Controlled Signaling and Transmitter Replenishment for MC with Functionalized Nanoparticles

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ABSTRACT
In this paper, we propose novel Transmitter (Tx) models for Molecular Communication (MC) systems based on functionalized Nanoparticles (NPs). Current Tx models often rely on simplifying assumptions for the molecule release and replenishment mechanisms. In contrast, we propose a Tx model where the signaling molecule release is controlled by a switchable membrane driven by an external trigger. Moreover, we propose a reloading mechanism, where signaling molecules are harvested based on an enzymatic reaction. Hence, no repeated injection of signaling molecules is required. For the proposed Tx model, we develop a general mathematical description in terms of a discrete-time transfer function model. Furthermore, we investigate two realizations of the proposed Tx model, i.e., an idealized Tx relying on simplifying assumptions, and a realistic Tx employing practical components for the reloading and release mechanisms. Finally, we numerically evaluate the proposed model and compare our results to stochastic Particle Based Simulations (PBSs).

CCS CONCEPTS
• Applied computing → Telecommunications; • Networks → Physical links; • Hardware → Wireless devices.

KEYWORDS
Molecular Communication, Nanoparticles, Transmitter Design

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1 INTRODUCTION
Molecular Communication (MC) is a bio-inspired communication paradigm employing molecules for information exchange. MC enables synthetic communication at the nanoscale, which paves the way for transformative applications in nanomedicine and health monitoring [2, 9]. For the design and optimization of MC systems it is crucial to develop models for its components, i.e., the Transmitter (Tx), the channel, and the Receiver (Rx). Various component models have been proposed, which can be roughly classified into point and volume Txs, diffusive, advective, and degradative channels, and active and passive Rxs [15]. However, most existing models do not properly reflect the characteristics of practical components due to various simplifications.

Specifically, the development of practical Tx models is crucial, since the majority of the works in the MC literature assume a point Tx, requiring instantaneous signaling molecule production and release [15]. However, realistic Tx models have to consider the following aspects: (i) the signal molecule production and propagation inside the Tx, and (ii) mechanisms for releasing signal molecules. A first step towards practical Tx models was made in [20], which studies a virtual spherical Tx with uniformly distributed molecules inside and a fully reflective spherical Tx with uniformly distributed molecules on its surface, respectively. However, both Tx models assume an instantaneous molecule production and release. The works in [5, 14, 21, 23] focus on the release mechanism and the propagation inside the Tx. In [5], a spherical Tx with ion-channels in its membrane is investigated, where the release of the signal molecules is controlled by the opening and closing of the ion-channels through a voltage or ligands. In [23], the molecule release from a spherical Tx is controlled by a spatially and temporally adjustable semi-permeable membrane. A membrane-fusion based Tx is considered in [14], which encapsulates the signaling molecules in vesicles. The molecules are released when the vesicles fuse with the Tx membrane. While the aforementioned models can be considered as reservoir-based Tx models that control the release by membrane functionalization, in [21] polymer matrices are considered as Txs, which are already employed as practical drug carriers in medical applications. However, none of the works mentioned above take the production of signaling molecules into account. Besides the generation of molecules (e.g., via chemical reaction networks), molecule harvesting is a promising approach to generate signaling molecules. Recently, in [1] a molecular harvesting Tx is proposed, where molecules are released by release units (e.g., ion-channels [5]) and re-captured if they hit a harvesting unit on the Tx surface.

In this paper, we propose a novel Tx model based on the properties of functionalized Nanoparticles (NPs), which are promising candidates to be used as nodes in nanonetworks for sensing and localized treatment [2, 9]. The envisioned Tx provides a controlled molecule release mechanism based on switching the NP membrane between the open and closed states by an external trigger, e.g., a pH change of the surrounding environment. Furthermore, the proposed Tx exhibits a reloading mechanism for repeated signaling
The paper is organized as follows. In Section 2, we introduce the main mechanisms, namely (i) a **controlled release mechanism**, which enables the release of signaling molecules controlled by an external stimulus (see Fig. 1, left hand side), and (ii) a **reloading mechanism** enabling the production of signaling molecules inside the Tx from molecules recruited from the surrounding environment (see Fig. 1, right hand side). Both mechanisms are facilitated by the design and functionalization of the NP. The controlled release mechanism (ii) is realized by enzymes encapsulated in the NP allowing for the conversion of molecules recruited from the surrounding environment, denoted as type A molecules, in signaling molecules, denoted as type B molecules. The switching of the NP membrane between the open and closed states is exploited for both the controlled release of type B molecules and the reloading of type A molecules, while the membrane is impermeable for enzymes in both states. In the following, we denote the number of type A molecules in the environment, $S_{\text{out}}$, and inside the NP volume, $S_{\text{in}}$, by $N_{\text{out}}^{A}$ and $N_{\text{in}}^{A}$, respectively (see Fig. 1).

