Reliability for drug targeting in cancer treatment through nanotechnology (A Stochastic differential equation-based flexible model)

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Abstract

The lack of a unified definition of reliability function in system design phase may contribute to the difficulty in improving the reliability of nanotechnology drug delivery systems. The reliability function is frequently used in reliability engineering and gives the probability of an item operating for a certain amount of time without failure. As such, the reliability function is a function of time. In this paper we define the notion of reliability function in the context of drug targeting in cancer treatment. This function gives the probability of all cancerous cells being destroyed in a certain amount of time. Having defined our notion of the reliability function, we propose a model for this function based on Ito type stochastic differential equations. We also describe an algorithm for computing the minimum dose level to achieve a desired value for expected time needed to destroy all cancerous cells.

Notation

\( C \) the number of nanoconjugates that are carrying the drug and they are injected into the blood stream

\( S(t) \) the number of nanoconjugates that are still at the site of administration at time \( t \)

\( S_1(t) \) the number of nanoconjugates that are in non-targeted tissues at time \( t \)

\( I_1(t) \) the number of nanoconjugates that are in cancerous cells population at time \( t \)

\( I_2(t) \) the number of nanoconjugates that are in healthy cells population at time \( t \)

\( R(t) \) the number of nanoconjugates that are eliminated at time \( t \)

\( d_1 \) the average number of nanoconjugates that penetrate cancerous cells population in the targeted tissue per unit time

\( d_2 \) the average number of nanoconjugates that penetrate healthy cells population in the targeted tissue per unit time

\( d_3 \) the average number of nanoconjugates that penetrate non-targeted tissues per unit time

\( d^* \) the average number of nanoconjugates that penetrate from non-targeted tissues per unit time

\( d^* = (d_1 + d_2 + d_3) \)

\( \gamma_1 \) the average number of nanoconjugates that are eliminated from cancerous cells population in the targeted tissue per unit time

\( \gamma_2 \) the average number of nanoconjugates that are eliminated from healthy cells population in the targeted tissue per unit time

\( \lambda_1 \) the average number of cancerous cells that are killed per unit time

\( \lambda_2 \) the average number of cancerous cells population is expanded

\( d^* \) the average number of cancerous cells being eliminated per unit time

\( \lambda \) the average number of cancerous cells population in the targeted tissue per unit time

\( k \) Number of nanoconjugates, carrying the drug, needed to destroy a cancerous cell in the tissue

\( N(t) \) the number of cancerous cells in the tissue at time \( t \)

\( n \) the number of cancerous cells in the tissue at time 0

\( T \) the first time all cancerous cells will be destroyed

\( P(t) \) the reliability of a nanodrug delivery system = \( P(T \leq t) \)

\( E(T) \) expected time required to kill all cancerous cells

\( B_j(t) \) standard Brownian motion, \( j=1,2,3,4,5 \)

\( \sigma_j(t) \) diffusion coefficient, \( j=1,2,3,4,5 \).

Introduction

The focus of the nanotechnology therapeutic approaches to treat cancer has been on early disease detection, drug discovery and monitoring, controlled release of therapeutic agents, and targeted drug delivery. See Amiji [1] for more details. Targeted drug delivery requires statistical modeling to establish the reliability in success of drug targeting. Unreliable nanotechnology drug delivery systems are a

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Key words: Ito concepts, gaussian process, stochastic differential equations, nanoconjugate

Received: May 10, 2016; Accepted: May 25, 2016; Published: May 30, 2016
major source of user frustration. We believe that the key to make more reliable systems is first understand what makes a nanotechnology drug delivery system Ebrahimi and Mansoori [2] defined the instantaneous (or point) reliability of a nanotechnology drug delivery system for cancer therapy as the probability of killing all cancerous cells at the single instant in time. Instantaneous reliability is typically used in the military, as it is sometimes necessary to assess the reliability of a system at a specific time of interest. However, we are often interested in the reliability of a nanotechnology drug delivery system over a period of time. Throughout this paper we refer to it as the reliability function. In this paper we first introduce the notion of the reliability function of a nanotechnology drug delivery system for cancer therapy. Our notion of reliability function is a generalization of Ebrahimi and Mansoori [2] definition and varies over time. We then report on our efforts to determine an optimal dose of the drug to achieve a desired average time required to kill all cancerous cells for a cancer nanotechnology drug delivery system. It should be mentioned that the question of how to assess reliability for nanotechnology based engineering systems was recently studied by some researchers. For more details about this line of research see Ebrahimi [3-5] and many references cited there.

The paper is organized as follows. In Section 2, we present a time dependent stochastic differential equation for modeling the number of nanoconjugates that penetrate cancerous cells population in the tissue. In section 3, we introduce notion of reliability function and propose a model for this function. In this section, we also give an algorithm to compute an optimum dose level to achieve a desired value for expected time needed to kill all cancerous cells. Two examples are provided in this section to illustrate our proposed methodology. Concluding remarks are provided in Section 4.

General formulation

Let us consider a nanoconjugate containing the drug which has potential either to attach to the surface of a cancerous cell or to go inside a cancerous cell in a targeted tissue. Suppose \( C \) is the number of these nanoconjugates that are injected into the bloodstream. Since our interest is only on cancerous cells, for simplicity of our presentation, we assume that the targeted tissue is made of two groups. Group one consists of all cancerous cells and group two consists of all noncancerous cells. Throughout this paper we refer to a noncancerous cell as a healthy cell. Now, as the time proceeds, each nanoconjugate can be in one of the five possible states; still at the site of administration, penetrated non-targeted tissues, penetrated group one, penetrated group two, or removed from the body. Let \( S(t) \) and \( S_1(t) \) be the number of nanoconjugates that are still at the site of administration and in non-targeted tissues at time \( t \), respectively. Also, let \( I_1(t) \) and \( I_2(t) \) be the number of nanoconjugates that are in groups one and two at time \( t \), respectively. Finally, let \( R(t) \) be the number of nanoconjugates that are already eliminated from the body at time \( t \). Note that \( I_1(0) = S(0) + R(0) = 0 \), \( i = 1, 2 \), and \( S(0) = C \) (Figure 1) summarizes the process of elimination of nanoconjugates.

Modeling the process of elimination of nanoconjugates using differential equations

It is known that most drugs used in clinical practice will show first order rate elimination processes, see Jambheker and Breen (2012) [6]. For a nanodrug delivery system this means that the number of nanoconjugates will decrease at a rate that is proportional to \( S(t) \). Using this fact, from Figure 1, we can describe the elimination of nanoconjugates from the body through the following four ordinary differential equations:

\[
\frac{dS(t)}{dt} = -d_2 S(t) - d_3 S(t) - d_4 S(t) dt,
\]

\[
\frac{dS_1(t)}{dt} = d_3 S(t) - d_4 S_1(t) dt,
\]

\[
\frac{dI_i(t)}{dt} = (d_2 S(t) - \gamma_i I_i(t)) dt, \quad i = 1, 2,
\]

\[
\frac{dR(t)}{dt} = \gamma_1 I_1(t) + \gamma_2 I_2(t) + d_4 S(t) dt,
\]

where \( \gamma_i \) is the rate of elimination of nanoconjugates from the group \( i \),

Figure 1. Process of elimination of nanoconjugates
where $d^*$ is the rate at which nanoconjugates penetrate the group $i$, $d_i$ is the rate at which nanoconjugates penetrate non-targeted tissues, and $d_{ii}$ is the rate of elimination of nanoconjugates from non-targeted tissues.

Modeling the process of elimination of nanoconjugates using stochastic differential equations

Typically, stochastic differential equations incorporate random white noise which is the derivative of a standard Brownian motion. Since it is a basic clinical observation that variability always exists within a group of patients, we introduce stochastic perturbation terms into the equations (1)-(3). Having done that the resulting stochastic differential equations are:

$$S(t) = C \exp(-d^* t) + \int_0^t \exp(-d^* (t-u)) \sigma(u) dB(u) du,$$

$$S_i(t) = \frac{Cd_i}{d^* - d_{ii}} (\exp(-d^* t) - \exp(-d^* t')) + \int_0^t \exp(-d_{ii} (t-u)) - \exp(-d^* (t-u)) \sigma(u) dB(u) (u), i = 1,2,$$

and

$$R(t) = C[1 - \frac{d_i}{d^* - d_{ii}} \exp(-d_{ii} t) - \frac{d_{ii}}{d^* - d_{ii}} \exp(-d^* t) - \frac{d_1}{d^* - d_{i1}} \exp(-d_{i1} t) - \frac{d_{i1}}{d^* - d_{i1}} \exp(-d^* t) - \frac{d_2}{d^* - d_{i2}} \exp(-d_{i2} t) - \frac{d_{i2}}{d^* - d_{i2}} \exp(-d^* t) - \frac{d_4}{d^* - d_{i4}} \exp(-d_{i4} t) - \frac{d_{i4}}{d^* - d_{i4}} \exp(-d^* t)] - \int_0^t \exp(-d_{ii} (t-u)) - \exp(-d^* (t-u)) \sigma(u) dB(u) (u), i = 1,2.$$

