

RESEARCH ARTICLE

On the Reception Process of Molecular Communication-Based Drug Delivery

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ABSTRACT One of the important applications of molecular communication is the targeted drug delivery process in which the drug molecules are released toward the target (receiver) in a way that the side effects are minimized in the human body. As the total number of released molecules increases, the receiver cannot receive all of the transmitted drug molecules. Therefore, the molecules accumulate in the system which results in side effects in the body. In order to diagnose the appropriate transmission rate of the drug molecules, it is important to investigate the reception process of the receiver. In this paper, a reception model is studied using queuing theory. In the proposed model, the rejection rate of the drug molecules due to different reasons, such as random movement of the molecules, as well as the rejection rate due to active receptors are taken into account. Moreover, an interval consisting of the lower and upper bounds for the number of released molecules is presented based on the proposed model in order to determine the range of allowable dosage of the drug molecules. It is shown that queuing theory can be successfully employed in accurate modeling of the reception process of the receiver in drug delivery applications.

INDEX TERMS Drug delivery, finite receptor, free diffusion, queuing theory, rejection rate.

I. INTRODUCTION

Molecular communication (MC) is an emerging communication technique in which molecules are used to transfer information among nanomachines [1], [2]. Each nanomachine is a nano-scale device which can perform a simple task in MC. Cooperation of nanomachines leads to performing a complex task [3], [4]. MC has various applications in Internet of Nano Things (IoNT) [5], Internet of Bio-Nano Things (IoBNT) [6], and Internet of Medical Things (IoMT) [7], such as health monitoring, healthcare, and targeted therapy [8]. This kind of communication can be found in biological systems such as communication between neurons in the human body nervous system [9], [10]. In particular, MC has a wide range of applications in the medical field which can be categorized into two main parts: diagnosis and treatment of disease [11]. Drug delivery is one of the branches of MC applications in the treatment category which

attracts a lot of recent attention among researchers [12], [13], [14], [15], [16]. It has a wide range of applications in the medical field in which a nanoparticle with relative long-term stability is employed as the drug carrier to perform the drug delivery process in the human body [17]. For instance, collagen is a biomaterial that is applicable in cases such as burn healing and bone filling. This biomaterial is extensively used as a carrier in different drug delivery systems [18]. Also, some technological improvements in glucose monitoring and hormone delivery have been achieved to control type 1 diabetes mellitus using the drug delivery process the goal of which is to develop a personalized treatment [19]. Moreover, microrobots have been studied for placement in blood vessels as carriers and perform drug delivery in which the microrobots are driven using a wireless control system [20]. In targeted drug delivery, the main goal is to manage the release rate of the drug molecules in a way that the diagnostic target (e.g., the cancerous cell) is attacked by the drug molecules while the side effects to the other parts of the body are minimized [21]. In the

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targeted drug delivery system, the drug molecules are injected toward the target site, and the released molecules are freely diffused in the environment until they reach the target. This type of drug delivery system is known as the local drug delivery system [22], which is the main focus of this paper. In order to release the drug molecules towards the receiver, different modulation techniques have been developed. Each of the modulation techniques was proposed according to a specific property (e.g., concentration, type, and releasing time of the molecules). In particular, in the commonly used concentration shift keying (CSK) modulation technique, the information is coded based on the concentration of the released molecules. Also, the molecular shift keying (MoSK) modulation technique relies on two different types of molecules to encode the information [23]. The pulse position modulation (PPM) method is another modulation technique in which the molecules are released within a specific time interval, i.e., the information is encoded based on the releasing time of the molecules [24]. The information can also be encoded based on the ratio of the molecules in the ligands' structure, such as isomer-based CSK [25]. Recently, the so-called binary direction shift keying (BDSK) modulation technique has been proposed in which the molecules are transmitted from the specific boundary of the transmitter towards the specific directions [26]. Some other modulation techniques have also been developed in which more than one property of the molecules is used for the encoding process [27].

It should be noted that not all of the released drug molecules would reach the target; some of them would be lost due to some reasons such as reaction with other molecules and the non-ideal performance of the receptors. On the other hand, it should be noted that if the concentration of the drug molecules exceeds the acceptable threshold, other parts of the body would be affected by the side effects of the drug molecules. Therefore, it is important to release the drug molecules at an appropriate rate in order to keep the drug dosage at a satisfactory level during the delivery procedure [28]. Since optimizing the release rate of the drug molecules greatly depends on the receive rate of the target, it is necessary to first examine the behavior of the target, or equivalently, the receiver part of the MC system. Therefore, the main focus would be on the receiver in the following.

The MC system consists of three main parts: the transmitter, the channel, and the receiver. One of the important issues in MC is the receiver structure. Generally, the receiver structure is categorized into three main categories [29]:

- 1) Fully cover receiver in which it is assumed that infinite receptors exist on the surface of the receiver. Therefore, the messenger molecule would be counted once it reaches the receiver.
- 2) Partially cover receiver in which it is assumed that a part of the receiver consists of infinite receptors. Therefore, the messenger molecule would be counted only if it reaches the part of the receiver which consists of the receptors.

- 3) Finite receptors in which it is assumed that the receiver consists of a finite number of receptors distributed uniformly on the surface of the receiver. Therefore, the messenger molecule would be counted only if it reaches the receptor, not other parts of the receiver.

Finite number of receptors in the receiver part is an important issue in the receiver structure which is necessary to be considered; due to the limited number of the receptors, the messenger molecules (ligands) are accumulated in the environment and result in some problems in the system. In particular, in the drug delivery application, this issue leads to side effects in the human body. In addition to the finite number of receptors, the interaction between the ligand and the receptor is also important to be considered in order to achieve a model which is closer to reality. More precisely, the following parameters are important to be considered which leads to a more accurate model:

- The ligand-receptor binding rate which results in the receptor being in active mode.
- The ligand-receptor unbinding rate which results in the receptor being in inactive mode.
- The rejection rate, which is defined as the case where the ligand is lost after a while without any binding process.

In many studies, the above parameters have been considered in the system model; the binding and unbinding rates of the ligand-receptor complex are taken into account. The rejection rate of the ligand due to the activation of the receptors is also considered. However, it should be noted that it is possible for a ligand to be rejected even if the receptors are in inactive mode. In other words, it is possible for a molecule to enter the system. However, it leaves the system after a while without any binding process. This case would occur due to several reasons including the random movement of the ligands, the lifetime of the ligands, and the non-ideal performance of the receptors. In this paper, a model for the reception process of the receiver is proposed in which the rejection rate of the ligands in the case that the receptors are in the inactive mode is also considered. Following the proposed reception model, an interval consisting of the lower and upper bounds is proposed to determine the allowable transmission rate of the drug molecules.

A. RELATED WORKS

In many studies, the receiver is assumed to be a fully cover receiver [23], [30], [31], [32]. In these models, the finite number of receptors is not taken into consideration. Moreover, the interaction between a receptor and a messenger molecule is ignored. In some cases, such as some processing performed by cells, having a fully cover receiver is an appropriate assumption [33]. Also, in some cases where the main focus of the study is on the other parts of the MC system, such as designing a modulation technique [23], [34], the receiver is usually considered to be fully cover. However, in order to study the behavior of the receiver more accurately, it is necessary to take some conditions into account, such as the limited number of receptors and the interaction between

the ligand and the receptor. A list of related works contains the following. In [35], the source of reception noise is investigated and mathematically modeled and analyzed with the consideration of the random movement of the molecules. In the mentioned study, the reception process is modeled as a Markov chain. In [36], the interaction between the receptors and the ligands is considered. In this model, it is assumed that a receptor can interact with multiple ligands simultaneously. Moreover, the environment is considered to be unbounded. This model is generalized to a model with a bounded environment in [37]. Moreover, the binding and unbinding rates of the ligand-receptor are considered in this model. Note that in the model proposed in [37], no limitation is considered for the number of receptors. In [38], the binding and unbinding rates of the ligand-receptor are also considered, and the number of received ligands is modeled using the Poisson distribution. In [29], it is assumed that the number of receptors is finite. Then, the considered model is approximated with the fully cover receiver to solve the problem. In [39], the finite receptor model is considered, and a maximum likelihood detection-based method is presented using the ligand-receptor unbinding duration. In the study conducted in [39], only one type of ligands and receptors is assumed. The mentioned model is generalized to multiple types of receptors and ligands in [40] and a detection method is presented in order to detect the concentration of each type of ligand. In [41], the blocking effect of the receptors caused by other types of molecules is considered in the finite receptor model. In [42], with the consideration of the finite receptor model, the rejection rate of the ligand by the receptor is taken into account. Note that in this study, it is assumed that the rejection rate occurs due to the activation of all of the receptors. This problem is further investigated in [43] and it is shown that the positions of the receptors on the receiver surface can be approximated to be concentrated in a single point. Considering the finite receptor model, in [44] the probability distribution of the active receptors is obtained in steady-state using the queuing theory principles, and the minimum release rate of the ligands is optimized at the transmitter part.