To provide a tractable mathematical description of the proposed Tx, we make the following assumptions:

- **A1** The environment $S_{\text{out}}$ with volume size $V_{\text{out}} = \frac{4}{3} \pi r_{\text{out}}^3$ is much larger than $S_{\text{in}}$ with size $V_{\text{in}} = \frac{4}{3} \pi r_{\text{in}}^3$, i.e., $V_{\text{out}} \gg V_{\text{in}}$.
- **A2** Both volumes $S_{\text{out}}$ and $S_{\text{in}}$ are well mixed and $N_{\text{out}}^{A} \gg N_{\text{in}}^{A}$.

A1 is motivated by the fact that the typical diameter of a NP is around hundreds of nanometer, while the diameter of a typical synthetic MC channel, e.g., a microreactor or a microfluidic channel, is around $1 \times 10^{-6} - 1 \times 10^{-3}$ m [12, 21, 22]. A2 is justified if the propagation of molecules due to diffusion is relatively fast compared to the absorption rate of these molecules at the boundary of the NP. For $S_{\text{out}}$, A2 is valid for the practical values chosen for the diffusion coefficient of the molecules, the number of molecules in $S_{\text{out}}$, $N_{\text{out}}^{A}$, and permeability of the NP. For $S_{\text{in}}$, A2 is validated by the excellent agreement of the numerical results obtained from our proposed Tx model, relying on A2, and the results obtained from stochastic Particle Based Simulations (PBSs).

### 2.1 Transmitter Reloading Mechanism

The Tx reloading is based on the diffusion of type A molecules from $S_{\text{out}}$ into the NP and their conversion into type B signaling molecules, see right hand side of Fig. 1. Based on A1 and A2, the concentration of the type A molecules inside the NP can be modeled by the following Ordinary Differential Equation (ODE)

$$\partial_t c_{\text{in}}^{A}(t) = -\rho(t) \left( c_{\text{in}}^{A}(t) - c_{\text{out}}^{A} \right) - G \left( c_{\text{in}}^{A}(t), \ldots \right),$$  

(1)

where $\partial_t$ denotes a derivative with respect to time $t$, and $c_{\text{in}}^{A}$ and $c_{\text{out}}^{A}$ denote the concentration of type A molecules in mol m$^{-3}$ in $S_{\text{in}}$ and $S_{\text{out}}$, respectively. The time-dependent permeability $\rho(t)$ in s$^{-1}$ models the switchable Tx membrane$^1$. The function $G$ models the change of concentration $c_{\text{in}}^{A}$ due to the conversion of type A molecules into type B molecules, which depends on the inner concentration $c_{\text{in}}^{A}$ and the actual production mechanism. For example, if the production of type B molecules is realized by an enzyme reaction (see Sections 3 and 4), function $G$ may also depend on the enzyme and cofactor concentrations inside the NP volume $S_{\text{in}}$.

Similar to (1), the concentration of type B signaling molecules in $S_{\text{in}}$ can be modeled by the following ODE

$$\partial_t c_{\text{in}}^{B}(t) = -\rho(t) \left( c_{\text{in}}^{B}(t) - c_{\text{out}}^{B} \right) + G \left( c_{\text{in}}^{A}(t), \ldots \right),$$  

(2)

where $c_{\text{in}}^{B}$ and $c_{\text{out}}^{B}$ denote the concentration of type B molecules in mol m$^{-3}$ in $S_{\text{in}}$ and $S_{\text{out}}$, respectively. Similar to function $G$ in (1), the function $G$ models the change of $c_{\text{in}}^{B}$ due to the production of type B molecules from type A molecules.

### 2.2 Controlled Release of Signaling Molecules

The controlled release of type B molecules from the Tx into the environment $S_{\text{out}}$ depends on the NP permeability $\rho(t)$ and on the

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$^1$We obtained $\rho$ in s$^{-1}$ from practical permeability values $\hat{\rho}$, actually measured in m s$^{-1}$, by a relation to the surface area $A$ and $V_{\text{in}}$ of the NP, i.e., $\rho = \hat{\rho} A / V_{\text{in}}$. 

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![Figure 1: Left hand side: Controlled release of signaling type B molecules (red) by controlled opening of the Tx membrane. Right hand side: Reloading of type A molecules (blue) from the surrounding environment and conversion into signaling type B molecules.](image-url)
difference between the inner and outer concentration of type B molecules which can be expressed as follows
\[
\partial_t C^B_{\text{in}}(t) = -\rho(t) \frac{V_{\text{in}}}{V_{\text{out}}} (C^B_{\text{in}}(t) - C^B_{\text{out}}(t)).
\]

### 2.3 Reception of Signaling Molecules

As Rx model, we adopt an absorbing spherical Rx with radius \( r_{\text{Rx}} \) and distance \( d \) from the Tx. Moreover, the Rx can only absorb type B molecules. The number of molecules \( N_{\text{Rx}}^B \) absorbed by the Rx is obtained by convolving the number of molecules \( N_{\text{out}}^B(t) \), released from the Tx surface over time, and the hitting probability \( \rho(t) \) of an instantaneous release from the surface of a spherical Tx previously proposed in [14], i.e.,
\[
N_{\text{Rx}}^B(t) = N_{\text{out}}^B(t) \ast \rho(t),
\]
where \( \ast \) denotes a convolution with respect to time \( t \) and the number of type B molecules released by the Tx is given by \( N_{\text{out}}^B = C_{\text{out}}^B(t) V_{\text{out}} N_{\text{A}} \) with Avogadro constant \( N_{\text{A}} \approx 6.022 \cdot 10^{23} \text{mol}^{-1} \). The analytical expression for \( \rho(t) \) is given by [14, Eq. (9)].

### 3 IDEALIZED TRANSMITTER MODEL

In this section, we investigate an idealized realization of the Tx model proposed in Section 2. This idealized model will serve later as a benchmark for the practical Tx proposed in Section 4. To this end, we specialize the reloading and release mechanism to obtain mathematically tractable functions. We assume an instantaneous switching and a first order irreversible reaction for type B molecule production inside the NP. In particular, we assume that the membrane of the NP can be switched instantaneously between the closed and open states with permeability \( \rho_{\text{max}} \), i.e., \( \rho \in [0, \rho_{\text{max}}] \). We model the production of type B signaling molecules from harvested type A molecules in \( S_{\text{in}} \) by a simple first order reaction [19]
\[
A \overset{k_{AB}}{\longrightarrow} B, \quad \mathcal{G} \left( C_{\text{in}}^A(t) \right) = \partial_t C_{\text{in}}^B(t) = k_{AB} C_{\text{in}}^A(t).
\]

As further idealization we assume that reaction (5) takes place anywhere in \( S_{\text{in}} \) with constant reaction rate \( k_{AB} \) in s\(^{-1}\). With this assumption for the production of type B molecules, (1) simplifies to
\[
\partial_t C_{\text{in}}^A(t) = -\rho(t) \left( C_{\text{in}}^A(t) - C_{\text{out}}^A(t) \right) - k_{AB} C_{\text{in}}^A(t),
\]
where we further assume a constant type A molecule concentration in \( S_{\text{out}} \), i.e., \( C_{\text{out}}^A(t) = C_{\text{out}}^A \). This assumption is justified by A1 and A2, i.e., due to the large number of molecules \( N_{\text{A}} \) uniformly distributed in \( S_{\text{in}} \) and the volume difference between \( S_{\text{out}} \) and \( S_{\text{in}} \), the number of molecules diffusing into the NP does not significantly change the number of type A molecules in \( S_{\text{out}} \). Similarly, the ODEs in (2) and (3) simplify as follows
\[
\partial_t C_{\text{in}}^B(t) = -\rho(t) C_{\text{in}}^B(t) + k_{AB} C_{\text{in}}^A(t),
\]
and
\[
\partial_t C_{\text{out}}^B(t) = \rho(t) \frac{V_{\text{in}}}{V_{\text{out}}} C_{\text{in}}^B(t),
\]
where we exploited A1 and A2 to assume an irreversible transmission of type B molecules through the Tx membrane, where the influx of type B molecules from the environment into the Tx is neglected (perfect sink).

