rmax} from t_i to t_{i+1}. Then, the algorithm of the optimal administration time T_{i+1} for the $(i+1)_{th}$ dose is given as:

- The drug concentration cannot exceed the expected peak concentration y_{Rmax}.

$$T_{i+1} > t_i \tag{10}$$

- The original drug concentration has dropped by Δy from t_i to t_{i+1}, while the supplemented drug concentration has increased by Δy from T_{i+1} to t_{i+1}

$$y_R(t_i) - y_R(t_{i+1}) = y_{R_{i+1}}(t_{i+1}) \tag{11}$$

The two curves satisfy the following three conditions at time t:

$$\begin{vmatrix} \frac{dy_{Ri+1}(t)}{dt}|_{t=t_{i+1}^-} \\ \frac{dy_{Ri+1}(t)}{dt}|_{t=t_{i+1}} \\ \frac{dy_{Ri+1}(t)}{dt}|_{t=t_{i+1}^+} \end{vmatrix} \begin{matrix} > \\ = \\ < \end{matrix} \begin{vmatrix} \frac{dy_R(t)}{dt}|_{t=t_{i+1}^-} \\ \frac{dy_R(t)}{dt}|_{t=t_{i+1}} \\ \frac{dy_R(t)}{dt}|_{t=t_{i+1}^+} \end{vmatrix} \tag{12}$$

According to (11)(12)(13), t_{i+1} and Δy can be obtained.

- Then, because the the drug dosage is constant for each administration, the time of the locoregional drug concentration rising from 0 to Δy for a single administration is Δt_1.

Consequently, the optimal administration time T_{i+1} can be expressed as :

$$T_{i+1} = t_{i+1} - \Delta t_1 \tag{13}$$

TABLE I
PARAMETERS

Parameters	Symbol	Values
Diffusion coefficient	D	$0.00001\text{m}^2/s$
Length of vessel	d	$0.1 \sim 5$m
Clearance rate constant	k	0.2
Degradation rate constant	B	0.05
Dosage per unit area	C_0	$0.39 \sim 1.27$g
Height of cylinder	h	3mm
Radius of cylinder	r	$3 \sim 9$mm

IV. Simulation Results and Analysis

In this section, the simulations of the proposed scheme are presented and the parameters in Table 1 is adopted as default.

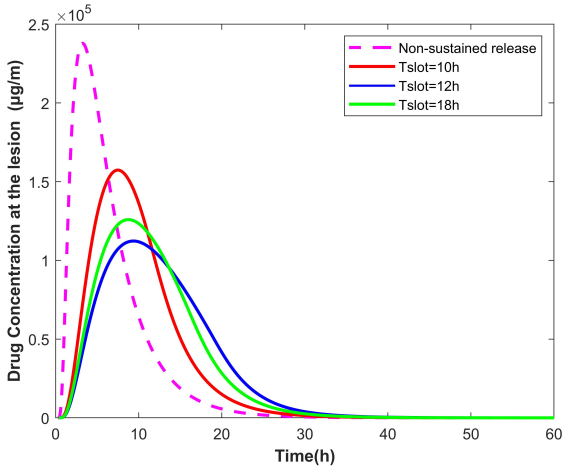

Fig. 3. Locoregional drug concentration at the lesion of sustained-release and non-sustained-release.

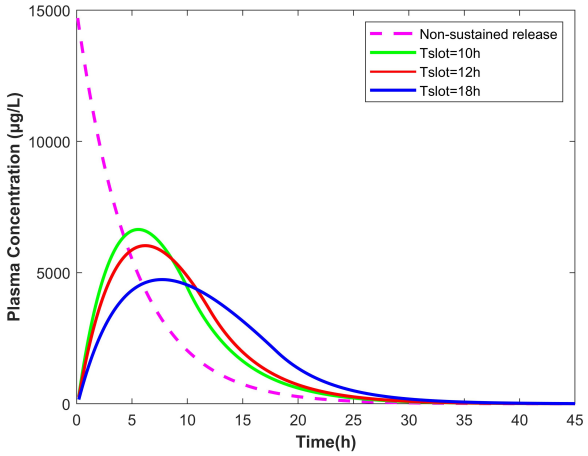

Fig. 4. Plasma concentration of sustained-release and non-sustained-release.

The locoregional drug concentration-time profiles of sustained-release agents and traditional drugs are investigated and compared. Fig. 3 illustrates that the time required for

sustained-release agents to reach the peak locoregional drug concentration at the lesion is more than conventional ones and the peak drug concentration of sustained-release agents is lower than conventional ones. Such features could effectively maintain the steady of the drug concentration to ensure a safe treatment. In addition, the plasma concentration is also a crucial factors of drug therapy. Hence, for drug dosage $x_T(t)$, characterization volume V, observing the plasma concentration of traditional drugs and sustained-release preparations, which are defined as $C_0(t) = x_T(t)e^{-kt}/V$ and $C_1(t) = x_T(t) \otimes e^{-kt}/V$, respectively. As shown in Fig. 4, the peak plasma concentration of sustained-release preparations is much lower than traditional drugs, and this trend has been enhanced with the increase of sustained-release levels.