The rejection rate of the ligands in the case where the receptors are in the inactive mode is not considered in recent studies. Also, the rejection process due to active receptors, which is investigated in [42] and [43], affects the arrival rate of the molecules; it is assumed that when the molecule, which is entering the system, faces an active receptor, it is rejected from the system. However, in the proposed reception model, the rejection rate, due to active receptors or random movement of the molecules is investigated in the exit rate of the molecules from the system. Moreover, in optimizing the release rate of the drug molecules, a lower bound is determined in the previous studies, as mentioned before. However, the upper bound of the release rate is not specified to the best of our knowledge. In this study, in addition to the lower bound obtained according to the proposed model,

an upper bound for the number of releasing drug molecules is also proposed.

B. OUR MAIN CONTRIBUTION

In this paper, a finite receptor model is considered. Also, it is assumed that the ligands are freely diffused in the environment. The capacity of the environment is considered to be bounded; it is assumed that there is a reception space around the receiver where a limited number of ligands can be placed in this space [45]. The system model is described using the queuing theory [46]. In the proposed model, the rejection rate of the ligands is also taken into account. Note that despite [42], [43], in the considered model, it is possible for a ligand to be rejected even if the inactive receptors exist in the system. In other words, due to the random movement of the ligands, it is possible for a ligand to enter the environment, walk randomly for a while, and then leave the system without any binding process. Another difference between the proposed reception model and [42], [43], is that the rejection rate is investigated in the exit rate of the molecules; it means that the arrival rate of the molecules is considered to be constant in the proposed model. After describing the proposed model, an interval consisting of the lower and upper bounds is expressed for the release rate of the drug molecules. Our main contributions are listed below:

- The rejection rate is considered in the model. More precisely, it is assumed that the ligands in the reception space can be rejected even if the receptors are inactive. Note that the rejection rate is investigated in the exit rate of the molecules from the system.
- The reaction rates (binding and rejection) of the ligands in the model are considered to change at each step. More precisely, each state in the considered queuing model equals the number of existing molecules in the system, and the reaction rates are considered to be state-dependent. Based on queuing theory, a mathematical model is obtained for each of these parameters.
- Mathematical analysis is performed to obtain the lower bound corresponding to the proposed model for the release rate of the drug molecules. In addition to the lower bound, an upper bound is also obtained. Consequently, an interval, consisting of a lower and an upper bound, is expressed with the aim of managing the release rate of the drug molecules in drug delivery applications.

The paper is organized as follows. In Section II, a brief explanation of the system model is presented. In Section III, the proposed reception process is discussed, and the mathematical model is expressed for the enter and exit rates of the ligands. In Section IV the upper bound for the number of released molecules is presented in addition to the lower bound. Numerical simulations illustrate the usefulness of the proposed model, and the desired bounds for releasing the drug molecules are presented in Section V. Finally, the conclusion is presented in Section VIII.

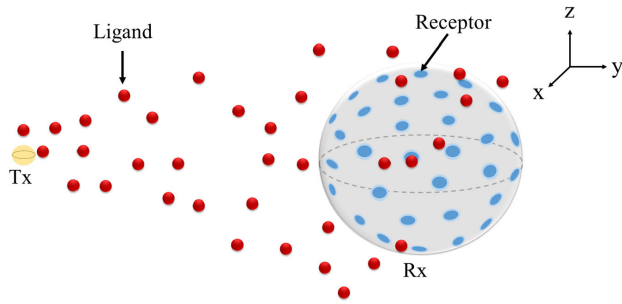


FIGURE 1. Schematic of the considered system. “Tx” denotes the transmitter, and “Rx” denotes the receiver. The Tx is considered as a point source. The Rx contains receptors that are distributed over the surface of the Rx.

II. SYSTEM MODEL

In this paper, a 3D MC system is considered where the ligands are freely diffused in the environment. Moreover, it is assumed that the number of receptors at the receiver side is finite and equals N_r . The receiver can receive the ligand molecule once the molecule reaches the receptor, not other parts of the receiver. The schematic of the considered system is depicted in Fig. 1. The transmitter, which is defined as the location where the drug molecules are released, is considered to be a point source. In drug delivery applications, continuous transmission is performed with a specific transmission rate in order to affect the target side. Binary CSK (BCSK) modulation technique is performed. The BCSK modulation technique is formulated as below [47]:

$$Q_{TX}(t) = \begin{cases} Q & \text{for } jT_s < t < (j+1)T_s, \\ 0 & \text{otherwise,} \end{cases} \quad (1)$$

where $j \in \mathbb{N}_0$, and $Q_{TX}(t)$ denotes the concentration of ligands emitted from the transmitter at time instance t . According to this modulation technique, a constant number of ligand molecules Q is transmitted during the pulse duration T_s . Based on this assumption, the reception model is discussed in the following.

III. THE PROPOSED MODEL BASED ON QUEUING THEORY

A. RECEPTION PROCESS

To analyze the reception procedure, the $M/M/N_r/N_m$ queuing system is considered where the molecules arrive at the reception space according to the Poisson distribution with the arrival rate of λ . It is assumed that at most N_m number of molecules can be placed in the reception space. The ligand-receptor complex is constructed once the molecule binds to the receptor. It is assumed that the receptor cannot interact with other molecules as long as the ligand-receptor binding process is retained. The time interval between two consecutive unbinding processes, which is obviously the result of the binding process, can be modeled using the exponential distribution with the parameter β [42], [46]. This parameter (β) can be interpreted as the service rate. The time

required for constructing a ligand-receptor complex, staying in the active mode, and finally, re-constructing another ligand-receptor complex is modeled as $\exp(\beta)$ with mean $1/\beta$. This demonstrates that as the parameter β increases, the time interval between two consecutive unbinding processes decreases. When a molecule enters the environment, two scenarios can occur: the molecule binds to the receptor, or it leaves the environment without any binding process. The second scenario, which is known as the **rejection process**, is also modeled using the exponential distribution with the rejection rate of γ . More precisely, consider that one molecule leaves the environment without any binding process (rejection process). The time duration it takes for another molecule in the system to be rejected after the last rejection process is modeled using the exponential distribution with the parameter γ (similar to the unbinding process). The time interval between two consecutive rejection processes is modeled as $\exp(\gamma)$. This process is known as “birth-death” process where entering a molecule equals the birth process, and leaving a molecule equals the death process. Based on the entering or leaving of a molecule, the state of the system is constantly changing. According to the above explanations, going from one state to the other state is modeled using the exponential distribution with the following probability density:

$$\begin{aligned} \lambda_{n,n+1} &= \lambda, \\ \lambda_{n,n-1} &= \mu_n + \gamma_n, \end{aligned} \quad (2)$$

where n denotes the state of the system. In the considered system, the n^{th} state is interpreted as the presence of n molecules in the reception space, or equivalently, the concentration of the molecules in the system. Note that the maximum number of molecules that can be placed in the reception space is N_m . Therefore, the expressed probability density is true for $n \leq N_m$. Also, note that $\lambda_{n,n+1}$ demonstrates the rate at which the system goes from state n to the state $n+1$, or equivalently, the birth process. Similarly, $\lambda_{n,n-1}$ shows the rate at which the system goes from state n to the state $n-1$, or equivalently, the death process. It is assumed that the discussed process has a constant birth rate. In other words, the molecules enter the reception area at a constant rate. However, the death rate depends on the status. Fig. 2 shows the state transition diagram of the explained birth-death process. In the following, how to obtain the rates is discussed in detail.