### 3.1 Discrete-time Transfer Function Model

Due to the time-dependent permeability \( \rho(t) \) in (6)–(8), no closed form solution in the continuous-time domain can be derived. Therefore, we derive a discrete-time transfer function model for the system of ODEs (6)–(8) via the Impulse Invariant Transformation (IIT) [22]. Applying the IIT to ODE (6) yields a scalar valued discrete-time state equation for the concentration of type A molecules in \( S_{\text{in}} \)
\[
C_{\text{in}}^A[k] = \exp \left( \lambda_{\text{in}}^A[k] T \right) C_{\text{in}}^A[k - 1] + T \rho[k] C_{\text{out}}^A[k],
\]
with discrete-time index \( k \), sampling time \( T \) (i.e., \( t = kT \)), and time-dependent parameter \( \lambda_{\text{in}}^A[k] = -(\rho[k] + k_{AB}) \). Similarly, applying an IIT to (7) and (8) yields
\[
C_{\text{in}}^B[k] = \exp \left( \lambda_{\text{in}}^B[k] T \right) C_{\text{in}}^B[k - 1] + T k_{AB} C_{\text{in}}^A[k],
\]
and
\[
C_{\text{out}}^B[k] = \frac{\rho[k]}{V_{\text{in}}/V_{\text{out}}} C_{\text{in}}^B[k],
\]
with \( \lambda_{\text{in}}^B[k] = -\rho[k] \) and \( \lambda_{\text{out}}^B[k] = -\rho[k] V_{\text{in}}/V_{\text{out}} \). The discrete-time solution in (9)–(11) has several benefits. First, the description in the discrete-time domain allows the incorporation of the time-variance introduced by permeability \( \rho(t) \) in terms of time-variant parameters \( \lambda_{\text{in}}^A \) and \( \lambda_{\text{in}}^B \). Second, the proposed model allows a simple and computationally efficient solution of the ODEs in (6)–(8).

### 4 PRACTICAL TRANSMITTER MODEL

In this section, we consider a realization of the Tx model proposed in Section 2 based on practical components for the production and controlled release of signaling molecules.

#### 4.1 Membrane Switching Mechanism

The key property of the proposed Tx for both controlled release and reloading is the ability to open and close the NP membrane upon a controllable trigger signal. As a practical type of NP, we employ polymericosomes, the synthetic counterpart of liposomes, with a pH-driven permeability switch, which consist of a multifunctional amphiphilic block copolymer. In particular, it consists of the biocompatible poly(ethylene glycol) (PEG) as the hydrophilic part and a statistical mix of two components in the hydrophobic part providing the pH sensitive membrane switching functionalities, see [10, 12] for details. For high pH values, i.e., \( \text{pH} > 7 \), the membrane of the NP collapses, i.e., the membrane is non-permeable and molecules cannot neither diffuse out of the NP nor into it (permeability \( \rho = 0 \)). When the pH value is low, i.e., \( \text{pH} < 7 \), the membrane swells and becomes permeable with permeability \( \rho_{\text{max}} \). Fig. 2 shows the switching process of the NP for multiple pH changes.

Compared to the idealized scenario, considered in Section 3, for practical NPs, the membrane switching is no longer instantaneous. In particular, upon the external pH trigger it takes approximately 30–100s until the membrane permeability reaches \( \rho_{\text{max}} \), see [10, Fig. 3]. A similar time delay applies for the closing process upon a pH increase. We note that the exact temporal evolution of the NP permeability \( \rho(t) \) is not known. Therefore, the change of \( \rho(t) \) from \( \rho = 0 \) (closed) to \( \rho = \rho_{\text{max}} \) (open) and vice versa is modeled by a linear increase and a linear decrease, respectively. Also the maximum permeability in the open state is not given in a closed form, but we estimated \( \rho_{\text{max}} \) from the measurements provided in [11] employing the methods from [6].
4.2 Production of Signaling Molecules

In the idealized scenario discussed in Section 3, we employed a first order reaction for signaling molecule production. In this section, we investigate a realistic mechanism for the production of signaling molecules by an enzyme reaction.

