Channel Clearance by Perfectly Absorbing Boundaries in Synaptic Molecular Communications

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ABSTRACT Molecular reuptake is a nature-inspired channel clearance strategy to mitigate intersymbol interference (ISI) in molecular communications. Reuptake is especially important if the communication medium is not cleared of the information-carrying molecules by other means, and if it is not done properly, it decreases the maximum signal rate. In a more practical sense, in nature, reuptake failure may be detrimental to the organisms. Many neurological disorders, including schizophrenia, are related to problems with the reuptake mechanisms in synaptic molecular communications (SMC). To understand the evolutionary solution to the ISI, we start with the glutamate reuptake process as part of SMC. We develop a stochastic approach to the reuptake problem and derive analytic expressions for the probability of absorption for rectangular volumes. To test the validity of perfectly absorbing boundary approximation for real systems, we derive the rate of first incidence and average glutamate transport time for EAAT2, the most prevalent transport molecule. When applied to SMC, our results indicate that perfectly absorbing boundaries assumption is not possible according to the available physiological data, due to the limited number of transporters and the finite amount of time a transporter requires to reuptake a glutamate molecule.

INDEX TERMS Molecular communication, synaptic communication, intersymbol interference, channel clearance, molecular reuptake.

I. INTRODUCTION

Molecular communications (MC) is a paradigm, where as the name suggests, information is encoded into molecules. MC is the innate mode of communication in nature. It is used very robustly in a myriad of applications, from short-range effective synaptic molecular communications (SMC) to long-range pheromones, from fast-acting hormones to timeless DNAs, which have been communicating our genetic code through history. Hence, the research on MC not only offers us a better understanding of the communications in nature but also helps us develop tools to be part of the ongoing conversation in nature.

MC has been studied extensively in the last decade. MC transmitters and receivers are theorised [1], [2], [3], [4], [5], [6], designed and tested. These studies reveal that intersymbol interference (ISI) is one of the bottlenecks of MC. Concurrently, ISI mitigation attracts the attention of many researchers working in MC [7], [8], [9]. Compared to the well-studied electromagnetic waves, molecules behave more unpredictably. Overlapping of symbols might be both from the past symbols and the future symbols. ISI due to future symbols occurs when a fast-moving fraction of molecules reach the receiver before their timeslot [10]. Similarly, slow-moving ones might stay in the medium much longer than necessary to convey the encoded information on them. Some extra slow molecules, which we denote as stray molecules might even accidentally trigger the MC receiver out of their timeslot, resulting in a false activation.

Another shortcoming of the MC studies is the modeling of the channel clearance mechanisms, i.e., reuptake. They usually assume perfectly absorbing or perfectly reflecting
Boundaries of the synaptic cleft. The neural connections to the pre-synaptic and post-synaptic terminals are not shown. The figure is not to scale as cleft width, i.e., $d$ is much smaller than the cleft base length, $2c$.

**FIGURE 1.** Boundaries of the synaptic cleft. The neural connections to the pre-synaptic and post-synaptic terminals are not shown. The figure is not to scale as cleft width, i.e., $d$ is much smaller than the cleft base length, $2c$.

boundaries, i.e., full reuptake or no reuptake at all [11], [12], [13], [14], [15]. Alternatively, to mitigate the reuptake problem, some MC experimental setups include a constant flow in their design. The constant flow itself is a nature-inspired solution for MC in an open medium. For example, hormones in the bloodstream and pheromones in the air use this mechanism to clear the channel.

SMC is the broad term used for many forms of molecular communication among neurons. In this work, we exclusively focus on glutamatergic chemical synapses. SMC in a glutamatergic chemical synapse starts with the release of glutamate molecules from the pre-synaptic terminal into the synaptic cleft, which is enveloped by peri-synaptic cells, i.e., glia. Glutamate molecules target their designated receptors, most commonly AMPA and NMDA receptors, located on the post-synaptic terminal. After the transmission, glutamate molecules are reuptaken by transport molecules, EAAT2, primarily expressed in peri-synaptic cells, being the most common one. Fig. 1 depicts the main parts of SMC.

Evident from Fig. 1, SMC happens in a completely bounded volume without any flow, rendering one of the most used solutions towards ISI in MC useless.