B. ARRIVAL AND EXIT RATES

In order to analyze the arrival and exit rates of the molecules in the system, consider Fig. 3. According to this figure, and also according to the explanations presented above, it can be concluded that the molecules enter the system with the constant arrival rate λ . Also, after spending a time duration, they leave the system. Leaving the system occurs due to the unbinding process, or the rejection process. The former reason is shown as “Unbounded” in Fig. 3. Also, the latter

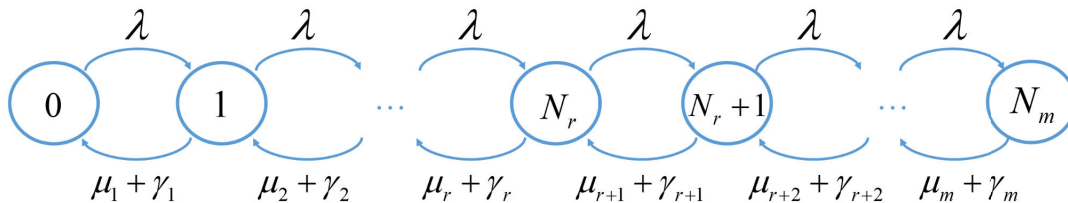


FIGURE 2. Schematic of the $M/M/N_r/N_m$ system where $N_m > N_r$. Each state represents the number of molecules in the reception space. N_r : number of receptors, N_m maximum number of molecules in the reception space, λ : arrival rate, $\mu_i + \gamma_i$: exit rate due to unbinding (μ) or rejection (γ) process.

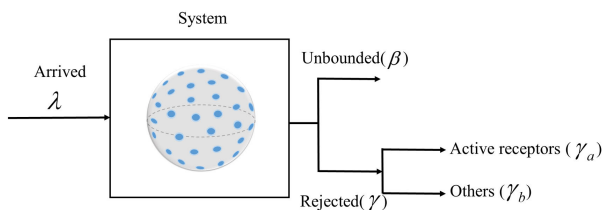


FIGURE 3. Schematic of the arrival and exit rates of the molecule to the system. The molecule enters the system with the rate of λ , and leaves the system due to unbinding process (β) or rejection process (γ). Also, the rejection of the molecule can be due to active receptors (γ_a) or other reasons (γ_b) such as its random movement.

is shown as “Rejected.” As can be seen from the figure, the rejection process is divided into two categories; 1- rejection due to the fact that the receptors are in the active mode, and 2- rejection due to other reasons, such as random movement of the molecules. Generally, the queuing parameters related to the considered system model are listed below, each of which will be discussed in the following:

- Arrival rate (λ),
- Exit rate due to:
 - unbinding process (β),
 - rejection process (γ).

1) ARRIVAL RATE

As mentioned before, the considered system is 3D. The impulse response of the diffusion equation in a 3D system is calculated as below [44]:

$$h(t, r) = \frac{Q}{(4\pi Dt)^{3/2}} \exp\left(-\frac{r^2}{4Dt}\right), \quad (3)$$

where D denotes the diffusion coefficient, t denotes the time, and r represents the distance between the transmitter and the center of the receiver. Consider the continuous transmission, which is performed in drug delivery application, the drug molecules are released with the rate of $Q/\Delta t$. This continuous transmission can be considered as the transmission of a large number of pulses, starting at $t = 0$. The concentration of the drug molecules at time t at the distance r from the transmitter is written as below [44]:

$$c(r, t) = \sum_{i=0}^{t/\Delta t} h(r, t - i\Delta t)$$

$$= \frac{1}{\Delta t} \sum_{i=0}^{t/\Delta t} h(r, t - i\Delta t)\Delta t \approx \frac{1}{\Delta t} \int_0^t h(r, \tau)d\tau. \quad (4)$$

More precisely, continuous transmission is considered as a large number of consecutive discrete transmissions where Q number of molecules are released at each time interval Δt . The formulation of such a scenario is inspired by the linear property of the impulse response of the diffusion equation [presented in (3)]. Then, by inserting (3) into (4), we have:

$$c(r, t) \approx \frac{Q}{\Delta t 4\pi Dr} \operatorname{erfc}\left(\frac{r}{(4Dt)^{1/2}}\right), \quad (5)$$

where $\operatorname{erfc}(\cdot)$ denotes the complementary error function [48]. In the steady-state condition, where $t \rightarrow \infty$, the concentration of the drug molecules per Δt in the system is obtained as $\frac{Q}{4\pi Dr \Delta t}$. This value is equivalent to the arrival rate of the molecules by considering the distance between the transmitter and the center of the target R . More precisely, we have:

$$\lambda \approx \frac{Q}{4\pi DR \Delta t}. \quad (6)$$

As expected, the arrival rate depends on the total number of transmitted molecules and the distance between the transmitter and the receiver; as the total number of transmitted molecules increases, the arrival rate of the molecules is increased. Also, the arrival rate is decreased by increasing the distance between the transmitter and the receiver.

2) EXIT RATE DUE TO REJECTION PROCESS

The exit rate of the molecule is equivalent to λP_{rej} , where P_{rej} is the probability of rejection. In the considered system, the arrival rate of the molecules equals the total exit rate of the molecules. In other words, considering Fig. 3, we have [49]:

$$\begin{aligned} \text{Unbounded} &= \lambda - \gamma \\ &= \lambda - \lambda P_{rej}. \end{aligned} \quad (7)$$

On the other hand, the unbind rate, or equivalently, “Unbounded” shown in Fig. 3, is calculated as below: i

$$\text{Unbounded} = \sum_{n=1}^{N_m} \beta P_n = \beta (1 - P_0), \quad (8)$$

where P_n is the probability of existing n molecules in the system. By equating (7) and (8), we have:

$$\beta (1 - P_0) = \lambda (1 - P_{\text{rej}}). \quad (9)$$

Using the above relation, P_{rej} is calculated as below:

$$P_{\text{rej}} = 1 - \frac{\beta (1 - P_0)}{\lambda}. \quad (10)$$

Now, it is sufficient to obtain P_0 and substitute it in the above equation to achieve P_{rej} , and consequently, γ . To this end, it is necessary to investigate the behavior of a single molecule in a system consisting of a single receptor. In other words, the $M/M/1/1$ queuing system should be considered which is a birth-death process with a single receptor and finite capacity of one molecule. This process is shown in Fig. 4. For such a system, the following relation is met:

$$\lambda P_0 = (\beta + \gamma) P_1 \Rightarrow P_1 = \frac{\lambda}{\beta + \gamma} P_0. \quad (11)$$

The above relation is written according to the balance equation in the queuing theory-based systems. More information about the details of the balance equation can be found in [49]. Moreover, according to $\sum_n P_n = 1$, we have:

$$P_0 \left[1 + \frac{\lambda}{\beta + \gamma} \right] = 1. \quad (12)$$

Therefore, P_0 is obtained as below:

$$P_0 = \frac{\beta + \gamma}{\beta + \gamma + \lambda}. \quad (13)$$

By inserting the obtained P_0 in (10), the rejection probability is rewritten as below:

$$P_{\text{rej}} = \frac{\gamma + \lambda}{\beta + \gamma + \lambda}. \quad (14)$$

Consequently, the rejection rate would be obtained as below:

$$\gamma = \lambda P_{\text{rej}} = \frac{\lambda \gamma + \lambda^2}{\beta + \gamma + \lambda}. \quad (15)$$

In order to obtain the rejection rate, the above equation should be solved; (15) is a quadratic equation (in terms of γ), the roots of which are as follows:

$$\gamma^2 + \beta \gamma - \lambda^2 = 0 \Rightarrow \gamma_{1,2} = \frac{-\beta \pm \sqrt{\beta^2 + 4\lambda^2}}{2}. \quad (16)$$

Note that the negative value cannot be assigned to the rejection rate. Therefore, among the obtained solutions, the positive value is selected for the rejection rate, and finally, we have:

$$\gamma = \frac{1}{2} \left(\sqrt{\beta^2 + 4\lambda^2} - \beta \right). \quad (17)$$

As can be seen from the above equation, the rejection rate depends on β and λ . According to (6), it can be seen that λ is a function of R and Q . Therefore, it can be concluded that the rejection rate depends on R , Q , and also, β .

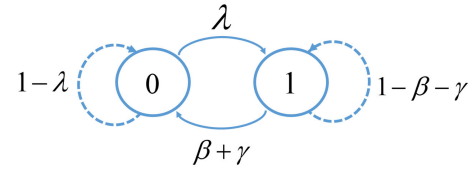


FIGURE 4. Schematic of the $M/M/1/1$ system. Each state represents the number of molecules in the reception space. One receptor and a single molecule is considered in this schematic. λ : arrival rate, $\beta + \gamma$: exit rate due to unbinding (β) or rejection (γ) process.

3) EXIT RATE DUE TO UNBINDING PROCESS

Similar to the previous section, in order to obtain the exit rate, the $M/M/1/1$ queue is considered first. In such a system, the exit rate due to the unbinding process is denoted by β . This value depends on the characteristics of the receptor, and therefore, it would not be changed by varying the parameters Q and R . The exit rate due to the unbinding process is considered a constant parameter. Note that the exit rate due to the rejection process depends on this constant term, as shown in the previous section.

4) EXIT RATE IN $M/M/N_R/N_M$ SYSTEM

Till now, the exit rates β and γ are obtained by considering the assumption that the system consists of a single receptor, and has a finite capacity of one molecule. However, the capacity of the considered system equals N_m . Also, the number of receptors is considered to be N_r . It is expected that the exit rate of the molecules from the system will be changed with respect to the number of molecules. In other words, the rates are state-dependent. Therefore, it is necessary to consider this parameter in calculating the rates. Each state in Fig. 2 denotes the number of molecules in the reception area, as mentioned before. For instance, the state N_r in Fig. 2, denotes the case where N_r molecules exist in the reception area. Assume the system is in the state i . The death process is a consequence of the unbinding process (μ_i) or the rejection process (γ_i). Therefore, the rate of the death process (from state i to the state $i - 1$) is denoted by $\mu_i + \gamma_i$, as shown in Fig. 2. For the considered system, we have:

$$\mu_i = \begin{cases} \sum_{k=0}^i (i - k) \beta & \text{for } i \leq N_r, \\ \sum_{k=0}^{N_r} (N_r - k) \beta & \text{for } N_r < i \leq N_m. \end{cases} \quad (18)$$

Also, for γ_i we have:

$$\gamma_i = \begin{cases} \sum_{k=0}^i (i - k) \gamma & \text{for } i \leq N_r, \\ \sum_{k=0}^{N_r} (i - k) \gamma & \text{for } N_r < i \leq N_m. \end{cases} \quad (19)$$

It can be seen that the values of μ_i and γ_i change with respect to the number of molecules, or equivalently, the state of the

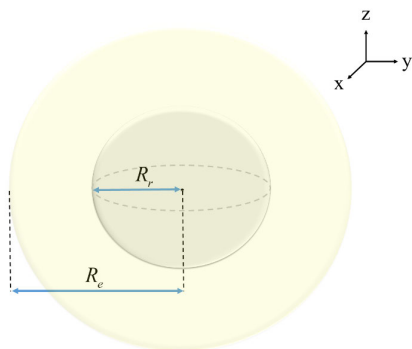


FIGURE 5. Schematic of the reception space around the receiver. R_r : radius of the receiver, R_e : radius of the reception space.

system. More explanations on how to obtain (18) and (19) are provided in Appendix A.

C. FINITE CAPACITY OF THE SYSTEM

The entering of the molecules into the reception space is modeled by a Poisson distribution, as mentioned before. It is worth noting that the Poisson distribution is the approximation of the Binomial distribution when the number of molecules (n) goes to infinity:

$$\lim_{n \rightarrow \infty} \binom{n}{k} \left(\frac{\lambda}{n}\right)^k \left(1 - \frac{\lambda}{n}\right)^{n-k} = \frac{e^{-\lambda} \lambda^k}{k!}. \quad (20)$$

On the other hand, the capacity of the environment is considered to be bounded; consider Fig. 5 where the radius of the receiver is denoted by R_r and the radius of the reception space is denoted by R_e . The capacity of the reception area (the yellow environment in Fig. 5) is obtained as below:

$$\text{capacity of the reception space} = \frac{4\pi}{3} (R_e^3 - R_r^3).$$

If the radius of the messenger molecule is R_a , the maximum number of molecules that can be placed in the reception area would be obtained as below:

$$\frac{4\pi}{3} (R_e^3 - R_r^3) = N_m \times \frac{4\pi}{3} R_a^3 \rightarrow N_m = \lfloor \frac{R_e^3 - R_r^3}{R_a^3} \rfloor, \quad (21)$$

where $\lfloor \cdot \rfloor$ is the lower round operator. It can be concluded that a large number of molecules are released in the environment, which is approximated to be infinite. However, only a finite number of them (N_m) can be placed in the reception space. Therefore, the finite number of molecules in the considered system is well justified.

IV. BOUNDS

In drug delivery applications, several drug molecules are transmitted from the transmitter toward the target (receiver). In order to deliver the drug molecules efficiently, the number of active receptors must exceed a specific threshold value. Otherwise, the transmitted drug molecules would not have any effect on the healing process of the disease. However, it should be noted that if the transmission rate of the drug

molecules is too high, the system would be saturated leading to side effects in the human body. In addition, some drugs are expensive, and therefore, using the optimum number of such drug molecules is a matter of concern. It is concluded that a transmission interval should be considered for the drug molecules; so that the transmission rate should not be less than the lowest possible level. Also, it should be adjusted in a way that it does not exceed the highest possible level. In this section, an interval, consisting of a lower and an upper bound, is considered for the transmission rate of the drug molecules; the lower bound is provided to determine the minimum transmission rate of drug molecules to be effective. Also, the upper bound is proposed to determine the maximum transmission rate, and consequently, prevent the accumulation of drug molecules that cause side effects.

A. LOWER BOUND

Consider the BCSK modulation technique in which the molecules are released in the environment with a constant rate of $Q/\Delta t$, according to (1). As discussed before, the concentration of the molecules in steady-state is obtained as below [44], [50]:

$$C \approx \frac{Q}{4\pi DR\Delta t}, \quad (22)$$

where R is the distance between the transmitter and the receiver, and D is the diffusion coefficient, as mentioned before. In order to make the drug delivery process efficient, the least number of receptors should be activated. To this end, an occupancy factor f is defined as the proportion of receptors that are activated in steady-state. This factor is given by the following equation:

$$f = \frac{K^+ C}{K^+ C + \beta + \gamma}, \quad (23)$$

where K^+ is the binding constant related to the ligand-receptor complex. This ratio is determined according to the type of drug molecule, and it expresses the minimum required active receptors in order for the delivery process to be effective. According to (23), it can be shown that the minimum effective concentration of molecules in order to make the drug delivery process efficient is obtained as below:

$$C = \frac{f(\beta + \gamma)}{K^+(1 - f)}. \quad (24)$$

The above conclusion is obtained using rate theory [51]. Using (22) and (24), the lower bound for the transmission rate Q_{min} during the delivery process is obtained as below:

$$\frac{Q_{min}}{\Delta t} = \frac{4\pi DRf(\beta + \gamma)}{K^+(1 - f)}. \quad (25)$$

Note that the parameter γ is a function of Q which is unknown here. Using (17) and (6), the above equation is rewritten as below:

$$\frac{Q_{min}}{\Delta t} = \frac{4\pi DR\beta f(1 - f)}{K^+(1 - f)^2 - f^2/K^+}, \quad (26)$$

and the lower bound is obtained accordingly. This value represents the minimum required concentration of the drug molecules. If the total number of released molecules is lower than the obtained Q_{min} , the delivery process would not be efficient.