We realize the production of signaling molecules by the encapsulation of Mandelate Racemase (MR) into the NP. The enzyme MR performs a reversible one-substrate-reaction of (R)-Mandelate (type A molecules) to (S)-Mandelate (type B signaling molecules), and the reaction equations are as follows [17, 18]

\[ E + (R)\text{man} \rightleftharpoons (S)\text{man} \rightleftharpoons E + (S)\text{man}, \]

where \( E \) denotes the enzyme MR, and \( E(R)\text{man} \) and \( E(S)\text{man} \) denote intermediate complexes of MR and (R)-Mandelate ((R)man) and (S)-Mandelate ((S)man), respectively. The corresponding reaction rates are denoted by \( k_1, k_2, k_3, k_4, k_5, k_6 \), respectively. The production of (S)man molecules from (R)man molecules harvested from the surrounding environment is illustrated in Fig. 2.

MR exhibits several benefits making it a suitable enzyme for the practical realization of the proposed Tx. First, MR does not require a cofactor for the reaction to take place. This property enables a longer operating life of the Tx in practice, as MR produces signaling molecules by an enzyme reaction. As previously mentioned, the reaction (12) cannot be solved analytically, i.e., we cannot express the number of (R)man molecules produces over time in terms of the number of (S)man molecules and vice versa. Therefore, functions \( R \) in (13) and \( S \) in (14) cannot be given in a closed form. Instead, \( R \) and \( S \) represent the numerical solution of (12) to calculate the change of \( C_{in}^{R} \) and \( C_{in}^{S} \) in each time step based on the previous time step. In general, a numerical solution for (12) can be obtained by the numerical methods described, e.g., in [13].

We obtain a numerical solution for (12) as follows: First, we assume a pseudo steady state and derive a reaction rate equation for the three individual bidirectional reactions in (12) see, e.g., [13, Sec. 7] and [24]. Second, we solve these individual reactions by an exponential approach and calculate them sequentially in each time step.

The concentration \( C_{out}^{S} \) of (S)man molecules in \( S_{out} \) adopts a similar shape as for the idealized realization in (11) as follows

\[ C_{in}^{S}[k] = C_{out}^{S}[k - 1] + \lambda^{S}_{out}[k] C_{in}^{S}[k], \]  

with \( \lambda^{S}_{out}[k] = \rho[k] V_{in}/V_{out}. \)

5 NUMERICAL EVALUATION

In this section, numerical results obtained for the models proposed in Sections 3 and 4 are presented along with results obtained from stochastic PBSs. The default parameter values are listed in Table 1.

5.1 Particle Based Simulation

For PBS we adopted the simulator design in [21]. The simulator features three dimensional Brownian motion of type A and type B molecules. Both the first order reaction and the MR based reaction

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Please find further information and the Python implementation used for numerical evaluation on: https://www.maximilianschafer.org/publication/nanocom22/
Table 1: Parameter values for simulation.

| Parameter | Default Value | Description | Ref. |
|-----------|---------------|-------------|------|
| $D$       | $2.6 \times 10^{-7}$ m$^2$ s$^{-1}$ | Diffusion coefficient | [8] |
| $k_{A\rightarrow B}$ | $10^{-6}$ s$^{-1}$ | Reaction rate $A \rightarrow B$ | |
| $k_1$     | $3.21 \times 10^{-4}$ m$^3$ mol$^{-1}$ s$^{-1}$ | Reaction rate MR | [17] |
| $k_{-1}$  | $948$ s$^{-1}$ | Reaction rate MR | [17] |
| $k_2$     | $809$ s$^{-1}$ | Reaction rate MR | [17] |
| $k_{-2}$  | $631.41$ s$^{-1}$ | Reaction rate MR | [17] |
| $k_3$     | $3896$ s$^{-1}$ | Reaction rate MR | [17] |
| $k_{-3}$  | $4.46 \times 10^{-4}$ m$^3$ mol$^{-1}$ s$^{-1}$ | Reaction rate MR | [17] |
| $r_{in}$  | $80 \times 10^{-4}$ m | NP radius | [10] |
| $r_{out}$ | $1 \times 10^{-4}$ m | Radius of surrounding volume | |
| $d$       | $2 \times 10^{-3}$ m | Receiver radius | |
| $\rho_{\text{max}}$ | $2.7 \times 10^{-6}$ s$^{-1}$ | Maximum permeability | [6, 11] |
| $N_{\text{out}}$ | $1 \times 10^{16}$ | Number of molecules in the surrounding environment | |
| $T$       | $1 \times 10^{-3}$ s | Simulation time step | |

