Estimation of drug shape in Drug Delivery System by simulation

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Abstract: In order to realize an effective Drug Delivery System (DDS) for solid tumor, we study the most suitable shape of a drug. For this purpose, we constructed a mathematical model of drug movement in blood vessel, and made a simulation of it [1, 2]. In the model, we take into consideration a particular reaction of tumor tissues called the Enhanced Permeability and Retention effect (EPR effect) and the recognition by the reticuloendothelial system. These have not been studied mathematically yet, thus the study is especially significant for DDS. We succeeded to estimate the drug shape which is most effective for remedy of tumor. In this paper, we show some of our results of calculation.

Key-Words: DDS, EPR effect, Drug shape, Drug carrier, Simulation

1 Introduction

Drug Delivery System (DDS) for solid tumors has been studied for several decades so as to make a riskless remedy without side effects. Nanoscale particles, such as liposomes and polymer micelles, are expected as drug carriers [3, 4]. They encompass a variety of submicron (< 1μm) colloidal nanosystems. One of their major advantages is their small size, which allows them to pass through certain biological barriers. Moreover, it is known that the particles can arrive in tumor selectively. Aggressive tumors inherently develop incomplete vasculature with 100-1000nm pores around there. This flawed vasculature coupled with poor lymphatic drainage makes biological polymers and nanoscale particles to enhance the permeation and retention with the tumor region. This is called the EPR (enhanced permeability and retention) effect, proposed by H. Maeda, and is a representative basis of passive targeting [5, 6, 7, 8]. Recently, the liposomal particle formulations have received clinical approval. Examples of it are Doxil (Caelyx), Myocet which enclose doxorubicin, and Daunosome which also enclose daunorubicin [3, 4]. However the shape, in particular, the size of drug particle is not studied well, in spite of a close relation with a question how much medicine should be dosed. To answer this, we constructed a mathematical model of drug movement in blood vessel with the EPR effect, and made a simulation of it [1, 2]. In this paper, we estimate the drug shape which is most effective for remedy of tumor.

2 Method

We estimate the configuration of drug which is most effective to remedy for tumors in various situation of human body, following the steps below.

(i) Construct the dynamical model of nanoparticles over the body, based on mathematical physics.

Taking various interactions, the dynamical model should be one of the many-body problems. This dynamical model is difficult to analytically be solved, so that we treat it under the following conditions:

(ii) Take some approximations to describe the interactions.

(iii) Analyze the movement of drug particles in the blood.

In addition, we consider the movement of nanoparticles as a stochastic process, and we approximate the blood plasma as a Newtonian fluid and the force working on the drug particle as a mean field.

Based on above conditions, we

(iv) calculate the probability that drug is in the tumor after fixed time;

(v) estimate the shape of the drug particle providing the maximum probability that the injected drug stays in tumor.
We denote the places by $B_1$: Blood, $B_2$: Tumor, $B_3$: Somewhere including RES (reticuloendothelial system), that drug particles stay. Then, let $p_i^{(n)}$ be the probability that a drug staying in $B_i$ after $n$ times circulation.

One has
\[ p_i^{(n)} = \sum_k t_{ik}^{(n)} p_k^{(n-1)}, \quad n > 0, \tag{1} \]
where $t_{ij}^{(n)}$ is the transition probability from $B_j$ to $B_i$ at $n$th body circulation. The initial condition $p_i^{(0)}$ at time $n = 0$ should be
\[ p_1^{(0)} = 1, p_2^{(0)} = 0, p_3^{(0)} = 0. \tag{2} \]
Let $T_{\text{once}}$ be the time for a body circulation, and let $T_{\text{max}}$ be the life time of a drug particle given by Drug maker. Let $n_{\text{max}}$ be the maximum integer $n$ such that $\sum_{k=1}^{n} T_{\text{once}} < T_{\text{max}}$. The probability in $B_i$ at time $T_{\text{max}}$ is denoted by $p_i^{(n_{\text{max}})}$. We compute the value $p_i^{(n_{\text{max}})}$ with respect to several parameters of drug and tumor. The details of the model will be explained in conference.

3 Simulation

In this section, we show some of our results of calculation. We calculate and plot the probability $p_2^{(n_{\text{max}})}$ in Fig.1 w.r.t. the diameter of the drug and its mass density. One can see the change of $p_2^{(n_{\text{max}})}$ of the drug with $\rho = 1.0 \text{g/cm}^3$ according to the change of its diameter in Fig.2(a). Then we plot $p_2^{(n_{\text{max}})}$ of the drug with its diameter 100nm in Fig.2(b), as a typical drug diameter is around 100nm.

![Figure 1: The probability $p_2^{(n_{\text{max}})}$ that a drug is in Tumor after a fixed time $T_{\text{max}}$.](image1)

![Figure 2: (a) Plot the probability each diameter for a fixed $\rho = 1.0 \text{g/cm}^3$. (b) Plot the probability each mass density for a fixed $2a = 100\text{nm}$.](image2)
4 Discussion

(I) There is a peak near 120 nm in Fig.2(a). This result well matches the result of in vivo study [9]. The result implies that our mathematical model can simulate the drug movement very well.

(II) In Fig.1 and Fig.2, the peak of the probability \( p_2^{(n_{\text{max}})} \) depends on the diameter of a drug particle and its mass density.

(III) In Fig.2(b), we can see that the probability \( p_2^{(n_{\text{max}})} \) is slightly increasing by increasing the mass density.

From (I), (II) and (III), our model makes clear a relation between the change characters of drug and its effect, so that our simulate will indicate the way how to design the drug. Our model improves the drugs more effectives has less side effects e.g., retention of other organs.

Consequently, our model and simulate will give us drug design to have the better effect. Moreover, setting parameters depending on the characters of target tumor and these of patient makes it possible to have individual patients DDS more accurately.

See the paper [2] for the details of this present paper.

References:


