In-Body Sequential Multi-Drug Delivery Scheme using Molecular Communication

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ABSTRACT This study explores the application of molecular communication (MC) for the enhancement of the performance of sequential drug delivery in combination therapy—a multi-drug treatment procedure. To achieve high efficacy, it is essential to maintain a delivery time interval (DTI) between consecutive drug administrations. To this end, this study proposes a coordination scheme that enables the control of the release times of a network of drug-carrying nanomachines to ensure the maintenance of the DTI. Particularly, MC is employed to develop a centralized network, wherein the release times of the drugs from the drug-carrying nanomachines are managed by a controller nanomachine. This nanomachine is named the internal controller nanomachine, as it is placed within the human body. The performance of the proposed scheme is evaluated in terms of the DTI error. Furthermore, the analytical expression of the error is derived and its correctness is validated using simulations.

INDEX TERMS Molecular communication, nanomedicine, nanonetworks, targeted drug delivery, combination therapy

I. INTRODUCTION

MC is a bio-inspired communication technique that transmits information using molecules [1], [2]. MC is composed of a nanomachine, which is a nano to micrometer-scale device, and is considered as the basic functional unit of MC. Therefore, it is capable of performing simple operations (e.g., computation, sensing, actuation) [1], [3]. However, owing to the limited capabilities of nanomachines, MC requires a group of nanomachines to collectively perform activities that cannot be performed by individual nanomachines. Accordingly, MC has attracted attention for different interdisciplinary applications (such as medical, biological engineering, environmental, and industrial) owing to its bio-compatibility and energy efficiency. Particularly, the medical application of MC as a targeted drug delivery (TDD) system has attracted significant attention [4].

TDD is utilized to address toxicity and drug wastage challenges. TDD systems utilize diverse methods to ensure the localization of drug molecules to the infected site without impacting other healthy areas of the body, which could have been otherwise affected. To reduce drug deterioration and loss during TDD, drug molecules are encapsulated in nanomachines [5]. Thereafter, the nanomachines are injected through the cardiovascular system or can be directly deployed to the infected site to deliver the drugs. The former is known as a systemic TDD system and the latter is known as the local TDD system [5]–[9]. This study focused on a local TDD system. Regardless of the deploying mechanism, nanomachines require an external (e.g., ultrasound) or internal (e.g., pH, temperature) trigger to achieve drug delivery [10]–[12]. In this study, local TDD systems that utilized MC for communication purposes were employed and denoted as MC-based TDD. Additional molecules are incorporated into the MC-based TDD system for communication purposes to provide controllability. The MC-based TDD system can be utilized to administer single or multi types of drugs at the infected site. The former is called single drug delivery, while the latter is called the multidrug delivery system. In this study, we focus on the multidrug delivery system.
The multidrug delivery system is required in combination therapy, where two or more therapeutic drugs with different functions are involved [13]. However, the simultaneous delivery of these drugs may cause severe complications. For example, anticancer drugs exhibit severe side effects even when used alone, and combining them with another drug can increase the severity and frequency of their side effects [14]–[16]. Moreover, depending on their molecular target, the concurrent co-delivery of multiple drugs may reduce the maximal therapeutic efficacy of one or more of them. Accordingly, sequential drug delivery (SQDD) systems have emerged as an effective method for reducing the side effects of the co-delivery of multiple drugs while simultaneously increasing the therapeutic efficacy. SQDD-based combination therapy involves the sequential delivery of different types of drug molecules to infected sites. In addition, in situations where drug resistance limits therapeutic efficacy, the therapeutic efficacy of the second medication can be enhanced by pretreatment with a resistance-inhibiting drug [17], [18]. Drug resistance refers to a phenomenon in which an infected cell does not respond to a drug capable of killing or weakening it [19]. Accordingly, SQDD-based combination therapy has been reported as an effective method for combating anticancer medication resistance.

The challenge is that in SQDD, drug delivery time interval (DTI) is a critical parameter that affects the performance of SQDD. DTI is the time duration between the delivery (or administration) of different drug types at the infected site. DTI varies depending on the drug type and disease properties, and the smallest variation in the DTI may have a substantial impact on the efficacy of a drug and lead to DTI error [20]. Accordingly, it is essential for a healthcare professional or patient to devote careful attention to ensure the DTI. Therefore, to efficiently control the DTI, it is crucial to develop a smarter and more efficient system that can coordinate the release and delivery of drugs to the infected site in a sequential manner while improving the drug’s efficacy and reducing the complexity of the MC-based TDD system [21].

Recently, various studies on MC-based TDD systems have been conducted. For example, a previous study investigated transmission control protocol (TCP) as a communication protocol [8] by considering a three-dimensional (3D) bidirectional communication channel with static nanomachines to control the suitable release rate of the transmitter and to avoid congestion at the receiver, which functioned as a control node for the transmitter. Similarly, another study [7] investigated the relationship between the release rate and the number of receptors in nanomachines to reduce congestion at the infected region. In addition, another study described the mechanism involved in an earlier congestion recognition and release rate control of drug molecules [22], in which one nanomachine functioned as a controller and the other as an actuator that releases drug molecules based on the demand of the controller. Furthermore, another study optimized the drug release rate of nanomachines [23], and found that the distance between drug-carrying nanomachines and the infected site affects the release rate. Additionally, a study investigated the lifetime of TDD systems [24] by considering encapsulated drug-carrying nanomachines. They found that the extension of the lifetime of TDD can to some degree overcome the constraints of the reservoir capacity of a drug-carrying nanomachine. Another study proposed the coordination of multiple drug-carrying nanomachines for single drug delivery [25], [26], where an internal controller nanomachine controls the release time of the drug-carrying nanomachines based on the estimated propagation delay between the controller and the drug-carrying nanomachine. However, these aforementioned studies focused on different aspects of MC-based TDD systems, whereas no study has investigated the control of the DTI. Therefore, this study focused on the control of DTI at the infected site for multiple drugs delivery while considering a similar coordination approach that used in [25], [26] to reduce the DTI error, by considering a dedicated in-body-located control nanomachine. We note that in this paper, due to the system’s internal control ability, we refer to the MC-based TDD system as an advanced TDD system (ATDD). We believe that the proposed system will be highly beneficial to the future ATDD system in sequential drug delivery to control the DTI.

The major contributions of this study are as follows:

- An in-body controller-based sequential drug delivery scheme, namely, molecular communication-based sequential (MOCS) drug delivery system, is proposed for the delivery of multiple drugs to an infected site, while maintaining the DTI.
- The sequential drug DTI error is analyzed and investigated using a Gaussian distribution for the propagation delay. In addition, an analytical model for the DTI error is developed, and its results are consistent with the simulation results.
- Computer simulations are performed at various distances, quantity of released molecules, diffusion coefficient values, and radius of the nanomachines to assess the effectiveness of the proposed scheme. Furthermore, the energy cost of the proposed scheme is investigated.

The rest of this paper is divided into the following parts. The system model is discussed in Section II. Section III illustrates the proposed system and describes its operation in a multi-nanomachine context. In Section IV, the simulation findings are discussed. Lastly, in Section V, the conclusions and future directions are discussed. The list of notations that are frequently used in the paper are listed in the Table.1.

II. SYSTEM MODEL

An overview of the system model is shown in Fig.1. To realize the envisioned network, three types of nanomachines were considered: controller (C), releaser (R), and monitor (M). C is nanomachine that controls and manages Rs, which are the nanomachines that carry and release the drugs. M is a nanomachine that assists C. In addition to the functionality differences, the locations of these nanomachines differ. M is located very close to the target site, C isfarthest from the
FIGURE 1. System model of an molecular communications (MC)-based targeted drug delivery (TDD) system. $C$, $M$, $R_i$, and $R_j$ denote the controller, monitor, releaser $i$, and releaser $j$, respectively.

TABLE 1. List of notations used in this study.

| Symbol | Description |
|--------|-------------|
| $C$    | Controller  |
| $R$    | Releaser    |
| $M$    | Monitor     |
| $r$    | $R$ distance |
| $Q$    | Number of emitted molecules |
| $N$    | Number of $R$s |
| $d_M$  | Distance between $C$ and $M$ |
| $d_i$  | Distance between $C$ and $R_i$ where $i \in N$ |
| $d_{i,M}$ | Distance between $R_i$ and $M$ |
| $\Omega$ | Diffusion coefficient |
| $INI$  | Initiation signal |
| $RSP$  | Response signal |
| $RRP$  | Relay response signal |
| $TRG$  | Triggering signal |
| $T_{\Omega}$ | Sending and receiving time of event $\Omega$ |
| $\leftarrow$ | Forward signal sending events |
| $\tau_{a,b}$ | Propagation delay between nanomachine $a$ and $b$ |
| $\varepsilon_{a,b}$ | Propagation delay between nanomachine $a$ and $b$ where the sending-time event of the signal is $\Omega$ |
| $\Delta t$ | Delivery time interval between consecutive doses |
| $\varepsilon$ | Delivery-time interval error |

target site, and $R$s are located between $C$ and $M$. In addition, $M$ can be used to identify the amount of drug molecules absorbed at the infected site, which is considered to be the infected site owing to its vicinity. $d_i$ is the distance between $C$ and $R_i$, where $i \in N$ and $N$ are the total number of $R$s. Moreover, $d_M$ is the distance between $C$ and $M$, and $d_{i,M}$ is the distance between $R_i$ and $M$. We consider two $R$s and denote them by $R_i$ and $R_j$.

All nanomachines act as transceivers: a reflecting transmitter blocked the molecules that were attempting to travel in the opposite direction. The absorbing nanomachine is assumed to be capable of absorbing the molecules when they collide with the nanomachines surface. Therefore, each molecule was counted only once by the nanomachine and it contributed to the received signal only once [27]–[30]. The transmitter instantaneously releases a fixed number of molecules ($Q$) into the molecular channel to transmit a signal to the receiver. In this study, a 3D, molecular channel environment, which exhibits infinite dimensions in all directions, was considered. The environment was filled with a liquid that exhibited viscosity, $\eta$, without drifts. Consequently, the molecules propagated in the environment through the Brownian motion dynamics. The receiver can detect the signal by measuring received peak concentration (maximum concentration) of the molecules [31]. Therefore, the propagation delay is the time difference between the release time of the signal at the transmitter and its peak concentration time at the receiver [27].

This study considered isomers for the signaling molecules: isomers are molecules that are similar in shape, size, and diffusion coefficients ($\Omega$), but different in chemical arrangement [32]. Therefore, each signal was represented using a specific isomer with identical propagation delays. Moreover, isomers molecules are safe for the human body. In addition, all the drug molecules were assumed to have similar sizes with the isomer molecules, thus having similar $\Omega$.

III. PROPOSED SCHEME

The main objective of the proposed scheme was to control the release-time of $R$s using $C$ to ensure the sequential delivery of drugs at the infected site. The delivery time of the first drug at the infected site was denoted as $\zeta$ and the delivery
FIGURE 2. Operations of the propagation delay estimation phase of the proposed molecular communication-based sequential (MOCS) scheme.

TABLE 2. List of events in MOCS scheme.

| Event | Description | Time of event | Record time |
|-------|-------------|---------------|-------------|
| 0     | C broadcasts INI | $T_0$ | Yes |
| 1     | R receives INI and sends RSP to C | $T_1$ | No |
| 2     | C receives RSP of R | $T_2$ | Yes |
| 3     | M receives INI and sends RSP to C | $T_3$ | No |
| 4     | C receives RSP of M | $T_4$ | Yes |
| 5     | R receives the RSP of M and sends RRP to C | $T_5$ | No |
| 6     | C receives the RRP of R | $T_6$ | Yes |
| 7     | C sends the TRG to R | $T_7$ | No |
| 8     | R receives the TRG and releases the drugs | $T_8$ | No |
| 9     | Infected site receives the drugs | $\zeta + \Delta t$ | No |

Time of the second drugs was denoted as $\zeta + \Delta t$. Here, $\Delta t$ is the DTI between the delivery of two drugs where the value of $\Delta t$ depends on the types of drugs. For simplicity, we assumed that $C$ has information on $\Delta t$ and $\zeta$. However, it had no information on the propagation delay in the channel. Therefore, the underlying principle of the proposed scheme was to estimate the propagation delay by $C$, after which $C$ informs the $Rs$ to release the drugs based on the estimated delay, while ensuring the $\zeta$ and $\Delta t$.