Figure 3: Top: Number of type A molecules $N_{\text{in}}^A$ and type B molecules $N_{\text{in}}^B$ inside the Tx over time for different reaction rates $k_{AB}$. Bottom: Membrane switching pattern.

inside the NP are implemented using the methods in [4, 19]. The propagation of molecules through the permeable membrane is realized by exploiting the concept for partial transmission presented in [3, Sec. 4.5]. Due to the large number of molecules $N_{\text{in}}^A = 10^{16}$ in the environment, it is not feasible to track the position of all molecules. Therefore, the PBS only considers the molecules entering the NP during the simulation time by realizing the influx of molecules into the NP by a Monte Carlo simulation. In particular, the number of molecules entering the NP per time step follows a Binomial distribution with the time-dependent mean value $\rho(t) | V_{\text{in}}^A, N_{\text{out}}^A, N_{\text{in}}^A T$.

5.2 Evaluation of the Idealized Tx Realization

In this section, we investigate the idealized Tx model described in Section 3. The idealized model has several parameters to influence the reloading and release mechanism, i.e., the reaction rate $k_{AB}$, membrane switching times $t_s$ and $\rho_{\text{max}}$. However, in this paper, we only vary the reaction rate $k_{AB}$ and keep the switching times $t_s$ and permeability $\rho_{\text{max}}$ fixed. For comparability, the default reaction rate $k_{AB} = 10^{-6}$ s$^{-1}$ is chosen to produce approximately the same amount of signaling molecules per second as the practical Tx model.

Reloading Mechanism. The top of Fig. 3 shows the amount of type A (blue curves) and type B molecules (red curves) inside the Tx for different reaction rates $k_{AB}$ for the membrane switching pattern shown at the bottom with $t_s \in \{0, 5\}$ s. We observe that the number of type A molecules $N_{\text{in}}^A$ increases during the open phase of the membrane and molecules can diffuse into the Tx from the environment. When the membrane is closed ($\rho = 0$), $N_{\text{in}}^A$ decreases because no molecules enter the Tx and the harvested type A molecules are converted into type B molecules. Next, we investigate the production of type B molecules and the impact of reaction rate $k_{AB}$. The red curves in Fig. 3 show the amount of type B molecules $N_{\text{in}}^B$ inside the Tx for different reaction rates $k_{AB}$. We observe, that the number of type B molecules $N_{\text{in}}^B$ produced per second increases for increasing $k_{AB}$ because the probability that a harvested type A molecule is converted into a type B molecule increases. For $k_{AB} = 10^{-2}$ s$^{-1}$ (dashed line) and $k_{AB} = 10^{-1}$ s$^{-1}$ (solid lines), $N_{\text{in}}^B$ increases faster than $N_{\text{in}}^A$ during the open phase. This behavior can be explained by inspecting (6): For a small reaction rate $k_{AB}$, the influx of type A molecules (first term on the left hand side of (6)) is larger than the amount of type A molecules converted into type B molecules (second term on the right hand side of (6)). Next, we observe that the $N_{\text{in}}^A$ saturates around $t = 2s$, while $N_{\text{in}}^B$ increases linearly for $k_{AB} = 1$ s$^{-1}$ (dotted lines). In this case, the production of type B molecules and the harvesting of type A molecules reaches an equilibrium, i.e., for $t > 2$, $N_{\text{in}}^A$ does not increase further because all type A molecules entering the Tx are converted into type B molecules. Finally, we observe that only for $k_{AB} = 1$ s$^{-1}$, the reaction is fast enough to convert all harvested type A molecules into type B molecules during the closed phase.

