A Simultaneous Drug Release Scheme for Targeted Drug Delivery Using Molecular Communications

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ABSTRACT In this paper, we consider drug release-time issue in molecular communication-based targeted drug delivery (MC-based TDD) systems. Typically, a trigger source sends out a signal to multiple nanomachines to indicate them when to release the drugs in a simultaneous manner. However, under a practical setting where the nanomachines are located at unequal distances from the source and the propagation delay of an MC channel is proportional to the third power of distance, the trigger signal may arrive at different times causing the nanomachines to release the drugs in a nonsimultaneous manner. This causes release-time errors. Therefore, we propose a simultaneous drug-release scheme to determine the precise time to emit the trigger signal, taking into account the propagation delay information to minimize the release-time errors. Using both analytical and simulation approach, we demonstrate the effectiveness of the proposed scheme in reducing the release-time errors, highlighting its robustness to large propagation delays. Additionally, we show that the analytical model is in good agreement with the simulation.

INDEX TERMS Molecular communication, nanomedicine, nanonetworks, release-time, targeted drug delivery.

I. INTRODUCTION Molecular communication (MC) is multidisciplinary field composed of biology, nanotechnology, information, and communication technology. It is a new communication paradigm where molecules act as information carriers between a transmitter and a receiver [1]. As MC is biocompatible by design, it is suitable for fluidic environments (e.g., living tissues) [2], [3], making it a promising candidate of communication technologies for healthcare applications inside the human body [4]. Thus, it is envisioned that MC could potentially enhance the performance of targeted drug delivery (TDD) systems, by affecting minimal damage to the surrounding healthy tissues through highly localized therapeutic drug delivery [5]. In particular, the drug molecules are encapsulated within a larger carrier, namely, nanocarriers, to prevent healthy tissue damages and drug degradation. The nanocarriers are delivered to the infected site either through the blood circulatory system (systemic drug delivery) or direct placement (local drug delivery) [6]. Once the nanocarriers are in the desired position, they release the drug in response to a trigger signal that may be generated externally (e.g., ultrasounds) or internally (e.g., pH) [7]. We shall refer to TDD systems that use MC as the communication technology as molecular communication-based targeted drug delivery (MC-based TDD) systems.

In MC-based TDD systems, the nanocarriers are envisioned to be equipped with additional capabilities (e.g., monitoring). For the sake of brevity we shall simply refer to such nanocarriers as nanomachines, which is also the term used to define the basic functional units of a nanonetwork [3]. Currently, nanomachines are envisioned to perform very simple and specific tasks (e.g., data storage, basic computing, actuation or sensing) [5], [6] because of their small energy supply, low computational power, and short communication range. Nanomachines are also limited in terms of drug-reservoir capacity; thus, a single nanomachine may not carry sufficient drug to maintain efficacy.

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Efficacy refers to the utmost effective output of the administered drug. An MC-based TDD system can be designed to administer either a single or multiple types of drug, which are known as single-drug therapy and multidrug therapy, respectively [8].

Regarding the drug-reservoir capacity problem, researchers have indicated to release the single drug from multiple nanomachines [9] to relieve a nanomachine’s burden to carry the total drug quantity, thereby alleviating the capacity problem while maintaining the efficacy. However, the release has to be coordinated and specifically, at a common time, thus referring it as simultaneous drug release. There are several ways to achieve simultaneous drug release, including the use of an external source [5], e.g., ultrasounds that are used to open blood-brain barrier, thereby facilitating drug release into the brain [10]; periodic pulsating mechanisms, such as biological oscillators [11], [12]; and the oscillations from rhythmic heartbeats or glycolytic oscillations, making a system sensitive to the oscillations. Synchronization schemes using timestamps [13], [14] or control messages [15] could also be applied to achieve simultaneous drug-release. For instance, after synchronization, the release time can be encoded on the messages. A similar approach can also be applied with synchronization schemes that do not use timestamps [16], but instead of sending the timing information, a special signal can be used for triggering purposes.

As stated earlier, in general, the drugs are released only in response to a trigger signal. Considering a realistic scenario where the nanomachines are located at unequal distances from a trigger source, the trigger signal will experience different propagation delays depending on the distance between the source and the nanomachine. In addition, as the propagation delay of an MC channel grows with the third power of distance, it tends to be very large [17]. Thus, the trigger signal will arrive at different times at each nanomachine, triggering them to release the drugs in a nonsimultaneous manner. This leads to release-time errors that are generated when the nanomachines are expected to release the drugs simultaneously but they do not.

