# Release Rate Optimization Based on M/M/c/c Queue in Local Nanomachine-Based Targeted Drug Delivery

Qingying Zhao[1,2(✉)] and Min Li[2]

[1] Changshu Institute of Technology, Changshu, Jiangsu Province, China
qyzhao@cslg.edu.cn
[2] Shanghai University, Baoshan District, Shanghai, China
min_li@shu.edu.cn

**Abstract.** As the basis for the modern medical therapeutics, targeted drug delivery is one of the most important topics in nanomedicine. In nanomachine-based targeted drug delivery, it should be taken into consideration that nanomachines have limited resources and drug molecules are expensive and lost molecules may cause undesired side effect. This paper aims to optimize drug release rate of nanomachine and is expected to pave a way for designing a drug delivery system. To this end, we proposed a method to calculate the optimized drug release rate producing a full drug response in local targeted drug delivery. In the method: first, a drug reception model based on M/M/c/c queue to simulate the interactions between ligands and receptors is established; second, the least effective concentration of drug molecules is derived from the least ratio of receptors occupied by drug molecules to produce full drug response according to the drug response theory named occupancy theory; finally, the optimized release rate is derived from the least concentration of drug molecules according to molecular diffusion law. Simulations reflecting diffusion of drug molecules and occupancy of receptors are established. The obtained simulation results match well with the results derived from the proposed analytical method.

**Keywords:** Nanomachine · Targeted drug delivery · Release rate · Molecular communication

## 1 Introduction

Targeted drug delivery is increasingly attracting the interest of the research community working in the fields of pharmacology and biomedical engineering. The term "targeted" usually implies that predominant injectable drug molecules accumulate within a target zone [1]. An effective targeted drug system usually requires four key requirements: retain, evade, target and release [2]. The four key requirements for intravenous administration means loading drug into delivery vehicle, sufficient systemic circulation times to reach target sites, retention within target sites and drug release at the target sites with an optimized release rate.


Y. Chen et al. (Eds.): BICT 2020, LNICST 329, pp. 130–140, 2020.
https://doi.org/10.1007/978-3-030-57115-3_11

Targeted drug delivery systems could generally be divided into two categories: passive targeting and active targeting. In [3], a review is presented related to passive targeting and active targeting. Passive targeting is based on extravasation and drug accumulation in some diseased tissues such as tumors with leaky vasculature, which is commonly known as the enhanced permeation and retention (EPR) effect [4]. Since only a small fraction ($<10\%$) of the administered drug/drug carriers actually reach diseased tissues depending on the EPR effect, passive targeting is inefficient and actually corresponds to blood circulation and extravasation. However, if ligands are added to the surface of drug/drug carrier, the passive targeting can be improved through the interactions between drug/drug carrier and target cells (i.e., ligand-receptor interactions). The specific interactions between drug and target cells are usually called active targeting [5, 6]. Unfortunately, the ligand-receptor interactions can occur only when they are in close proximity ($<0.5$ nm) [3]. It usually also depends on the blood circulation and extravasation that drug/drug carriers approach diseased cells.

Hence, it is significant that drug delivery systems are capable of autonomously swimming towards the disease site. Autonomous delivery vehicles such as nanomachine, modified bacteria, even sperms have been proposed to transport drug molecules in targeted drug delivery. Nanomahines which are able to perform tasks at nano-level can be used to travel through human blood vessel and microvasculature in recent studies. For example, Cavalcanti et al. proposed chemical communication techniques used to coordinate nanomachines to reach tumor site [7]. In addition, nanomachines or modified bacterium carrying drug molecules can be directly injected into the target site of a patient body. After entering into the diseased site such as tumor, nanomachines would release drug molecules to treat diseased cells depending on interactions between ligands on the surface of drug and receptors of diseased cells. Figure 1 shows the simplified spherical shapes for a diseased cell and its receptors on the surface.