The proposed MOCS has two phases: propagation delay estimation phase and sequential drug delivery phase. In the first phase, $C$ estimated the propagation delay between the nanomachines and in second phase, $C$ commands the $Rs$ to release their drugs based on the estimated delay. To differentiate the signals sent by $C$ to $R$ and $M$, the signals were named as forward signals and their propagation delays were marked using a symbol $\rightarrow$. Similarly, the signals that were sent by $Rs$ and $M$ towards $C$ were named as reverse signals and their propagation delays were marked using symbol $\leftarrow$. Sending and receiving time of event $i$ is denoted as $T_i$. Here, $i \in \{0, 1, 2, 3, 4, 5, 6, 7, 8, 9\}$. The propagation delay between the nanomachines $a$ and $b$ was denoted as $\tau_{a,b}$ where $a, b \in \{C, i, M\}$. Here, $i$ is the $R_i$. $\tau_{a,b}$ is the random propagation delay caused by the noise generated by the random movement of the molecule in the molecular channel. Consequently, we can write $\tau_{a,b}$ as [33]:

$$
\tau_{a,b} = E[\tau_{a,b}] + Y,
$$

where $E[\tau_{a,b}]$ is the expected $\tau_{a,b}$, which is equivalent to $\frac{\sigma_t^2}{\sigma^2_Y}$ [34], $Y$ is the delay noise that is a random variable having a Gaussian distribution as $Y \sim N(0, \sigma^2_Y)$, where the mean is 0 and variance is $\sigma^2_Y$. Moreover, the propagation delays of each signal were observed to be independent of one another owing to the environmental conditions in the MC channel, and we distinguish them using superscripts in brackets. Therefore, $\tau_{a,b}^{(i)}$ denotes propagation delay between nanomachines $a$ and $b$ where $i$ is the signal’s sending event. Since no solid analytical model of the propagation delay in a molecular diffusion channel exists, an approximation model was used in which the propagation delay was estimated once and all subsequent propagation delays were assumed to be equal to the estimated value [35].

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Table 2 shows the list of events of the proposed scheme. The operation of the MOCS is as follows.

1) Operation of the propagation delay estimation phase

Fig. 2 shows that at time \( T_{\text{G},i} \), \( C \) broadcasts a forward signal that initiates the delay estimation phase (event marked by \( \odot \)) and the \( C \) records the \( T_{\text{G},i} \). This signal was called the initiation signal, \( \text{INI} \) (red line in Fig. 2). After receiving the \( \text{INI} \), \( R_i \) and \( M \) immediately transmitted the reverse signal, namely, response signal, \( \text{RSP} \) (blue line), back to \( C \). The arrival time of \( \text{INI} \) at \( R_i \) was denoted as \( T_{\text{G},i} \) (event marked using \( \odot \), \( i \)), which is denoted as

\[
T_{\text{G},i} = T_{\odot} + \tau_{\text{G},i}. \tag{2}
\]

The alphabet in round brackets \( \tau_{\text{G},i} \) corresponds to the sending event of the signal’s sending event.