B. UPPER BOUND

In addition to the rate theory, another theory is considered in drug delivery, named occupancy theory [52]. This theory reveals that the effectiveness of the drug molecules would be maximized if all of the receptors are activated. In other words, the f ratio should be equivalent to 1. According to (24), the concentration of the molecules would be infinite when $f = 1$ is considered; an infinite number of molecules should be released in the system to make all of the receptors active. It should be noted that there is a limitation in the number of released molecules in the system; as the number of molecules increases, the number of active receptors would be increased. However, if the number of released molecules exceeds a certain value, side effects in the human body would happen. Therefore, the number of transmitted molecules should not be infinite. The maximum number of molecules that can be placed in the reception space equals N_m , as mentioned before. According to this issue, and also according to (22), the upper bound for the transmission of drug molecules (per μm^3) is obtained as below:

$$\frac{Q}{4\pi DR\Delta t} = N_m \rightarrow \frac{Q_{max}}{\Delta t} = 4\pi DRN_m. \quad (27)$$

Note that the upper bound is obtained according to the capacity of the reception space; the maximum number of molecules (per Δt) that can be placed in the reception space, such that side effect is prevented is considered to obtain the upper bound. In other words, the defined upper bound is not restricted to the finite receptor models. Also, note that the drug molecules exist in the volume beyond the reception space as well. Here, to specify the upper limit of the released molecules, it is assumed that as long as the entire reception space is not filled with molecules, side effects due to the injection of a large dosage of drug molecules will be prevented. From (26) and (27), it can be obtained that the rate of the released molecules should be in the following interval:

$$Q_{min} \leq Q \leq Q_{max}. \quad (28)$$

From the above interval, the release dose of the drug molecules is adjusted. The drug dosage lower than the minimum release rate Q_{min} does not affect the target. Also, if the dosage of the drug released exceeds the maximum limit Q_{max} , it would cause side effects in the body [28].

V. NUMERICAL RESULTS

In this section, the numerical results related to the proposed system are presented. More precisely, the solution of the proposed queuing model is evaluated in this section. The initial parameters adjusted for simulation are expressed in Table 1. Firstly, the behaviors of the parameters λ , γ , and β are examined.

TABLE 1. Initial parameters of the considered system.

Parameter	Variable	Value
Diffusion coefficient	D	100 ($\mu m^2/sec$)
Distance between TX and RX	R	10-20 (μm)
Number of receptors	N_r	4000-10000
Total number of released molecules	Q	$10^8 - 9.1 \times 10^9$
Step size	Δt	10^{-4} (sec)
Ligand-receptor binding constant	K^+	0.5 ($\mu m^3/sec$)
Unbinding rate	β	10^{-3} (1/ μsec)
Radius of RX	R_r	2.5 (μm)
Radius of the reception space	R_o	2.8 (μm)
Radius of the drug molecule	R_a	2 (nm)

A. THE BEHAVIOR OF THE PARAMETERS γ AND β

Fig. 6 shows the rejection rate of the molecules for different values of R and β . It can be seen from Fig. 6 (a) that the value of γ decreases by increasing the distance between the transmitter and the receiver. This is due to the fact that as the distance between the transmitter and the receiver increases, the arrival rate is decreased. According to (17), it can be concluded that decreasing the parameter λ , leads to lower rejection rates. Also, Fig. 6 (b) shows the dependency of the rejection rate on the unbinding rate; it can be seen that the value of γ decreases by increasing the unbinding rate. This is due to the fact that as the parameter β increases, the number of molecules that are received by the receptor increases. In other words, the expected value of the time interval between two consecutive unbinding processes (1/ β) is decreased. Therefore, fewer molecules would leave the system without binding to the receptors. This means that the rejection rate would be decreased.

B. COMPARISON BETWEEN PARAMETERS γ AND γ'

The difference between the rejection rate obtained in [43], which we show hereafter as γ' , and the rejection rate obtained in this study is discussed before. Note that $\gamma' = \frac{\lambda^2}{\beta + \lambda}$. It is worth comparing these two parameters in order to see if there is a difference between them. Fig. 7 shows the difference between these two parameters for different values of Q and β . It can be seen from the figure that the parameters γ and γ' are not equivalent; in the proposed system, the rejection rate γ is not only influenced by active receptors. In addition to active receptors, the rejection process can occur due to some other reasons such as random movement of the molecules. Therefore, it is expected that $\gamma \geq \gamma'$ in all situations. Fig. 7 (a) shows that the difference between γ and γ' is increased as the total number of released molecules increases. This means that considering the proposed system model, it can be seen that more molecules would be rejected from the system compared to the model presented in [43]. Moreover, it can be observed from Fig. 7 (b) that the obtained γ would reach the parameter γ' as the unbinding rate β increases; as the parameter β increases, more molecules would be caught by the receptors, as concluded from Fig. 6 (b). Therefore, fewer molecules would be rejected (especially,

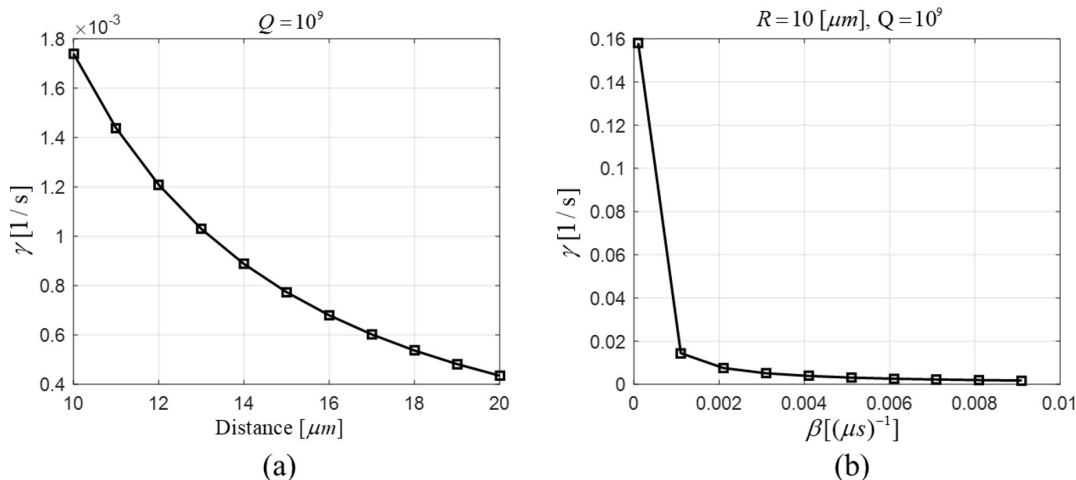


FIGURE 6. Exit rate of molecules due to the rejection process for different values of (a) distance between the transmitter and the receiver R , and (b) unbinding rate β . The rejection rate decreases by increasing the parameters R and β .

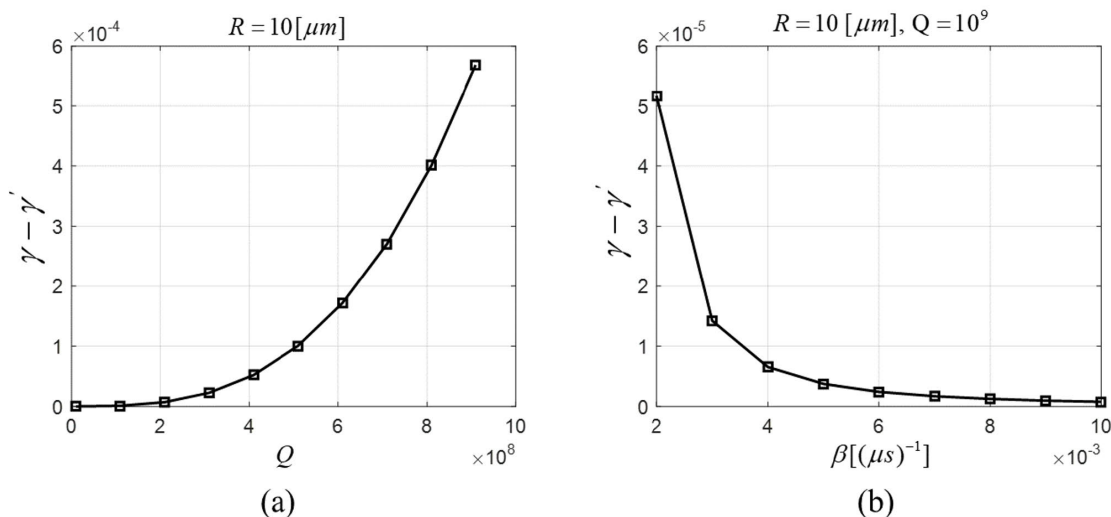


FIGURE 7. The difference between the obtained γ and γ' for different values of (a) Q and (b) β . The difference between the parameters γ and γ' increases by increasing the values of Q and β .

due to other reasons such as random movement of the molecules). Therefore, $\gamma \approx \gamma'$ as the parameter β increases.