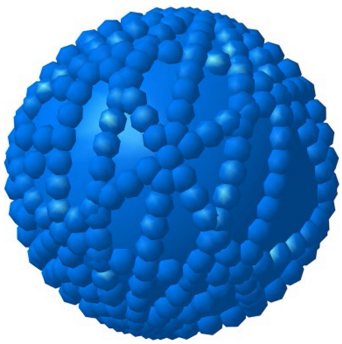

**Fig. 1.** The simplified spherical shapes for a diseased cell and its receptors on the surface

There has been a drug response theory named occupancy theory [8] associated with the ligand-receptor interactions. It is considered that the drug response is proportional to the proportion of receptors occupied by drug molecules in occupancy theory. However, the full drug response does not always require that all receptors on diseased cell are occupied by drug molecules. Some drugs require only less than 10% occupancy of

receptors [9] and a least effective drug concentration [10, 11] to produce a full drug response. Accordingly, it could be an approach to estimate the optimized drug release rate of nanomachine according to the least occupancy proportion of receptors in order to decrease the loss of drug molecules while maintain a full drug response. In the paper, we modeled an absorption process of drug molecules based on an M/M/c/c queue to simulate the interactions between ligands (i.e., drug molecules) and receptors of diseased cell. The optimized drug release rates to produce a full drug response were derived through the least receptor occupancy ratio in ligand-receptor interactions.

The rest of the paper is organized as follows. The processes of drug release and propagation are covered in Sect. 2. Section 3 presents the drug reception process based on an M/M/c/c queue. In Sect. 4, the optimized release rate is derived through receptor occupancy ratio according to occupancy theory. Simulations are conducted and the obtained results are analyzed in Sect. 5. Finally, in Sect. 6, the paper is concluded with a summary of results and an outline of the future directions.

## 2 Drug Release and Propagation

After nanomachines enter into target site, as shown in Fig. 2, it is assumed that the distance is $d$ between the centers of nanomachine and diseased cell, and the center of nanomachine is located at the origin of the system of coordinate. Drug molecules released by nanomachine propagate in an aqueous environment. In the paper, we consider that the target site is located in outside of blood vessels (i.e., in extracellular matrix). In extracellular matrix, drug molecules diffuse without drift, and not considering the effect of collisions with other cells because the concentration of drug molecules would be much lower than the medium molecules. The drug molecules diffuse based on Fick's second law of diffusion [12]

$$\frac{\partial c(r,\ t)}{\partial t} = D\nabla^2 c(r,\ t) \tag{1}$$

where $c(r, t)$ is the concentration of drug molecules at time $t$ and distance $r$ given the initial coordinate origin (i.e., the center of nanomachine), $D$ the diffusion coefficient of the medium, $\nabla^2$ Laplacian for the 3-dimension considered in the paper. If the nanomachine releases $Q$ molecules at time $t = 0$, it would create a spike in the molecular concentration at the nanomachine location, which then propagates throughout the space. The molecular concentration at any location in 3-D space is given according to [13, 14]

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

where $r$ is the distance from the center of nanomachine location.

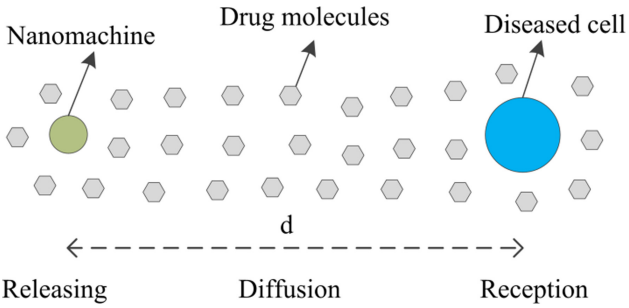


**Fig. 2.** The releasing, diffusion and reception process of drug molecules in drug delivery by nanomachine.

Continuous emission of drug molecules by nanomachines is necessary for drug delivery. It is assumed that the nanomachine releases drug molecules with rate $Q/\Delta t$, which simulates a continuous emission of drug molecules. Due to the linearity of the diffusion Eq. (1), the solution for a train of bursts of size $Q$ spaced by a period $\Delta t$ and started at $t = 0$ is

$$\begin{aligned} c(r,t) &= \sum_{i=0}^{t/\Delta t} c_Q(r,\ t\ -\ i\Delta t) \\ &= \frac{1}{\Delta t}\sum_{i=0}^{t/\Delta t} c_Q(r,\ t\ -\ i\Delta t)\ \Delta t \\ &\approx \frac{1}{\Delta t}\int_0^t c_Q(r,\ \tau)d\tau \end{aligned} \tag{3}$$