The arrival time of \( \text{RSP}_i \) at \( C \) was calculated as (marked by \( \odot \), \( i \))

\[
T_{\text{G},i} = T_{\odot} + \tau_{\text{G},i}. \tag{3}
\]

After obtaining the \( T_{\text{G},i} \), \( C \) estimated the propagation delay \( \tau_{\text{G},i} \),

\[
\tau_{\text{G},i} = \frac{T_{\text{G},i} - T_{\odot}}{2}. \tag{4}
\]

Similarly, \( C \) estimates the \( \tau_{\text{G},i} \) using the receiving time of \( \text{RSP}_M \) at \( T_{\odot} \),

\[
\tau_{\text{G},i} = \frac{T_{\odot} - T_{\odot}}{2}. \tag{5}
\]

The \( \text{RSP}_M \) was also received by \( R_i \). Subsequently \( R_i \) immediately transmitted another reverse signal, namely, relay response signal, \( \text{RRP}_i \), to \( C \). Therefore, the receiving times of \( \text{RSP}_M \) at \( R_i \) (marked by \( \odot \), \( i \)) and \( \text{RRP}_i \) at \( C \) (marked using \( \odot \), \( i \)) can be written as

\[
T_{\text{G},i} = T_{\odot} + \tau_{\text{G},i}. \tag{6}
\]

and

\[
T_{\text{G},i} = T_{\odot} + \tau_{\text{G},i}. \tag{7}
\]

After obtaining the \( T_{\text{G},i} \), \( C \) determines the round trip time between \( C \) and \( M \) through \( R_i \) using:

\[
T_{\text{RTT},i} = T_{\text{G},i} - T_{\odot}. \tag{8}
\]

Lastly, \( C \) estimated the \( \tau_{\text{G},i} \) using \( \tau_{\text{C},i} \), \( \tau_{\text{C},M} \), and \( T_{\text{RTT},i} \) as follows

\[
\tau_{\text{C},i} = T_{\text{RTT},i} - \tau_{\text{C},M} - \tau_{\text{G},i}. \tag{9}
\]

2) Operations of the MOCS drug delivery phase

To maintain the drug delivery time of the first drug at \( \zeta \) at the infected site using \( R_i \), \( C \) determined a time instant \( T_{\text{G},i} \) (marked using \( \odot \), \( i \) in Fig. 3) at which \( C \) sends the triggering signal, \( \text{TRG}_i \), to trigger the release of the drug by \( R_i \). Subsequently

\[
T_{\text{G},i} = \zeta - \tau_{\text{C},i} - \tau_{\text{G},i}. \tag{10}
\]

\( R_i \) released the drug molecules (marked as \( \odot \), \( i \)) after it was triggered by \( C \). Hence, the drug release time of \( R_i \) can be calculated using:

\[
T_{\text{G},i} = T_{\text{G},i} + \tau_{\text{C},i}. \tag{11}
\]

Hence, the actual drug delivery time by \( R_i \) at the infected site (marked by \( \odot \), \( i \)) was calculated using

\[
T_{\text{G},i} = T_{\text{G},i} + \tau_{\text{C},i}. \tag{12}
\]

However, owing to the randomness of the molecules in the molecular channel, \( T_{\text{G},i} \) of (12) might be differ from \( \zeta \).

Similarly, the actual drug delivery time of the second drug at the infected site by the \( R_j \) (marked by \( \odot \), \( j \)) which is denoted by

\[
T_{\text{G},j} = T_{\text{G},j} + \tau_{\text{C},j}. \tag{13}
\]

might also be different from \( \zeta + \Delta t \). Accordingly, the erroneous DTI, which was targeted by \( \Delta t \), was obtained using:

\[
\Delta t = T_{\text{G},j} - T_{\text{G},i}. \tag{14}
\]

3) Analytical error model

The drug-delivery time interval error, \( \varepsilon \), is the time difference between the expected drug DTI and the actual drug DTI, which can be calculated as follows,

\[
\varepsilon = \Delta t - \Delta t. \tag{15}
\]

Substituting (14) in (15)

\[
\varepsilon = T_{\text{G},j} - T_{\text{G},i} - \Delta t. \tag{16}
\]
Using (12) and (13), (16) can be expressed as,

$$
\varepsilon = T_{\Theta,i} + \tau_{C,i} - T_{\Theta,i}^\oplus + \tau_{C,i}^\oplus - \Delta t. \tag{17}
$$

In addition (17) can be obtained from (11) as:

$$
\varepsilon = T_{\Theta,i} + \tau_{C,i} + \tau_{j,M}^\oplus - T_{\Theta,i}^\oplus - \tau_{i,M} - \Delta t. \tag{18}
$$