Multiple Switching Phases and Reception. Now, we consider multiple switching intervals to investigate repeated reloading phases and molecule releases. The top plot of Fig. 4 shows the reloading of type A molecules $N_{\text{in}}^A$ and the production of signaling molecules $N_{\text{in}}^B$ for two different reaction rates $k_{AB}$. The center plot shows the accumulated number of signaling molecules released from the Tx, $N_{\text{in}}^B$, and the accumulated number of signaling molecules absorbed by the Rx, $N_{\text{RX}}^B$. The bottom plot of Fig. 4 shows the membrane switching pattern for $t_s \in \{0, 5, 10, 15, 20, 25\}$ s. First, we observe that the behavior of the individual reloading processes is similar to that observed in Fig. 3. Next, we observe from the top plot of Fig. 4 that the number of type B molecules $N_{\text{in}}^B$ inside the Tx increases over the switching intervals. This effect has two reasons. First, due to the small permeability $\rho_{\text{max}}$ the amount of released type B molecules $N_{\text{out}}^B$ is smaller than the amount of type B molecules produced (see (7)). Second, the maximum capacity of the Tx, which is around $N_{\text{max}} = C_{\text{out}} V_{\text{in}}^A N_A \approx 5 \times 10^7$, is not reached for the considered switching pattern. Each opening of the NP membrane not only starts a reloading process but also triggers a controlled release of signaling molecules from the Tx.
To investigate the signaling properties, the center plot of Fig. 4 shows the amount of type B molecules released from the Tx $N_{B_{RX}}$ (red curves) and received by the Rx $N_{B_{RX}}$ (black curves). First, we observe that the individual releases of type B molecules from the Tx are clearly distinguishable (red curves). This clear differentiation between individual releases is due to the instantaneous switching of the Tx membrane which immediately starts and stops the molecule transport when the membrane opens and closes. This leads to a clearly distinguishable reception of the individual releases at the Rx (black curves). Moreover, we observe from Fig. 4 that the amount of released $N_{B_{out}}$ and received molecules $N_{B_{RX}}$ increases for an increasing reaction rate $k_{AB}$. This effect is directly related to the rate dependent production of type B signaling molecules inside the Tx as previously discussed, cf. Fig. 3. Finally, we note that all results obtained with our model and the results from PBS match very well.

### 5.3 Evaluation of the Practical Tx Realization

In this section, we investigate the practical realization of the proposed Tx model described in Section 4. The practical model has two parameters to influence the reloading and release mechanism, i.e., the membrane switching times $t_s$ and the number of encapsulated enzymes $N_{MR}$. The permeability $\rho_{max}$ in the open state cannot be influenced as it depends on the practical components, e.g., the polymers, used for NP fabrication, see Section 4.1 and [10, 12]. For the considered NP, the membrane permeability is controlled by the pH-value of $S_{out}$, cf. Section 4.1. In the following, we assume that the pH in $S_{out}$ can be controlled perfectly, and therefore, we express different switching patterns in terms of the permeability $\rho(t)$.

**Reloading Mechanism.** First, we investigate the signaling molecule production facilitated by MR, and therefore, we employ the instantaneous switching pattern from Fig. 3. Fig. 5 shows the amount of (R)man (blue curves) and (S)man molecules (red curves) inside the Tx for different number of encapsulated enzyme $N_{MR}$. The permeability $\rho_{max}$ in the open state cannot be influenced as it depends on the practical components, e.g., the polymers, used for NP fabrication, see Section 4.1 and [10, 12]. For the considered NP, the membrane permeability is controlled by the pH-value of $S_{out}$, cf. Section 4.1. In the following, we assume that the pH in $S_{out}$ can be controlled perfectly, and therefore, we express different switching patterns in terms of the permeability $\rho(t)$.