When we plug Eq. (2) into Eq. (3), yields

$$\begin{aligned} c(r,\ t) &\approx \frac{1}{\Delta t}\int_0^t \frac{Q}{(4\pi D\tau)^{\frac{3}{2}}}\exp\left(-\frac{r^2}{4D\tau}\right)d\tau \\ &= \frac{Q}{\Delta t 4\pi Dr} erfc\frac{r}{(4Dt)^{\frac{1}{2}}} \end{aligned} \tag{4}$$

Due to $erfc\frac{r}{(4Dt)^{1/2}} \rightarrow 1$ for large values of $t$, we can obtain the steady-state concentration at location $r$

$$c(r,t) \approx \frac{Q}{\Delta t\ 4\pi Dr} \tag{5}$$

## 3 Drug Reception Model Based on M/M/C/C Queue

Once drug molecules diffuse into a diseased cell, each molecule can mate with a receptor and be absorbed by the diseased cell. In order to simplify the complexity of drug reception process, it is assumed that [15]:

- The drug reception process takes place inside a receptor space which has a spherical shape of radius $\rho$.
- There are $N$ receptors homogeneously distributed inside the receptor space in which the molecule concentration $c(r, t)$ is considered homogeneous at the same time $t$ and equal to the value at the diseased cell location.
- The receptors can be changed between "bound" referred to as occupied by drug molecules, whose binding rate is $k$, and "unbound" referred to as unoccupied or undergoing bond internalization with the rate $\mu$.
- Moreover, due to the continuous emission of drug molecules, it is considered that the concentration $c(r, t)$ of drug molecules is not affected by the ligand-receptor binding.

Drug reception process is based on the chemical theory of the ligand-receptor binding. Under the assumptions mentioned above, the ligand-receptor binding status could be described only accounting for the populations of bound and unbound receptors: the random variable $n(t)$ represents the bound receptors at time $t$, $N - n(t)$ denotes unbound receptors. Consequently, the random process $\{n(t), t \geq 0\}$ is applied to model the ligand-receptor binding status. The random variable $n(t)$ increases if ligand-receptor bonds are formed, and decreases when ligand-receptors are internalized. Inspired by the queuing theory, the process of ligand-receptor's formation and internalization can be modeled as an M/M/c/c queuing (i.e., the Erlang B queuing model). In the Erlang B queuing model, customers arrive at a queuing system having $c$ servers but having no waiting positions. If a new customer finds upon arrival that servers are available, a server is invoked and used. When a customer finishes service, the customer leaves the system. Hence, the ligand-receptor's formation and internalization correspond to customer's arriving and leaving in the Erlang B queuing model respectively.

In the M/M/c/c queuing applied in drug reception process, $n(t) \in \{0, 1, 2, \ldots, N\}$ is a birth-death, discrete-valued, continuous-time Markov process. The state transition probability diagram is shown in Fig. 3, where $n$ denotes the number of bound receptors, the parameters $\lambda_n$ and $\mu_n$ depend on the currently occupied state of the system, namely, state $n$. Let $p_n(t)$ be the probability that the population of ligand-receptor bonds is of size $n$ at time $t$, that is, the system has $n$ ligand-receptor bonds at time $t$. The dynamics of this birth-death process is that the set of differential-difference equations:

$$\begin{aligned} \frac{dp_n(t)}{dt} &= \lambda_{n-1}p_{n-1}(t) + \mu_{n+1}p_{n+1}(t) - (\lambda_n + \mu_n)p_n(t), \quad n \geq 1 \\ \frac{dp_0(t)}{dt} &= \mu_1 p_1(t) - \lambda_0 p_0(t) \end{aligned} \tag{6}$$

where $\lambda_n$ represents the arrival rate of customers in queuing systems when it is in state $n$. In our drug reception process, it is associated with the per receptor binding reaction rate equal to constant $k$, the concentration of drug molecules $c(r, t)$ and the number of unoccupied receptors $N - n$ in receptor space. Consequently, the coefficient $\lambda_n$ can be formulated as [15, 16]

$$\lambda_n = k\, c(r, t)(N - n) \tag{7}$$

In queuing system, $\mu_n$ is the rate at which the customer is served when the number of customers is $n$. Similarly, it denotes the bonds internalization rate in drug reception

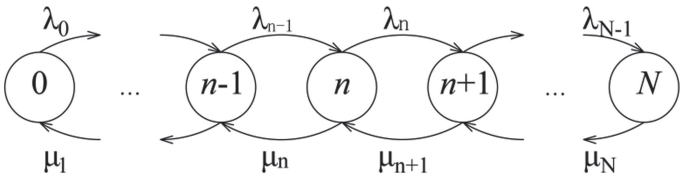


**Fig. 3.** State transitions in the M/M/c/c queue.

model when system has $n$ ligand-receptor bonds and can be formulated as

$$\mu_n = n\mu = \frac{n}{T} \tag{8}$$

where $T$ is the average value of bond internalization time which is a random variable exponentially distributed in M/M/c/c queuing theory.

It turns out to be hard to solve for $p_n(t)$ in the set of differential-difference Eqs. (6) representing the dynamics of the system, but not for the steady-state probability which represents the mean time of the system in status $n$. It can turn out that the steady-state exists because the number of system statuses is finite and the system statuses can be transferred from one to any other. Since the steady-state probability $p_n(t)$ is constant and its differential is equal to zero, the steady-state probability equations can be obtained from Eqs. (6)

$$\begin{aligned} 0 &= \lambda_{n-1}p_{n-1}(t) + \mu_{n+1}p_{n+1}(t) - (\lambda_n + \mu_n)p_n(t), \quad n \geq 1 \\ 0 &= \mu_1 p_1(t) - \lambda_0 p_0(t) \Rightarrow p_1 = \frac{\lambda_0}{\mu_1}p_0 \end{aligned} \tag{9}$$

Rearranging Eq. (9), we can get iterative equation

$$\begin{aligned} \mu_{n+1}p_{n+1} - \lambda_n p_n &= \mu_n p_n - \lambda_{n-1}p_{n-1} \\ &= \mu_{n-1}p_{n-1} - \lambda_{n-2}p_{n-2} \\ &= \cdots \\ &= \mu_1 p_1 - \lambda_0 p_0 = 0 \end{aligned} \tag{10}$$

Thus

$$p_{n+1} = \frac{\lambda_n}{\mu_{n+1}}p_n = \frac{\lambda_n}{\mu_{n+1}}\frac{\lambda_{n-1}}{\mu_n}p_{n-1} = \frac{\lambda_n}{\mu_{n+1}}\frac{\lambda_{n-1}}{\mu_n}\cdots\frac{\lambda_0}{\mu_1}p_0, \quad n \geq 0 \tag{11}$$

which eventually yields

$$p_n = p_0\prod_{i=0}^{n-1}\frac{\lambda_i}{\mu_{i+1}} = p_0\prod_{i=1}^{n}\frac{\lambda_{i-1}}{\mu_i}, \quad n \geq 1 \tag{12}$$

Now it remains to determine $p_0$. According to regularity condition, we have

$$1 = \sum_{i=0}^{N}p_n = p_0\left[1 + \sum_{n=1}^{N}\prod_{i=1}^{n}\frac{\lambda_{i-1}}{\mu_i}\right] \tag{13}$$

and therefore

$$p_0 = \frac{1}{1 + \sum_{n=1}^{N} \prod_{i=1}^{n} \frac{\lambda_{i-1}}{\mu_i}} \tag{14}$$