By applying values from (10), (18) can be written as

$$
\varepsilon = \zeta + \Delta t - \tau_{C,i} - \tau_{i,M} - \tau_{C,j}^\oplus - \tau_{j,M} + \tau_{C,i} + \tau_{i,M} - \tau_{C,j}^\oplus - \tau_{j,M} - \Delta t
$$

Subsequently, the values from (4) and (9) was substituted into (19)

$$
\varepsilon = -\tau_{C,j} + \tau_{C,j}^\oplus + \tau_{C,i} + \tau_{i,M} - \tau_{C,i}^\oplus - \tau_{i,M}
$$

$$
+ T_{\Theta,i} - \tau_{C,i} - \tau_{C,j}^\oplus + \tau_{C,i}^\oplus - \tau_{i,M} - \Delta t
$$

$$
+ T_{\Theta,i} + \tau_{C,j} + \tau_{C,j}^\oplus + \tau_{C,i} + \tau_{i,M} - \tau_{C,i}^\oplus - \tau_{i,M}
$$

$$
+ T_{\Theta,i} - \tau_{C,i} - \tau_{C,j}^\oplus + \tau_{C,i}^\oplus - \tau_{i,M} - \Delta t
$$

$$
+ T_{\Theta,i} + \tau_{C,j} + \tau_{C,j}^\oplus + \tau_{C,i} + \tau_{i,M} - \tau_{C,i}^\oplus - \tau_{i,M}
$$

Therefore, due to $\mu_\varepsilon = 0$,

$$
\sqrt{E[\varepsilon^2]} = \sigma_\varepsilon. \tag{23}
$$

which is the root mean squared error (RMSE) and $E[\cdot]$ is the expectation operator.

### IV. NUMERICAL ANALYSIS

#### A. SIMULATION SETUP

The performance of the proposed schemes was evaluated by developing a network simulator over the well-recognized MolecUlar CommunicatIoN (MUCIN) simulator in Matlab [39]. The evaluated metrics include the root mean square error (RMSE) of $\varepsilon$ in terms of distance, the number of released molecules, diffusion coefficient, and nanomachines radius. Moreover, we also considered the cumulative distribution function (CDF) of $\varepsilon$ and also energy efficiency in terms of $N$ as performance metrics. The network was simulated by considering four different cases where different distances were utilized in each case with case-4 having the highest distance and case-1 with the lowest (Fig. 4). The value of $r$ and $d$ is chosen based on the different sizes of the cell and the distances among them [40]–[42]. A simulation step time of $\Delta T = 0.001$ was considered. All the parameters that are utilized in the simulation are given in Table 3.

#### B. SIMULATION RESULTS

1) Changes in the RMSE with distance

RMSE expresses the difference between the actual $\Delta t$ and the expected $\Delta t$. For the simulation, the RMSE was calculated using:

$$
RMSE = \sqrt{\frac{1}{K}\sum_{k=1}^{K}\varepsilon(k)}, \tag{24}
$$

where $K$ is the simulation replication number and $\varepsilon(k)$ is the sequential drug DTI error in the $k$-th replication.

Fig. 5 shows the performance of the proposed scheme of the four simulated cases at different distances (topology shown in Fig. 4). A linear relationship was observed between the performance and distance, that is, RMSE increased with...
an increase in distance. This could be attributed to the fact that the decrease in the number of signal molecules received by the receiver with an increase in the distance between the transmitter and receiver, thereby, increasing the noise in the measured concentrations. Consequently, the noise affected the propagation delay variance, thus increasing the RMSE. Accordingly, the RMSE of case-4 was higher than those of the other three cases owing to its larger distances. Moreover, the different value of $\Delta t$ had no effect on the performance of the proposed MOCS, causing the RMSE result to overlap for $\Delta t = 2$ min and $\Delta t = 30$ min. This could be attributed to the fact that the proposed scheme considered the propagation delay to trigger $R_s$ to maintain the drug DTI and $C$ knows the value of $\Delta t$. Therefore, once the propagation delays were estimated by the controller, that system can be implemented for any $\Delta t$. Thus, the proposed scheme reduced the complexity of maintaining the different $\Delta t$ for identical system, which enabled its application for any value of $\Delta t$ without any effect on the system performance. Additionally, the analytical model results were consistent with the simulation results, which confirmed the effectiveness of the mathematical model of the proposed scheme.