C. THE BEHAVIOR OF THE PARAMETERS μ_i AND γ_i

The parameter γ is obtained from (17), and its behavior is investigated v.s different values of β and R in Fig. 6 for a system consisting of a single receptor and one molecule. However, it is assumed that the receiver consists of N_r number of receptors. Moreover, the number of drug molecules in the system is assumed to be $\leq N_m$, as mentioned before. In such a case, it is expected that the number of receptors affects the value of the parameters β and γ , as shown in (18) and (19). Fig. 8 shows the behavior of these parameters for different values of N_r . From Fig. 8 (a), it can be seen that the value of the parameter μ_i increases by increasing the number of receptors. More precisely, the expected value

of the unbinding process $1/\mu_i$ is decreased as the number of receptors increases. Therefore, it can be concluded that increasing the number of receptors leads to more molecules being caught by the receiver, as expected. Note that the parameter μ_i increases until the number of molecules is less than (or equal to) the number of receptors. As the number of molecules in the system equals the number of receptors, the parameter μ_i would be constant; i.e. $\mu_i = \mu_{const}$ for $i > N_r$, as shown in (18). From Fig. 8 (b), it can be concluded that for different values of N_r , the rejection rate would be increased as the number of molecules in the system increases. Also, it can be seen that for different values of N_r , the rejection rate is not changed until the number of molecules in the system reaches a threshold (approximately 550). Note that as the number of receptors increases, increasing the rejection rate (by increasing the number of molecules) slows down.

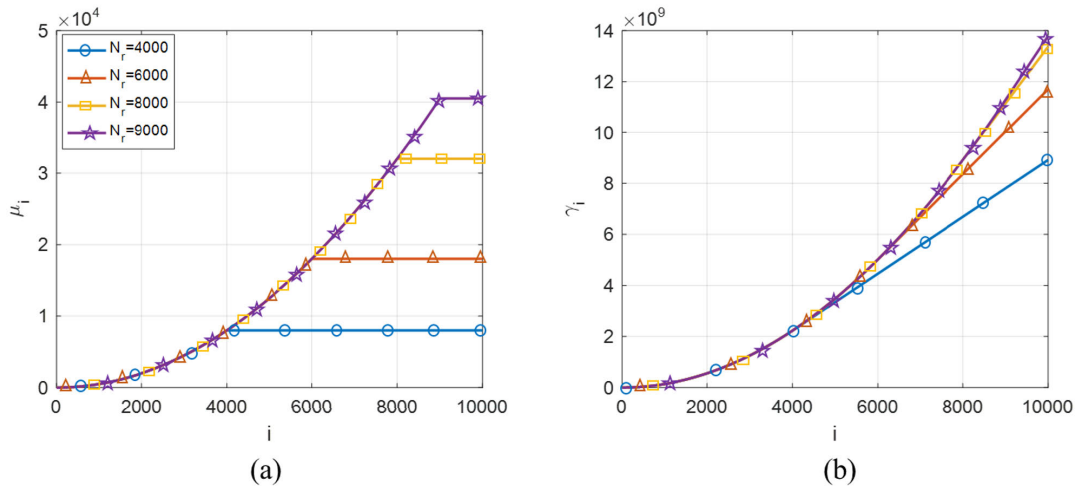


FIGURE 8. The behavior of (a) μ_i and (b) γ_i for different values of N_r . For all values of N_r , the unbinding rate increases by increasing the number of molecules until the number of molecules reaches the number of receptors [according to (a)] Once the mentioned equality is met, the unbinding rate reaches a constant value. Also, for all values of N_e , the rejection rate increases by increasing the number of molecules [according to (b)].

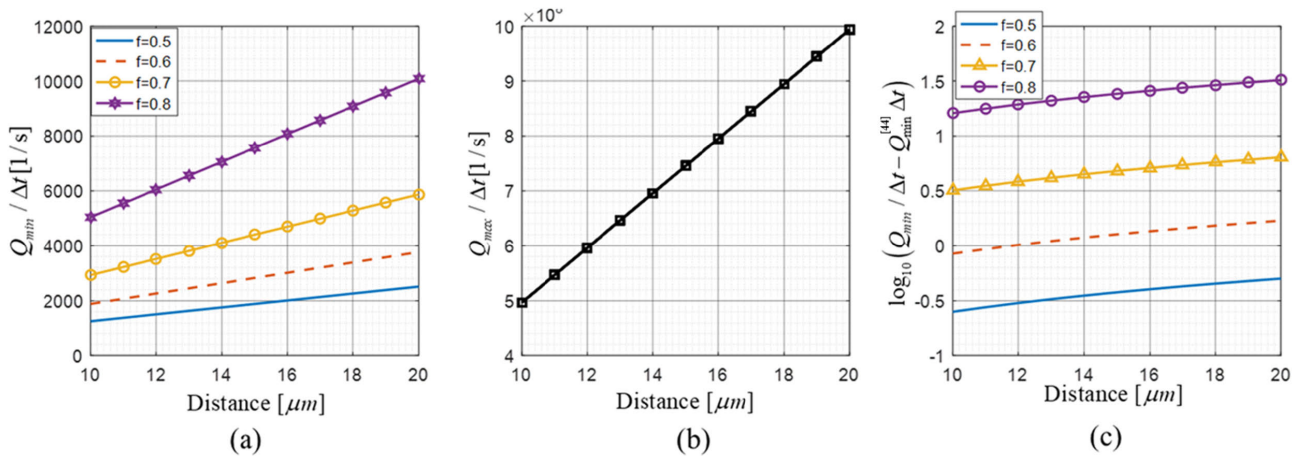


FIGURE 9. (a) Q_{min} and (b) Q_{max} (per each step size) v.s different values of distance between the transmitter and the receiver, (c) the difference between the proposed minimum release rate and the one obtained in [44].

D. THE LOWER AND UPPER BOUND FOR RELEASING THE MOLECULES

An interval, consisting of a maximum and minimum allowable dosage for releasing the drug molecules is defined according to (26) and (27), respectively. Referring to the defined interval, it can be seen that the lower bound depends on the type of drug molecules. In other words, it depends on the f ratio. However, according to (27), it can be seen that the upper bound is independent of this factor. Fig. 9 shows the defined interval for different values of R . The lower bound for different values of f ratio is depicted in Fig. 9 (a). Also, the upper bound for the number of released molecules is presented in Fig. 9 (b). It can be seen from the figure that as the distance between the transmitter and the receiver increases, the lower and upper bounds of the transmitted drug molecules are increased, as expected. Note that there

is a linear relationship between the minimum releasing rate and distance, as shown in Fig. 9 (a). This issue is obvious from (26).

In [44], the minimum release rate is obtained for the corresponding system model in which the rejection rate is not considered. It is worth comparing the minimum number of released molecules obtained in this study with the one obtained in [44]. The logarithmic graph of the difference between these two parameters can be seen from Fig. 9 (c). The minimum release rate obtained from [44] is shown as $Q_{min}^{[44]}$ here. It can be seen that the lower bound corresponding to the proposed system model results in a higher value of released molecules, as expected; according to the proposed reception model, some of the drug molecules in the system would leave the system without any binding process. Due to the so-called rejected molecules, more molecules are required

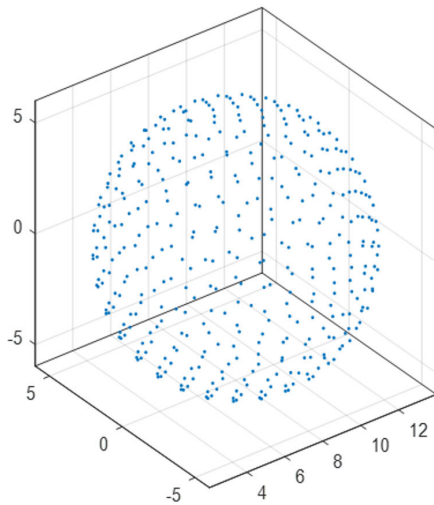


FIGURE 10. The simulated receiver in a 3D space, where the receptors are distributed over its surface. Simulation is performed using the K-wave MATLAB toolbox.

to be released toward the target in order to reach the minimum acceptable active receptors. Note that as the parameter f increases, the length of the interval would be smaller. This issue is due to the fact that as the parameter f increases, more receptors should be activated in order to make the drug delivery process efficient. As a result, the minimum number of transmitted molecules would be increased. This can be also concluded from Fig. 9 (a). Also, note that by increasing the value of f ratio, the difference between the proposed Q_{min} and $Q_{min}^{[32]}$ would be increased, as shown in Fig. 9 (c).