Combining Eqs. (7), (8), (12) and (14) results in

$$p_n = \frac{(-c(r,\ t)\ T\ k)^n (1 + c(r,\ t)\ T\ k)^{-N}\ Pochhammer[-N,\ n]}{n!} \tag{15}$$

Pochhammer[$a$, $n$] is mathematical function of $(a)n$, which can be formulated as

$$(a)_n = a(a + 1) \cdots (a + n - 1) = \Gamma(a + n)/\Gamma(a) \tag{16}$$

## 4 Calculation of Optimized Release Rate

For drug reception through ligand-receptor binding process in a local drug delivery system, the drug effect is closely associated with the status of ligand-receptor binding. According to [8, 9], the drug effect produced by specific drug depends on the number of receptors occupied by drug molecules. Inspired by the M/M/c/c queuing theory, the average number of receptors occupied by drug molecules in our drug reception model can be formulated as

$$N_s = \sum_{n=0}^{N} n\ p_n \tag{17}$$

Thus, the occupancy ratio $f$ is formulated as

$$f = \frac{N_s}{N} = \frac{\sum_{n=0}^{N} n\ p_n}{N} \tag{18}$$

The required least ratio of occupancy receptors $f$ for a specific type drug to produce a full drug effect can be obtained by means of experiment in vitro. From Eqs. (15), (17) and (18), we can obtain the least effective concentration of drug molecules to produce the required least ratio of occupancy receptors

$$c(r, t) = \frac{f}{(1 - f)T\ k} \tag{19}$$

Combining Eqs. (5) and (19) results in the optimized drug release rate

$$\frac{Q}{\Delta t} = \frac{4\pi D\ r\ f}{(1 - f)T\ k} \tag{20}$$

where $T$ is the average value of bond internalization time which can be obtained by means of experiments in vitro, $k$ reaction rate constant which can be deduced from the

kinetics of the receptor potential [17]. When the values of these parameters are known, optimized release rate could be derived from Eq. (20) depending on the least average number of busy receptors. For example, we assumed that: the required least occupancy ratio of receptors $f = 0.5$, the number of receptors per cell $N = 500$, the average bond internalization time $T = 1000$ μs, the per receptor binding reaction constant rate $k = 0.2 \times 10^{-6}\mu m^3/\mu s$, molecule diffusion coefficient $D = 1 \times 10^{-3}\mu m^2/\mu s$ and distance between the nanomachine and diseased cell $r = 1$ μm. Accordingly, the optimized drug release rate $Q/\Delta t = 32$molecules/μs if the time period $\Delta t$ is set to one microsecond. The drug release rate $Q/\Delta t$ varies depending on time period $\Delta t$ obviously.

## 5 Simulations and Results

In order to exemplify the validity of the proposed method to optimize drug release rate, we establish our simulations. In this paper, we conduct a 3-dimensional simulation in which there are no collisions among emitted drug molecules due to the much lower concentration of drug molecules than the medium molecules. Furthermore, we simulate drug molecule reception process based on M/M/c/c queuing theory. The simulation scenario consists of a nanomachine transmitting drug molecules and a receiver (i.e., the diseased cell) with receptors locating at a distance of one micrometer from the transmitter. First, the nanomachine performs a continuous emission of drug molecules with an optimized release rate calculated in Sect. 4. The next involves carrying out diffusion process of a large number of drug molecules. Finally, when drug molecules enter into reception space and collide with receptors, the ligand-receptor binds would be formed and the number of binds would be recorded in real-time. The main simulation parameters and physical descriptions are shown in Table 1. It should be noted that we have set the number of receptors per cell to 500 in our simulations, since the values can range from 50 to 5000 receptors per cell [18].