2) Changes in the RMSE as a function of the number of molecules

Fig. 6 shows the RMSE of case-1 and case-4 at different $Q$ values, as case-1 and case-4 exhibited best and worst results, respectively, in the Fig. 5. The RMSE increased with a decrease in $Q$. This could be attributed to the fact that the noise reduced with an increase in $Q$ during the estimation of the maximum number of received molecules to determine the propagation delay. Therefore, the RMSE at $Q = 16000$ was lower than the RMSE at $Q = 10000$ for both cases. The RMSE value for case-1 at $Q = 10000$ and 16000 molecules were 0.013143 s and 0.011892 s, respectively, whereas those of case-4 were 0.038711 s and 0.033816 s, respectively. In addition, the RMSE curve of case-4 exhibited more fluctuations than that of case-1. This could be attributed to the increase in the variations in the propagation delay with an increase in the distance. In addition, owing to the higher diffusion coefficient, $\Omega$, the number of molecules that diffused away from the higher-distance receiver was higher than that of the smaller-distance receiver. Therefore, owing to the larger propagation delay variations in the larger-distance receiver, the changes were larger in case-4 than in case-1.
3) Changes in the RMSE as a function of the nanomachines radius

The relationship between the $r$ and RMSE of case-1 and case-4 is shown in Fig. 7. The numerical result revealed that the RMSE decreased with increasing $r$. For example, the value of RMSE at $r = 6$ and 12 for case-1 were 0.013506 s and 0.011818 s, respectively, whereas those for case-4 were 0.043403 s and 0.03776 s, respectively. As expected, the larger receiver absorbed more molecules than the smaller one owing to its larger reception space. Therefore, the influence of noise on the propagation delay estimation in the larger receiver was lower than that on the smaller receiver, which decreased the RMSE.

4) Changes in the RMSE as a function of the diffusion coefficient

The RMSE of case-1 and case-4 at different $\Omega$ is shown in Fig.8. The RMSE decreased with an increase in $\Omega$. In addition, the number of molecules received by the receiver increased with an increase in $\Omega$. This could be attributed to the fact that a higher $\Omega$ corresponds to a faster channel and it also determines the speed at which the molecules move in the channel. Consequently, the number of molecules received increased; and as a result, the propagation delay variation decreased, which has also been reported in [44]. Furthermore, the $\Omega$, which determines the speed at which the molecules move in the channel, was inversely proportional to the variations in the propagation delay; thus, RMSE of both cases for $597.25 \mu m^2/s$ was lower than those at other lower $\Omega$. In addition, the changes in the RMSE as $\Omega$ increased were larger in case-4 than in case-1. This could be attributed to the fact that the larger distance of case-4 resulted in larger variations in delay, as described in Fig. 6.

5) Changes in the CDF as a function of the distance

Fig. 9 shows the CDF of $|\varepsilon|$ in case-1 and case-4 when $Q = 10000$ molecules. Here, $|\varepsilon|$ corresponds to the absolute operator. The results revealed that the CDF of $|\varepsilon|$ in case-1 exhibited a smaller error than that in case-4. In case-1, approximately 80% (marked by the circle in the figure) of $|\varepsilon|$ was less than 0.0165 s (marked by green ‘x’), whereas that of case-4 was approximately 0.0485 s (marked by cyan ‘x’), which was approximately four times higher than that of case-1 at $\Delta t = 30$. The higher error of Case-4 could be attributed to the larger distance. As expected, this could be attributed to the fact that fluctuations in propagation delay increased as the distance increased. In addition, the CDF for both cases at $\Delta t$ values of 2 min and 30 min was observed to overlap, indicating that $\Delta t$ had no effect on $|\varepsilon|$.
6) Changes in the CDF as a function of the released molecules
The CDF of $|\varepsilon|$ based on $Q$ for case-1 and case-4 is shown in Fig. 10 where $Q = \{10000, 16000\}$. Approximately 80% of the $|\varepsilon|$ values of case-4 were less than 0.0135 s (marked by pink ‘x’) and 0.0153 s (marked by black ‘x’) at $Q = 16000$ and 10000, respectively. In contrast, these values were approximately 0.0445 s (marked by blue ‘x’) and 0.00485 s (marked by green ‘x’) for case-4. In addition, the CDF of case-1 converged to 1 earlier than that of case-4, indicating that the proposed scheme can ensure sequential drug delivery with minimal errors at a smaller distance than at a larger distance.