From the equation (8) it is clear that as $t$ approaches to infinity, the $R(t)$ approaches to C. Also, since $R(t)$ must be a non-decreasing function in $t$, we need $\gamma_i, \gamma_{ii}$, and $d^*$ to be less than or equal to $d^*$. Notion of reliability function and a criteria to find $C$

Let $N(t)$ be the number of cancerous cells still in the targeted tissue at time $t$. Define,

$$T = \text{Inf}[t : I(t) - kN(t) \geq 0].$$

In equation (15), $T$ represents the first time that all cancerous cells will be destroyed and a targeted tissue will be cancer free. Now, we define

$$P(t) = P(T \leq t) = 1 - P(T > t) = 1 - P(\text{sup}_{t \geq 0} I(t) - kN(t) \leq 0)$$

We refer to $P(t)$ as the reliability function of nanotechnology drug delivery systems for cancer therapy.

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From (16), $P(t)$ gives the probability of a targeted tissue be cancer free before time $t$. A higher $P(t)$ suggests the system is more reliable. Also, expected value of $T$, $E(T)$, gives average time required to kill all cancerous cells. It should be noted that $k$, the number of nanoconjugates needed to kill a cancerous cell, depends on the size of a cancerous cell and can be determined in an Vivo experiment. Usually, if the size of a nanoconjugate is much smaller (or larger) than the size of a cancerous cell, then one needs to deliver hundreds of (or few) nanoconjugates.
to kill a cancerous cell. See for example Zharov et al., Mansoori et al., Keyhanian et al., Hashemi et al., and Letefullin and George [10-14].

It is worth mentioning that the classical definition of reliability function is defined in terms of the survival distribution function of its lifetime. For more details about the classical notion of reliability see Lawless [15].

Now to calculate $P(t)$ we need to model $N(t)$. Following arguments similar to the ones used in sections (2.1) and (2.2), we use the following stochastic differential equation,

$$dN(t) = -\lambda N(t) + \lambda_i N(t) + \sigma_i(t) dB_i(t),$$

where $\lambda$ is the rate cancerous cells are killed, $\lambda_i$ is the rate cancerous cells proliferate and $B_i(t)$ is a standard Brownian Motion.

Given $N(0)=n$ solving the equation (17) gives

$$N(t) = n \exp(-d^*_t) + \int_0^t \exp(-d^*_t)(t-u)\sigma_i(u) dB_i(u)$$

Where $d^*_i = \lambda - \lambda_i$. From the equation (18), it is clear that $E(N(t))=n(d^*_t)$ and $\text{Var}(N(t)) = n \sigma_i^2$. The following example we illustrate our method by assigning numbers to all the parameters in the model.

Example 1. Suppose we have designed a nanotechnology drug delivery system with $C = 420$ and $n = 100$, $a_i = a_j = a = 0.1$, $\sigma_i = \sigma_j = \sigma = 1$, $d_i = 0.8, d_j = 0.1, d = 0.1$. Also, assume that the size of a nanocjugate is much larger than a cancerous cell and we only need $k=3$ to kill the cancerous cell. For this system, $B(t) = 8.5 \exp(-2t) - 7.5 \exp(-1.4t) - 12.1 \exp(-1.6t) + 26.3 \exp(-1.8t) - 8.9 \exp(-2t)$, $A(i) = 1680 \exp(-0.8t) - 1680 \exp(-0.7t)$.

Using the equation (23), the reliability function is given by,

$$P(t) = \int_0^t \left[ 2 \pi B(x,t) \right]^{1/2} \exp\left(-\frac{0.5A(x,t)^2}{B(x,t)}\right) dx.$$
Concluding remarks

In this paper, we have introduced a unified definition of reliability function for nanotechnology drug delivery systems in cancer therapy. Our notion provides a general framework for assessing reliability and it is very flexible and easy to use. As one expects, our finding shows that, one can achieve a specific value for \( E(T) \) with low dose level by having small \( k \). By increasing \( k \) the dose level increases exponentially. Also, by increasing \( E(T) \), the dose level decreases.

Acknowledgment

The work of the first author is partially supported by the National Science Foundation, DMS1208273.

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