**Multiple Switching Phases and Reception.** Similar to the idealized realization, we now consider multiple switching intervals. The top plot of Fig. 6 shows the number of (R)man and (S)man molecules inside the Tx. The center plot shows the accumulated number of (S)man molecules released from the Tx, $N_{S_{RX}}$, and the accumulated number of (S)man molecules absorbed at the Rx, $N_{S_{RX}}$. In order to make these results comparable to those from Fig. 4, we applied the same instantaneous switching pattern (see bottom plot of Fig. 6). First, we observe that behavior of each individual switching process is similar to that observed in Fig. 5. In particular, whenever the Tx membrane is closed an equilibrium is reached between (R)man and (S)man. Next, we observe that the individual releases of signaling (S)man molecules $N_{S_{out}}$ are clearly distinguishable. Similar to the idealized Tx model, this effect is due to the instantaneous membrane switching pattern. Moreover, we observe that the amount of molecules released from the Tx $N_{S_{in}}$ and received by the Rx $N_{S_{RX}}$ in each opening phase of the Tx membrane is approximately half as large as the amount released by the idealized Tx, see Fig. 4. This observation is consistent with the results shown in Fig. 5. In particular, MR does not convert all harvested molecules into signaling molecules but pursues an equilibrium between (R)man and (S)man inside the Tx. Therefore, only half of the harvested molecules are available as signaling molecules. Finally, we observe that the number of encapsulated enzyme $N_{MR}$ only has minor influence on the number of released molecules, but it controls the time until the equilibrium is reached inside the Tx, see also Fig. 5. This is plausible, because increasing the number of enzymes increases the probability that a harvested molecule reacts, but does not influence the reaction rates nor the equilibrium, see (12). However, Fig. 6 shows that $N_{MR}$ is an important design parameter for the proposed Tx. In particular, increasing $N_{MR}$ decreases the time until the maximum number of signaling molecules is produced, and therefore, the duration of the closed phase between two transmission can be reduced. Finally, we note that the results obtained from the proposed model and the results obtained from PBS match very well.
we observe that the equilibrium inside the Tx is reached faster for

Influence of Non-Instantaneous Switching. Now, we investigate the impact of a non-instantaneous membrane switching pattern \( \rho_{\text{dis}}(t) \) for the practical NP described in Section 4. Therefore, we compare two switching patterns in the following. An idealized instantaneous switching pattern \( \rho_{\text{in}} \) with \( t_s \in \{0, 55, 110, 165\} \text{s} \) and a realistic switching pattern \( \rho_{\text{dis}} \) where each membrane switch from open to close and vice versa is distributed over \( t_{\text{dis}} = 45\text{s} \) (see bottom of Fig. 7). The resulting long simulation durations for realistic switching durations makes the usage of PBS infeasible. Instead, we rely on the results of our proposed model as it can handle longer time sequences and we have shown in the previous sections that it matches the results from PBS very well. Fig. 7 shows the number of (R)man and (S)man molecules inside the Tx (top) and the number of molecules released from the Tx and received at the Rx (center). First, we observe that the total number of molecules inside the Tx, released from the Tx, and received by the Rx increased significantly due to the long switching intervals. Next, we observe that the equilibrium inside the Tx is reached faster for the instantaneous switching pattern \( \rho_{\text{in}} \) than for the practical \( \rho_{\text{dis}} \). Comparing the number of received molecules \( N_{\text{Rx}} \) for \( \rho_{\text{dis}} \) (solid lines) and the instantaneous \( \rho_{\text{in}} \) (dashed lines), we observe that the individual releases of signaling molecules from the Tx are no longer clearly distinguishable for the practical pattern \( \rho_{\text{dis}} \). This effect is expected, because \( \rho_{\text{dis}} \) also spreads the release of molecules from the Tx over the switching intervals, i.e., the number of released molecules per second increases with increasing permeability. In contrast, for the instantaneous pattern \( \rho_{\text{in}} \) the molecule release starts and stops immediately. These results reveal that the non-instantaneous switching of the practical Tx model has a significant influence on the received number of molecules. The resulting implication for the design of suitable detectors is left for future work.

6 CONCLUSIONS

In this paper, we proposed a novel Tx model for MC based on functionalized NPs, which overcomes common assumptions of existing Tx models. We presented a general mathematical model and specialized the system to a realization relying on idealized assumptions and a practical realization. In our numerical evaluation, we investigated the signaling molecule production mechanisms and the influence of multiple, (non-)instantaneous membrane switching cycles. By comparison to PBS, we confirmed the validity of our models.

The results of this paper are a first step towards the development of more practical Tx models for MC. Interesting topics for future work include a more detailed investigation of all design parameters for both the idealized and the practical realization of the proposed Tx model, the evaluation of the communication theoretical measures, e.g., the bit error rate, and the development of an experimental testbed to validate the proposed models with experimental data.

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