We note that reducing the release-time errors could improve efficacy of MC-based TDD systems. In that regard, the optimal efficacy of a drug at the infected site is when the drug concentration measured over a period of time lies within a certain therapeutic range [18], [19]. The therapeutic range of a drug is the range in which the drugs are usually expected to achieve efficacy [20] with the lower and upper boundary called as the least effective concentration (LEC) and the maximum effective concentration (MEC), respectively. When an MC-based TDD is used for drug delivery, the drug-release task is such that each nanomachine will release some amount of drug and a cumulative concentration of the drug is anticipated at the infected site. As such, if the nanomachines do not release the drugs in a simultaneous manner, it may lead to the drug concentration that is below the LEC or above the MEC, which leads to the drug becoming ineffective or toxic, respectively. Both these cases impact the efficacy of a drug [21], [22].

| Table 1. List of notations. |
|---------------------------|
| Notation | Name |
| CN | control nanomachine |
| DN | drug-carrying nanomachine |
| SYN | synchronization signal |
| RSP | response signal |
| DRG | drug-release signal |
| K | number of DN | |
| d_i | distance between CN and DN_i, i ∈ K | |
| D | diffusion coefficient | |
| r | radius of the nanomachines | |
| T_{delay(i)} | propagation delay between CN and DN_i, i ∈ K | |
| T_{release} | release-time |
| ε | release-time error | |
| Q | number of emitted molecules | |
| T_{start} | starting time of coordination |

As the first in the literature, we define the drug release-time error in MC-based TDD systems. Under the influence of Gaussian propagation delay, we propose an energy-efficient simultaneous drug-release scheme to enable an internal trigger source to coordinate multiple nanomachines for achieving simultaneous TDD.

We derive the analytical expression for drug release-time errors and validate its accuracy via a particle-based simulator.

Although by no means exhaustive, we test the proposed scheme under different environmental conditions, such as varying the distance and the number of signal molecules released. The results show that the proposed scheme achieved gains in terms of the error and energy cost, which demonstrates the effectiveness of our scheme over a timestamp scheme.
The remainder of this paper is organized as follows. In Section II, we detail the system model that we consider for this study. In Section III, we present the proposed scheme and describe its operation using a multiple nanomachine setting. In Section IV, we discuss the performance of the proposed scheme based on the results obtained from simulations. Finally, in Section V, we provide the conclusions.

II. SYSTEM MODEL

As shown in Fig. 1, we consider an MC-based TDD system consisting of a total of three nanomachines in an unbounded 3D environment. We assume the nanomachines to be spherical bodies with a radius of $r$ [23]. The boundary of a transmitting nanomachine is a reflecting surface, that is, a molecule can be obstructed and reflected [24]. On the other hand, the boundary of a receiving nanomachine is a fully-absorbing surface, that is, whenever a molecule hits the receiver boundary, it is absorbed by the receiver [24]–[26]. Therefore, each molecule contributes to the signal only once [27]. The receiver is also capable of counting the number of molecules per unit time [24], [28]. We assume that the transmitter spontaneously releases $Q$ number of molecules from a point on its surface that is close to the receiver. Furthermore, we consider a free-diffusion fluidic channel having a certain viscosity and uniform temperature, where molecules diffuse freely and propagate by Brownian motion [29], [30]. Therefore, a bidirectional communication can be realized [14]. Finally, we assume that nanomachines are immobile [6], [31]–[33]. We note that we only consider the partial system as shown by the dotted part in the Fig. 1 because our focus is on the communication protocol for simultaneous release time. Our future efforts will consider the complete system.

Based on functionality, we consider two types of nanomachines: control nanomachine (CN) and drug-carrying nanomachine (DN). CN refers to an internal trigger source that coordinates the drug release, and DN refers to a drug carrier that releases the drug when commanded by the CN. We assume that the CN has more processing capability than the DN and that CN does not know a priori the number and identity of the DN. In that respect, the proposed scheme is simple and easy to implement. For simplicity, we consider two DNs and denote them as DN$_A$ and DN$_B$. However, we note that our scheme can be extended over any number of DNs. The DNs are equidistant from the target. Such special topology designs are reportedly feasible in medical applications [34]. However, we assume that the DNs are at unequal distances from the CN, which is also a realistic assumption. Thus, DN$_A$ is located closer to the CN than DN$_B$. Then, the distance between DN$_A$ and CN, denoted by $d_A$, is smaller than the distance between DN$_B$ and CN, denoted by $d_B$.

We consider molecular concentration on-off keying (MC-OOK) modulation, where the information is encoded through the concentration [35]. The receiver detects the signal based on the peak concentration (maximum concentration) of absorbed molecules [36]. Thus, the propagation delay is the duration between the signal’s emission from the transmitter and the observation of the signal’s maximum concentration at the receiver [25].

For the signaling molecules, we consider isomers (e.g., hexose) for two reasons. Firstly, isomers are molecules with different chemical arrangements, but they hold the same diffusion coefficient value. Thus, each isomer represents a different signaling message. As such, we assume that CN can receive more than two types of signals and discriminates them by the inherent structural difference of isomers [5], [37], [38]. The DN, on the other hand, is required to be capable of receiving, at least, two types of molecules. Secondly, isomers are safe for the human body [39]. We assume that
nanomachines can synthesize any type of molecules to send a signal [40]. For simplicity, we ignore the collisions between the molecules and assume that the motion of each molecule is independent from others [25], which diffuses with a constant diffusion coefficient, $D$.

### III. SIMULTANEOUS DRUG RELEASE SCHEME

Compared to the traditional communication technologies, MC has severe propagation delay, which is a tough challenge for transferring signals simultaneously especially when nanomachines are in different distances from the trigger source. By considering propagation delay as well as nanomachines’ limited capacity, and to design an energy efficient simultaneous drug release system, we propose a novel simultaneous drug release scheme. In the following Section III-A, we describe the proposed scheme signal exchanges among CN with DNs. Then, in Section III-B, we derive an analytical model for the release-time error.

#### A. OPERATION OF SIMULTANEOUS DRUG RELEASE SCHEME

Fig. 2 shows the operation of the proposed scheme. Briefly, in the proposed scheme, CN sends two types of signal: synchronization signal (SYN) and drug-releasing signal (DRG). SYN is used to estimate the propagation delay $T_{\text{delay}(i)}$ between CN and DNs, where $i \in K$ and $K$ are the number of DNs. DRG is used to command the DNs to release drugs where DRG of a far DN will be sent earlier than that of a near DN under the constraint that the DRGs arrive at the same time at each DN. DNs only send one kind of signal namely, response signal (RSP) to the CN when they receive SYN signal from CN. All the signals, SYN, RSP, and DRG, incur propagation delays which are denoted as $T_{\text{delay}(i)}$, $T_{\text{delay}(i)}$, and $T_{\text{delay}(i)}$, respectively. We note that propagation delays of each signal are independent of each other due to the environmental conditions and we differentiate them by using superscripts in the brackets that represent the signal type.

At time $T_{\text{start}}$, CN transmits SYN signal to $D_{A}$, which contains $Q$ molecules. SYN arrives at $D_{A}$ with an unknown propagation delay, $T_{\text{delay}(A)}^\text{(SYN)}$. Then, the arrival time of SYN can be written as

$$T_{A} = T_{\text{start}} + T_{\text{delay}(A)}^\text{(SYN)},$$

After receiving SYN, $D_{A}$ immediately sends RSP$_A$ to CN. RSP$_A$ will reach CN at time $\bar{T}_A$ with a propagation delay $T_{\text{delay(A)}}^\text{(RSP)}$, such that $\bar{T}_A = T_{A} + T_{\text{delay(A)}}^\text{(RSP)}$. CN records the value of $T_{A}$. By using $\bar{T}_A$ and $T_{\text{start}}$, CN estimates the round trip time between CN and $D_{A}$, $\tilde{T}_{\text{RTT(A)}} = \bar{T}_A - T_{\text{start}}$. Then, the propagation delay can be calculated as

$$\tilde{T}_{\text{delay(A)}} = \frac{\tilde{T}_{\text{RTT(A)}}}{2} = \frac{\bar{T}_A - T_{\text{start}}}{2}.$$  

In a similar way, the estimated propagation delay between CN and $D_{B}$ can be written as

$$\tilde{T}_{\text{delay(B)}} = \frac{\tilde{T}_{\text{RTT(B)}}}{2} = \frac{\bar{T}_B - T_{\text{start}}}{2},$$

where $\tilde{T}_{\text{RTT(B)}}$ is the estimated round trip time between CN and $D_{B}$.

After obtaining $\tilde{T}_{\text{delay(A)}}$ and $\tilde{T}_{\text{delay(B)}}$, CN determines the time instants $Z_A$ and $Z_B$ at which CN sends the drug-releasing signal, namely, DRG$_A$ and DRG$_B$ to $D_{A}$ and $D_{B}$, respectively.

$$Z_A = T_{\text{release}} - \tilde{T}_{\text{delay(A)}},$$
and

\[ Z_B = T_{\text{release}} - \bar{T}_{\text{delay(B)}}. \]  

where \( T_{\text{release}} \) is the simultaneous drug release-time.

Upon receiving DRGA and DRGB, DN\(_A\) and DN\(_B\) are supposed to release the drug at the common time, \( T_{\text{release}} \). Due to the randomness of propagation delay, the actual drug-releasing times of DN\(_A\) and DN\(_B\) might be different from each other. The release times can be expressed as

\[ T_{\text{release}(A)} = Z_A + T^{(\text{DRG})}_{\text{delay(A)}}; \]

and

\[ T_{\text{release}(B)} = Z_B + T^{(\text{DRG})}_{\text{delay(B)}}. \]  

**B. ANALYTICAL MODEL OF RELEASE-TIME ERROR**

The release-time error \( \varepsilon \), which is the time difference between the actual drug release-time of DN\(_A\) and DN\(_B\), can be defined as

\[ \varepsilon = T_{\text{release}(B)} - T_{\text{release}(A)}. \]  

Substituting (6) and (7) in (8), we obtain,

\[ \varepsilon = Z_B - Z_A + T^{(\text{DRG})}_{\text{delay(A)}} - T^{(\text{DRG})}_{\text{delay(B)}}. \]  

Further, substituting (4) and (5) in (9), we obtain,

\[ \varepsilon = \bar{T}_{\text{delay(A)}} - T^{(\text{DRG})}_{\text{delay(A)}} - \bar{T}_{\text{delay(B)}} + T^{(\text{DRG})}_{\text{delay(B)}}. \]  

Finally, inputting (2) and (3) in (10), we obtain,

\[ \varepsilon = \frac{T_{\text{start}}}{2} - \frac{T^{(\text{SYN})}_{\text{delay(A)}}}{2} + \frac{T^{(\text{RSP})}_{\text{delay(A)}}}{2} - \frac{T^{(\text{SYN})}_{\text{delay(B)}}}{2} + \frac{T^{(\text{RSP})}_{\text{delay(B)}}}{2} - \frac{T^{(\text{SYN})}_{\text{delay(B)}}}{2} + \frac{T^{(\text{RSP})}_{\text{delay(B)}}}{2}. \]  

We note that in diffusion-based MC system, there is no rigid analytical model for propagation delays. Thereby, \( T^{(\text{SYN})}_{\text{delay(A)}} \), \( T^{(\text{RSP})}_{\text{delay(A)}} \), and \( T^{(\text{DRG})}_{\text{delay(A)}} \) are assumed to be independent and identical (i.i.d.) random variables with normal distribution having mean \( \mu_A \) and variance \( \sigma_A^2 \) [13]. Similarly, \( T^{(\text{SYN})}_{\text{delay(B)}} \), \( T^{(\text{RSP})}_{\text{delay(B)}} \), and \( T^{(\text{DRG})}_{\text{delay(B)}} \) are also i.i.d. random variables with Gaussian distribution having mean \( \mu_B \) and variance \( \sigma_B^2 \).

Due to the summation property of Gaussian distribution [41, 42], \( \varepsilon \) is also a Gaussian distributed random variable with mean \( \mu_\varepsilon \) and variance \( \sigma_\varepsilon^2 \) where

\[ \mu_\varepsilon = \frac{1}{2} \mu_A + \frac{1}{2} \mu_B - \frac{1}{2} \mu_A - \frac{1}{2} \mu_B + \mu_B = 0, \]  

and

\[ \sigma_\varepsilon^2 = \left( \frac{1}{2} \right)^2 \sigma_A^2 + \left( \frac{1}{2} \right)^2 \sigma_B^2 \]  

Due to \( \mu_\varepsilon = 0 \),

\[ \sqrt{\text{Var}(\varepsilon)} = \sqrt{\text{Var}(\varepsilon) + E[\varepsilon]^2} \]  

which is the root mean squared error (RMSE). Here, \( \text{VAR}(\varepsilon) \) and \( E[\cdot] \) are the variance and the expectation, respectively.

**IV. SIMULATION MODEL AND RESULTS**

**A. SIMULATION ENVIRONMENT**

We built a network simulator over a particle-based simulator (MolecUlar CommunicatIoN (MUCIN)) based on MATLAB-R2018b software on a system with i5 processor, 16 GB RAM, and 1 TB HDD [28]. Through MUCIN simulator, we record the values of the propagation delays of a signal among CN with DNs. Moreover, using MUCIN, we obtained the values of variances (ref. Table 3). We note that the DNs are equidistant from the infected site, but they are at unequal distances to the CN [34].

We define a new term, namely distance difference \( d = |d_B - d_A| \). Unless stated otherwise, all the simulation parameters are given in Table 2. We denote the sampling step time by \( \Delta t \). In MUCIN simulator, we sampled each data at \( \Delta t \) time difference.

As a comparison scheme, we selected the two-way message exchange-based coordination scheme [13] to demonstrate the possibility of coordinating the drug-release without timestamps and also to study if reducing the perturbation
issue (which is the goal of [13]) can decrease the release-time errors. Briefly, in the comparison scheme, a sender nanomachine sends a signal to the receiver nanomachine as a means to achieve coordination with the receiver nanomachine. After receiving the signals, the receiver nanomachine sends its timestamp to sender nanomachine. The sender nanomachine estimates the perturbations using the timestamp information and coordinate with the receiver nanomachine. To improve the estimation accuracy, they exchange n rounds of timestamped signals. We note that, for fairness, we add an additional timestamped signal to the comparison scheme to let the receiver nanomachine know when to release drugs. To draw analogies to our system model, the sender and receiver nanomachine are the CN and DN, respectively.

The performance metrics to evaluate the proposed scheme are the RMSE, the cumulative distribution function (CDF) of $\varepsilon$, and the energy consumption in comparison with the compared scheme. In simulator, the RMSE is calculated as

$$RMSE = \sqrt{\frac{1}{M} \sum_{j=1}^{M} \varepsilon_{(j)}^2},$$

(15)

where $\varepsilon_{(j)}$ is the release-time error of $j$th replication and $M$ is the number of simulation replications.

Energy consumption is investigated based on the energy model developed in [45] and [43]. Here, we reproduce the figure of energy model in [45] and [43]. Fig. 3 illustrates the four stages of energy consumption. In stages 1 and 2, energy is spent in synthesizing the molecules and the vesicles, respectively. Then, the signal molecules are loaded into the vesicles. In stage 3, energy is spent by the vesicles to travel on the microtubules to the surface of the nanomachine. Finally, in stage 4, energy is spent to release the molecules to the environment. The energy spent in each stage is denoted by $E_{ms}$, $E_{v}$, $E_{cv}$, and $E_{mr}$, respectively [46]. Thus, the total energy required to synthesize, transport, and release $Q$ number of molecules can be expressed as,

$$E_{ps} = QE_{ms} + (E_{v} + E_{cv} + E_{mr}) \times \frac{Q}{C_v} \times zJ,$$

(16)

where $C_v$ is the capacity of the vesicle which is $(\frac{r_v}{(r_m \sqrt{3})} \times \frac{1}{2})^3$. $zJ$ stands for zeptojoule and 1 $zJ$ is equal to $10^{-21}$ J. For more details, we refer reader to [45] and [43]. Finally, by considering the number of signal exchanges, the total energy consumption can be denoted by

$$E_t = N \times P \times E_{ps},$$

(17)

where $P$ denotes the number of signal exchanges among CN with DN_A and DN_B and $N$ denotes the number of bits, in each signal. In the following subsections, we evaluate the performances of the proposed scheme based on the above performance metrics.

B. SIMULATION RESULTS

1) ROOT MEAN SQUARED ERROR ANALYSIS

We study the RMSE for various $d$ as shown in Fig. 4 where the number of released molecules is $Q = 3000$. By using (14), we obtain the analytical results and from (15) we obtain the simulated RMSE. The agreement of the simulation result with the analytical one validates the correctness of the analytical error model in Section III-B. From Fig. 4, we can clearly observe that RMSE is increasing with increasing $d$. This is because as $d$ increases, due to the random movement of molecules, the concentration of received molecules decreases, which leads to higher noises in the received concentration. The RMSE of the comparison scheme is higher than that of the proposed scheme, and it also increases with distances. We can observe that for each value of $d$, the error of the comparison scheme is almost two times higher than the proposed scheme.