**Table 1.** Simulation parameters.

| Symbol | Description | Value |
|---|---|---|
| $D$ | Diffusion coefficient | $10^{-3}(\mu m^2/\mu s)$ |
| $r$ | Distance | 1 (μm) |
| $r_m$ | Radius drug molecule | 0.2 (nm) |
| $r_c$ | Radius diseased cell | 500 (nm) |
| $t_t$ | Total simulation time | 30000000 (ns) |
| $\Delta t$ | Emission period | 500 (ns) |
| $k$ | Receptor binding reaction rate | $0.2 \times 10^{-6}$ $(\mu m^3 \mu s^{-1})$ |
| $T$ | Average bond internalization time | 1000 (μs) |
| $N$ | Number receptors | 500 |
| $\rho$ | Spherical receptor space radius | 500 (nm) |

We would perform different simulations depending on receptor occupancy ratio $f$. In particular, if $f$ is set to 0.3, 0.5 and 0.8 respectively, three different optimized release rates $Q/\Delta t$ could be derived from the method in Sect. 4. The optimized release rates derived from Eq. (20) and average numbers of occupancy receptors depending on receptor occupancy ratios $f$ are listed in Table 2. The fluctuation of receptor occupancy number versus time can be easily obtained by plotting the number of ligand-receptor binds read in simulations. Figure 4 shows the number of ligand-receptor binds in simulation depending on three different optimized release rates calculated from Eq. (20) depending on receptor occupancy ratio $f$. The three dashed horizontal lines represent the analytical average number of occupancy receptors from three cases ($f = 0.3, 0.5$ and $0.8$). As we can see, the numerically simulated number of occupancy receptors approaches the analytical ones as time increases in all cases.

**Table 2.** Different release rates derived from Eq. (20) and average numbers of occupancy receptors depending on receptor occupancy ratios $f$.

| Receptor occupancy ratio $f$ | Average receptor occupancy number ($N * f$) | Release rate ($Q/\Delta t$) |
|---|---|---|
| 0.3 | 150 | 14/500 ns |
| 0.5 | 250 | 32/500 ns |
| 0.8 | 400 | 126/500 ns |

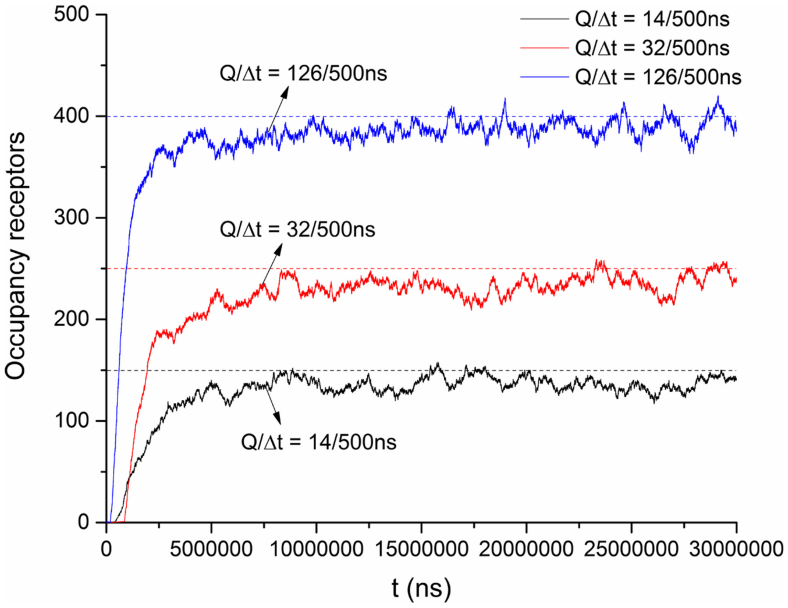


**Fig. 4.** The number of occupancy receptors versus time depending on different release rates in simulations.

## 6 Conclusions

Molecular communication may improve the targeted drug delivery techniques by determining the appropriate drug release rate of nanomachines. In this paper, we investigate the issue concerning releasing rate optimization in local nanomachine-based targeted drug delivery. To this end, a drug reception model based on M/M/c/c queue to simulate the ligand-receptor interactions is established. The least effective concentration of drug molecules is derived from the least effective receptor occupancy ratio to produce full drug response. According to the molecular diffusion law, the optimized release rate is derived from the least effective concentration of drug molecules at the location of diseased cell. We established simulations in order to evaluate the method to calculate the optimized release rate. The simulated results match well with the ones derived from our proposed method.