VI. SIMULATION RESULTS

To evaluate the numerical results in more detail, a particle-based simulation is performed using MATLAB software. To this end, the K-wave MATLAB toolbox is used to obtain the positions of the receptors distributed over the receiver [53]. The schematic of the designed receiver is shown in Fig. 10. In the demonstrated schematic, each blue point represents the center of the receptor. In the performed simulation, 400 receptors are considered for the receiver. Also, R_r , R_e , and R_a are considered as 6 nm, 6.4 nm, and 0.3 nm respectively. The distance between the transmitter and receiver is considered to be 8 μm , and $D=500$ ($\mu\text{m}^2/\text{sec}$). The simulation results are shown in Fig. 11. It can be seen from the figures that as the system reaches the steady-state, the parameters such as active receptors [Fig. 11 (a)], the rejected molecules [Fig. 11 (c)], and the molecules in the system [Fig. 11 (d)] tend to be stable, as expected. It can be concluded from the results that as the number of transmitted molecules exceeds a certain value, the molecules in the system reach their maximum value since the finite reception space is considered in the model. In such a case, no more molecules can be placed in the system, and therefore, side effects would occur due to increasing the number of rejected molecules.

As stated in Section IV-B, the maximum efficiency of the drug molecules will be achieved if all of the receptors

are activated. Considering this issue, the upper bound is obtained according to the volume of the reception space, or equivalently, the parameter N_m . In this simulation, we have $N_m \approx 1709$ according to (21). From Fig. 11 (b) which demonstrates the zoomed version of the active receptors shown in Fig. 11 (a), it can be seen that all of the receptors are activated at the time instance of 28 milliseconds. At this time instance, the existing molecules in the system, and also, the rejected molecules approximately equal 867 and 842, respectively, which can be seen from Figs. 11 (c) and (d). It can be concluded that the total number of released molecules in the system equals 1709 at this time instance, which corresponds well with the numerical prediction.

Finally, to better investigate the effect of considering the rejection rate due to other reasons, pay attention to Fig. 12 which is obtained from the simulation. It can be concluded from this figure that if the rejection of the molecules due to other reasons (e.g., random movements of the molecules) is not considered, a considerably greater number of molecules will be assumed in the system compared to the case in which the rejection of the molecules is considered. This issue negatively affects the calculated upper bound as well as the lower bound. In such a case (where the rejection rate of the molecules is not considered), a huge number of molecules will accumulate in the system which results in side effects in the human body due to an overdose of the drug molecules. The rejection rate due to active receptors has been previously investigated, as reported in [42] and [43] for instance. In these studies, queuing theory is used to model the reception process in each state which represents the active receptor. In the proposed model, the rejection rate due to some reasons such as random movement of the molecules is considered in addition to the rejection rate due to active receptors. This makes the system model more accurate compared to the case in which this condition is not considered. Moreover, each state in the proposed model represents the concentration of the molecules. The difference between the rejection rate obtained in this way and γ' that denotes the rejection rate due to active receptors only is illustrated in Fig. 7. In particular, consider Fig. 7 (a); it can be concluded that considering the rejection rate due to active receptors, as well as other reasons, lets more molecules be rejected from the system, as expected. Note that for a lower number of molecules, this difference is not significant. However, as the number of molecules in the system increases, the difference between these two cases would increase and the role of the rejection rate due to other reasons will become prominent. Also, even in the condition where the difference between γ and γ' is not significant, one should note that considering γ makes the decisions more rigorous and more accurate.

VII. DISCUSSION

The rejection rate is caused by the random movement of the drug molecules in the reception space, as mentioned before. Furthermore, other factors such as the non-ideal

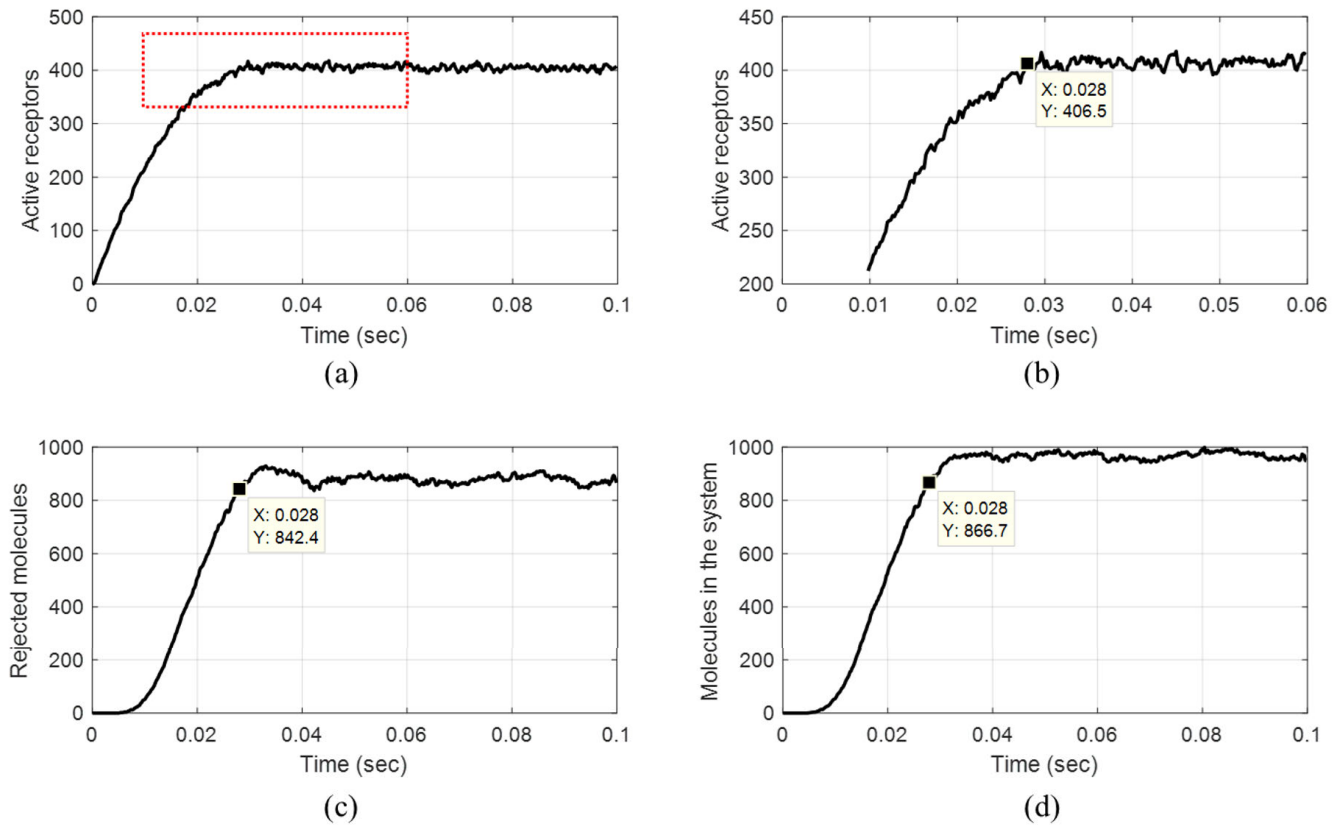


FIGURE 11. Simulation results: (a) active receptors, (b) the zoom-in version corresponding to the red box shown in (a), (c) rejected molecules, and (d) the molecules that exist in the system as a function of time.