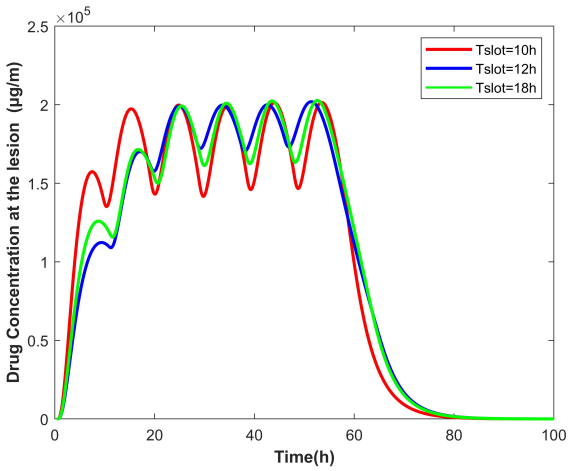

Fig. 5. Under different sustained-release degrees, the locoregional drug concentration-time curves of the optimal strategy for individualized drug therapy.

In the continuous administration, the locoregional drug concentration-time curves using the proposed strategy are shown in Fig. 5. It can be seen that the locoregional drug concentration at the lesion is maintained within a stabilized range because the optimal administration time results in a dynamic equilibrium of the evolution in drug concentration. In addition, as the degree of sustained drug release increases, the locoregional drug concentration will be maintained within a safer range. Furthermore, most cytotoxic drugs used in cancer treatment have a narrow therapeutic window, meaning that the dosage of these drugs that significantly affect the tumor is close to the dosage that causes unacceptable toxic effects [6]. Therefore, using the sustained-release agents and optimal administration time could play a significant role in cancer treatment.

V. Conclusion

In this work, the proposed strategy inspired by MC enhances therapy efficacy of drug treatment. In the proposed strategy, with the assistance of the MC system and sustained-release preparations schemes, the optimal administration time is obtained to maintain the locoregional drug concentration at the lesion within the therapeutic window, which significantly improves the effect of drug treatment. Future work will consider optimizing the individualized drug delivery schemes from perspectives of the administration time, drug dosage, and the routing plan.

References

[1] S. Wilhelm et al., "Analysis of nanoparticle delivery to tumours," Nat. Rev. Mater., vol. 1, no. May 2018, 2016.

[2] Akyildiz, I. F. , F. Brunetti , and C Blázquez, "Nanonetworks: A new communication paradigm," Computer Networks, vol. 52, no. 12, pp. 2260-2279, 2008.

[3] U. A. K. Chude-Okonkwo, R. Malekian, B. T. Maharaj, and A. V. Vasilakos, "Molecular Communication and Nanonetwork for Targeted Drug Delivery: A Survey," IEEE Commun. Surv. Tutorials, vol. 19, no. 4, pp. 3046–3096, 2017.

[4] S. Salehi, N. S. Moayedian, S. S. Assaf, R. G. Cid-Fuentes, J. Solé-Pareta, and E. Alarcón, "Releasing rate optimization in a single and multiple transmitter local drug delivery system with limited resources," Nano Commun. Netw., vol. 11, pp. 114–122, 2017.

[5] L.Brunton, B. Chabner, and B. Knollman, "Goodman and Gilman's The Pharmacological Basis of Therapeutics, Twelfth Edition," 2011.

[6] A. Floares, C. Floares, M. Cucu, and L. Lazar, "Adaptive Neural Networks Control of Drug Dosage Regimens in Cancer Chemotherapy," International Joint Conference on Neural Networks IEEE, 2003.

[7] A. Vafamand, "Multi-Objective Optimal Strategies For HIV Drug Dosage Scheduling Using NSIWO," 2018 25th Natl. 3rd Int. Iran. Conf. Biomed. Eng., no. 1, pp. 1–5, 2018.

[8] W. He, S. Zhan, Q. yang, C. wang, W. Yang, Y. Ding and Y. Zheng, "Pharmacokinetic model of sustained-release agents," 2010 Int. Conf. Biomed. Eng. Comput. Sci. ICBECS 2010, no. 1, pp. 1–4, 2010.

[9] H. B. Hopfenberg, "Controlled Release from Erodible Slabs, Cylinders, and Spheres", 1976.

[10] N. Farsad, H. B. Yilmaz, A. Eckford, C. B. Chae, and W. Guo, "A comprehensive survey of recent advancements in molecular communication," IEEE Commun. Surv. Tutorials, vol. 18, no. 3, pp. 1887–1919, 2016.

[11] A. Krause, D. Lott, and J. Dingemanse, "Estimation of Attainment of Steady-State Conditions for Compounds With a Long Half-Life," J. Clin. Pharmacol., vol. 61, no. 1, pp. 82–89, 2021.

[12] P. Y. Muller and M. N. Milton, "The determination and interpretation of the therapeutic index in drug development," Nat. Rev. Drug Discov., vol. 11, no. 10, pp. 751–761, 2012.

[13] Y. Zhou and Y. Chen, "Latticed Channel Model of Touchable Communication over Capillary Microcirculation Network," IEEE Trans. Nanobioscience, vol. 18, no. 4, pp. 669–678, 2019.