Fig. 5 exhibits the decrease in RMSE with an increase of released molecules when $d = 5 \, \mu m$, where the proposed
scheme performs better than the comparison scheme. This is because when the number of released molecules is increased, the noise in received molecules concentration is reduced. Hence, the receiver can detect the maximum concentration efficiently when it observes more molecules. Due to the random movement of the molecules, the received molecules decreased with a decrease in the released molecules. Thereby, the receiver cannot detect the maximum concentration properly which can increase the error. From Fig. 5, we can clearly perceive that the released-time error in the proposed scheme dropped largely with increasing the $Q$ compared to the comparison scheme.

2) CDF ANALYSIS

Fig. 6 shows the CDF of $|\varepsilon|$ with regard to different values of $d$ and fixed values of $Q$, where $d = [5, 6] \, \mu m$ and the $Q = 3000$, respectively. Here, $|.|$ is the absolute operator. We observe that for all values of $d$, CDF of the proposed scheme shows a smaller error than the comparison scheme. In the case of the proposed scheme, we observe that almost 90% of error values is less than 0.0355 and 0.0555 s for $d = 5 \, \mu m$ and $d = 6 \, \mu m$, respectively. These values are almost 0.0695 and 0.1045 s, respectively, for the comparison scheme. The comparison scheme makes more error because the accuracy of the estimation of the perturbations seems to be influenced by the propagation delay and its variations. In cases where simultaneous drug release is expected from distributed DNs, estimation of the perturbations alone might be less effective than it was thought to be. The effectiveness of such mechanism would require the knowledge of the statistical standard deviation of the propagation delay, which would come at the expense of increased computational complexity.

The CDF of release-time error concerning the number of released molecules is demonstrated in Fig. 7, where the set of a number of molecules is $Q = \{1000, 3000\}$, and the value of $d$ is $5 \, \mu m$. Almost 90% error values is less than 0.0365 and 0.0505 s for the proposed scheme for $Q = 3000$ and $Q = 1000$, respectively. One the other hand, these values are almost 0.0695 to 0.0835 s, respectively, for the comparison scheme. The proposed scheme convergence was 1 earlier than that of the comparison scheme, which implies that our proposed scheme can ensure to release drugs simultaneously with minimal errors than the comparison scheme.

3) ENERGY COST ANALYSIS

Fig. 8 shows the consumption of energy versus $Q$. The value of $P$ is $(2K + 1)$ for the proposed scheme and $(n(K + 1) + 1)$ for the comparison scheme, where $n$ and $K$ are the number of rounds exchanging timestamped signals and number of DNs, respectively. All the parameter values in (17) are same as those in [43] and [45]. As expected, when the number of released molecule increases, the required energy also
increases linearly. We observe that almost for all values of $Q$, the energy consumption of the proposed scheme is about 96% less than that of the comparison scheme. Thus, the proposed scheme is more efficient than that of the comparison scheme in terms of energy efficiency.

V. CONCLUSION

In this paper, an internal control node-based simultaneous drug delivery scheme was proposed to reduce the release-time errors in MC-based TDD systems. We studied the influence of distance and the number of released molecules on the error. Simulation results reveal that by increasing the number of released molecules as well as decreasing the distance, the release-time error can be further reduced. Moreover, the proposed scheme outperformed a timestamped scheme, which demonstrates its effectiveness.

Our future plan is to study the error considering a complete system. It would include the simultaneous delivery of drugs that would ensue from a simultaneous release. The main challenge is to determine the propagation delay from the DNs to the infected site so as to achieve simultaneous drug delivery. Estimation of this propagation delay may increase the signaling overhead of the system and eventually increase the complexity. Therefore, the goal is to develop low-complexity TDD systems for simultaneous drug delivery. Additionally, it would ensure drug efficacy at the infected site by optimizing the release rate of drug-carrying nanomachine which may also increase the probability of the infected site receiving the desired amount of drugs at a particular time without any congestion [32], [47].

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![FIGURE 8: Energy cost versus Q.](https://example.com/figure8.png)
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