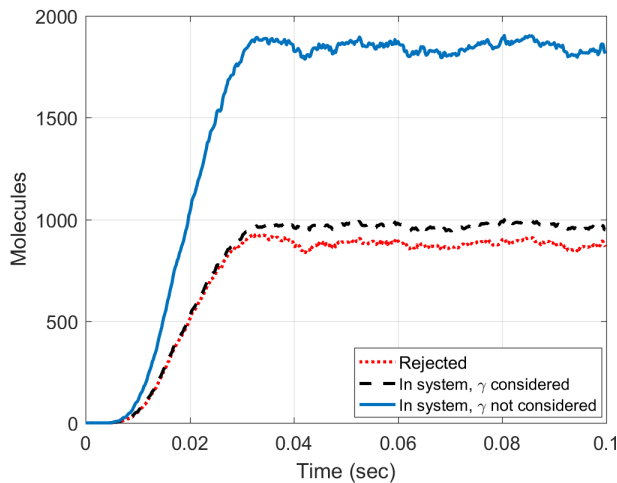


FIGURE 12. Simulation result: comparing the existing molecules with and without considering the rejection due to other reasons. Without the consideration of the rejection rate, a greater number of molecules will be assumed in the system (comparing the blue and dashed black graphs) which results in accumulation of the molecules and side effects in the human body.

the reception space which can bind to the receptors or interact with the desired ligands, and consequently, cause the receptors to be failed to receive the ligands. The mentioned factors are referred to as noise in the considered model which affects the behavior of the receiver. In this study, such factors are included in the proposed rejection rate and their effects on the reception process are evaluated. To accurately model the procedure performed during the reception process, the birth-death process is a good candidate; in some biological systems such as synaptic communications between the neurons [54] and calcium signaling [55], the molecules are freely diffused toward the receiver and they are received by the receptors after some time. Finally, after performing a chemical interaction that results in the ligand-receptor complex, an action is performed (e.g., nervous signal transmission). To accurately model the reception process of such communications systems, the processing steps such as the time it takes for the ligand-receptor complex construction, the number of active receptors at each time instance, and the molecules that interact with the receptors are desired to be considered. The birth-death process makes it possible to involve these issues in the analytic investigations. Therefore, many researchers have been motivated to apply it, e.g., [35], [39], and [56]. One should note that in this study, the effect of the rejection rate is considered in the system model and the

performance of the receptors and the limited lifetime of the ligands affect the rejection rate. For instance, the presence of other types of molecules (non-desired molecules) in

performance of the receiver under the considered condition is evaluated. Further analysis and discussions of the proposed model, such as formulating the bit error rate, remain open issues that require to be addressed in a separate study.

Note that the Tx and Rx are considered to be static in our study [12]. By dynamic movement of the Tx and Rx, the distance between them, and consequently, the arrival rate of the drug molecules will change according to (6). In such a case, the release rate should be adjusted such that the arrival rate of the molecules to the reception space (i.e., λ) remains constant over time. Alternatively, the behavior of the reception process (with the consideration of the proposed rejection rate) can be investigated in the case of a time-varying arrival rate. This issue can be analyzed in future studies. Also, note that the arrival rate is considered to be equivalent to the total exit rate, as stated in (7); the case in which the arrival rate is greater than the total exit rate of the molecules, the molecules will be accumulated in the system, and consequently, side effects will occur in the human body. In contrast, if the arrival rate is considered to be smaller than the total exit rate of the molecules, the injected drug molecules will not be effective because, in order to make the drug delivery process efficient, at least a specific percentage of the receptor is necessary to be activated. Therefore, to adjust the parameters optimally, in the proposed model, it is considered that the arrival rate equals the total exit rate of the molecules. Finally, note that in the proposed system model, the arrival rate is considered to be a constant value; the system model studied is in the steady-state condition. Since the transmission process reaches a stable rate in the steady-state condition, the constant arrival rate is a reasonable assumption in such a case.

VIII. CONCLUSION

In this paper, a reception model was proposed for drug delivery applications using queuing theory. In contrast to previous reception models, in the proposed model the rejection rate of the molecules was considered to be not only due to active receptors but also from other reasons, such as random movement of the molecules. Moreover, the rejection rate was investigated by the exit rate of the molecules. In other words, in the proposed model, the arrival rate of the molecules to the system was considered to be constant. In order to model the reception process, a system consisting of a single receptor and one molecule was investigated first. Then, the result was generalized to the $M/M/N_r/N_m$ queuing system. When the molecules enter the system, different scenarios could happen; each of them can be received by the receptor or leave the system without any binding process. Leaving the molecules, or equivalently, the rejection process could be due to active receptors or random movement of the molecules. The rate of each scenario was discussed in this study and their behavior was analyzed numerically for different values of the system parameters. Finally, in order to define a range of allowable dosages of the drug molecules and manage the drug delivery

process, an interval, consisting of lower and upper bounds was presented.

APPENDIX A MORE EXPLANATIONS ABOUT OBTAINING THE PARAMETERS μ_i AND γ_i

The parameters μ_i and γ_i denote the unbinding rate and the rejection rate of the molecule, respectively. It should be noted that the unbinding and rejection probabilities of the molecules is obtained by multiplying the corresponding rates with Δt , which is defined as the time duration in which the state of the system is changed.

In particular, consider the probability of unbinding a molecule as $\beta\Delta t$. The time duration that the process goes from state i to the state $i-1$ is modeled using the exponential distribution as $\beta e^{-\beta t}$. It can be found that the probability that the state is changed during the interval $[0, \Delta t]$ is obtained as below:

$$\int_0^{\Delta t} \beta e^{-\beta t} dt = 1 - e^{-\beta\Delta t} = \beta\Delta t + o(\Delta t). \quad (29)$$

Note that the right-hand side of the above equation is written according to the Taylor series. The probability that the state is not changed during this interval is obtained as below:

$$P(\text{the state is not changed}) = 1 - \beta\Delta t + o(\Delta t). \quad (30)$$

Note that when i molecules exist in the system ($i \leq N_r$), $i+1$ different scenarios could be imagined:

- Scenario 1: i number of receptors are activated,
- Scenario 2: $i-1$ number of receptors are activated,
- \vdots
- Scenario i : a single receptor is activated,
- Scenario $i+1$: none of the receptors are activated,

Note that $i \leq N_r$ is assumed. Consider the first scenario; the case in which i parallel and independent receptors are activated. The probability that none of the receptors are activated is equivalent to the probability that no unbinding process occurs. This probability is obtained according to (30) as below:

$$P(\text{none of the } i \text{ receptors is unbounded} | i \leq N_r) = [1 - \beta\Delta t + o(\Delta t)]^i, \quad (31)$$

and consequently, the probability that at least one receptor is unbounded would be achieved as below:

$$P(\text{at least one receptor is unbounded} | i \leq N_r) = 1 - [1 - \beta\Delta t + o(\Delta t)]^i = i\beta\Delta t + o(\Delta t). \quad (32)$$

Note that $o(\Delta t)$ is a small value (≈ 0). Also, note that the considered Δt is small enough, and therefore, the probability that at least one receptor is unbounded, equals to the probability of unbinding exactly one receptor, which is equivalent to $i\beta$.

The above explanation is performed based on the first scenario (i active receptors). The other scenarios are similar to the above explanation, except that the number of active

receptors is considered instead of i . Finally, the summation of the rates obtained from each scenario results the final exit rate due to unbinding process. For $i > N_r$, one should note that maximum number of active receptors cannot exceed N_r . Therefore, in such a case, $N_r + 1$ different scenarios could be imagined as below:

- Scenario 1: N_r receptors are activated,
- Scenario 2: $N_r - 1$ receptors are activated,
- Scenario N_r : $N_r - N_r + 1 = 1$ receptor is activated,
- Scenario $N_r + 1$: none of the receptors are activated.

By calculating the probability of each scenario and performing a summation over the obtained probabilities, the following probability would be obtained:

$$P(\text{n receptors are unbounded} | i > N_r) = \sum_{j=0}^{N_r} (N_r - j) \beta \Delta t, \quad (33)$$

which is a constant value. Therefore, (18) is concluded. Similar explanations are also true for the rejection rate, and therefore, (19) is concluded.

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