7) Energy efficiency analysis
Fig. 11 shows the energy cost, $E_{\text{cost}}$, versus the number of drug releaser, $N$, based on the energy model in [25], [32], [45]. The total energy cost was calculated using the following formula:

$$E_{\text{cost}} = s \times n \times E_{\text{con}},$$

where $s$ and $n$ are the number of bits in a signal and the number of signal exchanges among nanomachines, respectively, and the value of $n$ depends on the number of releasers, $N$, which is $(2 + 3N)$. $E_{\text{con}}$ is the amount of energy used to synthesize of molecules, transport molecules via vesicles, and release the molecules to the environment [26], [32]. The energy spent in these processes are represented by $E_{m_{\text{syn}}}$, $E_{v_{\text{syn}}}$, $E_{v_{\text{trn}}}$, and $E_{m_{\text{rls}}}$, respectively. Therefore, the value of $E_{\text{con}}$ can be obtained as follows

$$E_{\text{con}} = QE_{m_{\text{syn}}} + (E_{v_{\text{syn}}} + E_{v_{\text{trn}}} + E_{m_{\text{rls}}}) \times \frac{Q}{v_{\text{cap}}},$$

where $v_{\text{cap}}$ is the capacity of the vesicle. The values of the parameters in (26) are identical to those found in [25], [26], [32], [45].

Fig. 11 shows that the $E_{\text{cost}}$ increased as $N$ increased. This could be attributed to the increase in the number of releasers, 4, which resulted in an increase in the $E_{\text{con}}$. In addition, doubling the value of $N$ did not result in the doubling of the value of $E_{\text{cost}}$, indicating the energy efficiency of the proposed scheme. For example, when $N = 2$ the value of $n$ was 8; however, when $N = 4$ the value of $n$ was 14. This indicates that doubling $N$ did not result in the doubling of $n$; thus, the increase in $E_{\text{cost}}$ was not doubled.

V. CONCLUSION
This study developed an internal controller nanomachine-based sequential drug delivery system, MOCS, that utilized bio-inspired molecular communication as a communication paradigm. We positioned that such a bio-inspired approach would be beneficial for medical applications. In the proposed system the controller nanomachine utilized propagation delay to trigger the releaser to release their drugs and minimize...
sequential drug DTI errors. The effects of distance, number of released molecules, the radius of the nanomachines, and the diffusion coefficient on the DTI error are investigated. The simulation data revealed that DTI error can be reduced by increasing the number of released molecules while decreasing the distance. Furthermore, the accuracy of the scheme increased with an increase in the size of the nanomachines and diffusion coefficients. Furthermore, the analytical model of DTI error under the Gaussian approximations of the delay agrees well with the numerical simulations, validating the correctness of the model.

In the future, we aim to investigate the control of the release type and rate of multiple distant drug-carrying nanomachines. The significant difficulty involves the determination of the propagation delay of numerous distant drug-carrying nanomachines with the fewest possible signal exchanges. The estimation of this propagation delay may enhance the communication system overhead, thus enhancing its complexity. Therefore, we aim to develop TDD systems with minimal complexity for sequential drug administration. Additionally, it would ensure drug efficacy at the infected site by optimizing the release rate of drug-carrying nanomachines, increasing the probability of the infected area receiving the desired amount of drugs at a particular time without any congestion.

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