## References

1. Torchilin, V.P.: Drug targeting. Eur. J. Pharm. Sci. **11**(S2), S81–S91 (2000)
2. Mills, J.K., Needham, D.: Targeted drug delivery. Expert Opin. Ther. Pat. **9**(11), 1499–1513 (1999)
3. Bae, Y.H., Park, K.: Targeted drug delivery to tumors: myths, reality and possibility. J. Controlled Release **153**, 198–205 (2011)
4. Maeda, H., Matsumura, Y.: EPR effect based drug design and clinical outlook for enhanced cancer chemotherapy. Adv. Drug Deliv. Rev. **63**(3), 129–130 (2011)
5. Beduneau, A., Saulnier, P., Hindre, F., Clavreul, A., Leroux, J.-C., Benoit, J.P.: Design of targeted lipid nanocapsules by conjugation of whole antibodies and antibody Fab' fragments. Biomaterials **28**(33), 4978–4990 (2007)
6. Deckert, P.M.: Current constructs and targets in clinical development for antibody-based cancer therapy. Curr. Drug Targets **10**(2), 158–175 (2009)
7. Cavalcanti, A., Hogg, T., Shirinzadeh, B., Liaw, H.C.: Nanorobot communication techniques: a comprehensive tutorial. In: ICARCV 2006 International Conference on Control, Automation, Robotics and Vision. IEEE (2006)
8. Clark, A.J.: The Mode of Action of Drugs on Cells. Eduard Arnold, London (1933)
9. Lambert, D.: Drugs and receptors. Contin. Educ. Anaesth. Crit. Care Pain **4**(6), 181–184 (2004)
10. Salehi, S., Moayedian, N.S., Assaf, S.S., Cid-Fuentes, R.G., Solé-Pareta, J., Alarcón, E.: Releasing rate optimization in a single and multiple transmitter local drug delivery system with limited resources. Nano Commun. Netw. **11**, 114–122 (2017)
11. Siepmann, J., Siegel, R.A., Rathbone, M.J.: Fundamentals and Applications of Controlled Release Drug Delivery. Springer, New York (2011). https://doi.org/10.1007/978-1-4614-0881-9
12. Philibert, J.: One and a half century of diffusion: fick, Einstein, before and beyond. Diffus. Fundam. **4**, 1–19 (2006)
13. Bossert, W.H., Wilson, E.O.: The analysis of olfactory communication among animals. J. Theor. Biol. **5**(3), 443–469 (1963)
14. Llatser, I., Cabellos-Aparicio, A., Pierobon, M., Alarcón, E.: Detection techniques for diffusion-based molecular communication. IEEE J. Sel. Areas Commun./Suppl.-Part 2 **31**(12), 726–734 (2013)

15. Pierobon, M., Akyildiz, I.F.: Noise analysis in ligand-binding reception for molecular communication in nanonetworks. IEEE Trans. Signal Process. **59**(9), 4168–4182 (2011)
16. Bialek, W., Setayeshgar, S.: Physical limits to biochemical signaling. Proc. Nat. Acad. Sci. U.S.A. **1**, 10040–10045 (2005)
17. Meng, L.Z., Wu, C.H., Wicklein, M., Kaissling, K.E., Bestmann, H.J.: Number and sensitivity of three types of pheromone receptor cells in Antheraea pernyi and A. polyphemus. J. Comp. Physiol. A **165**(2), 139–146 (1989)
18. Keegan, A.D.: IL-4. In: Oppenheim, J.J. (ed.) Cytokine Reference, pp. 127–136. Academic Press, San Diego (2001)