Perfectly absorbing boundaries and first incidence rates, for MC, have recently received greater attention. The existing works either assume infinite dimensions [16], [17] or study one-sided absorption in 2D [18]. However, solutions for infinite dimensions cannot be extended to finite dimensions, and the problem of one-sided absorption is a subset of the absorption problem from both ends.

Molecular reuptake, known as glutamate reuptake for glutamatergic synapses, is investigated within an MC framework before. However, in these works, problems with the glutamate reuptake are usually considered as part of the synaptic noise. A work similarly focusing on SMC as a basis for MC solves the reuptake problem through incident flux [19]. While our results are in correlation with the results given in [19], for perfectly absorbing boundaries, our approach is much more robust and easily adaptable to any cuboid volume. Contrary to the previous studies in the literature, in this work, we use a stochastic approach to the molecular reuptake problem. Accordingly, our results provide both the molecular concentration and the probability of outliers, i.e., the probability of a few stray molecules remaining in the cleft. Note that since perfectly absorbing boundaries perform the fastest reuptake, the probabilities we obtain for the stray molecules are the limiting probabilities. Thus, we present an upper limit on the channel clearance rate. Our results are aligned with the hypothesis that glutamatergic receptors, NMDA and AMPA, require two glutamate molecules instead of one for full activation, to reduce the probability of false activation.

While we exclusively focus on the contribution of peri-synaptic cells, i.e., glia, for the glutamate reuptake, our analysis can easily be extended to include the reuptake from pre-synaptic and post-synaptic terminals, or to reuptake of any molecule in any isotropic medium enclosed with rectangular surfaces.

In this work, we use SMC as a starting point. However, similar approaches can be used in any MC setup with closed, perfectly absorbing boundaries.

Our conclusions challenge the widely used perfectly absorbing boundary assumption in MC. Moreover, our analytical results for the channel clearance rates are essential for the design and implementation of MC setups without any reuptake mechanisms.

The main contributions of our work are as follows:

- Analytic solution to the stray molecule concentration for perfectly absorbing boundaries,
- Analytical solution to the rate of the first incidence, i.e., the rate at which released molecules reach a boundary for the first time,
- Average glutamate transport time for EAAT2,
- Discussion of the MC assumptions,
- Discussion of the evolutionary process leading to glutamatergic receptors.

We verify the important end results of our work with Monte Carlo simulations. We use Python 3.10 as our simulation environment and use the Python random module to create pseudo-random numbers for our simulations.

The rest of this paper is organised as follows. In Sec. II, we outline the general mechanisms of the glutamate reuptake. We present the numerical values pertaining to transport molecules in Sec. III. We calculate the stray glutamate concentration with perfectly absorbing boundaries, in Sec. IV-A. We present our numerical results and provide the ISI discussion in Sec. V. We discuss the general assumptions on perfectly absorbing boundaries, both for SMC and MC, in general in Sec. VI. Sec. VII is the conclusion.
II. GLUTAMATE REUPTAKE IN SYNAPTIC COMMUNICATION

SMC uses several information-carrying molecules, including glutamate, which accounts for 99% of the SMC. After the information is transmitted, these molecules are cleared from the synaptic cleft by transport molecules to prepare the cleft for the next transmission. Glutamate reuptake proteins are also known as Excitatory Amino Acid Transporters or EAAT. Five such proteins are responsible for glutamate removal in the human nervous system. EAAT 1-2 are predominantly expressed in PeS cells [20]. EAAT 3-4 occur mostly in neurons [21], [22]. EAAT 5 is observed in retina tissue.

The removal of glutamate molecules from the cleft by EAATs prevents false activation in healthy neurons. However, in case there is a problem with the glutamate reuptake, stray glutamate molecules can lead to unintended neuronal activity in the post-synaptic (PoS) terminal. Constant neuronal activity due to glutamate removal failure, known as excitotoxicity, may damage the neurons, or even lead to neuron death [23]. Intermittent failures in glutamate removal may either lead to a false activation of the PoS neuron or reduce the transmission period [24], [25]. Furthermore, some neurological disorders implicate glutamate reuptake failures [26]. Regardless of the outcome, a large concentration of stray glutamate molecules is undesired.

Glutamate reuptake is a complex procedure involving many different proteins employed by various mechanisms. The majority of the reuptake occurs in peri-synaptic (PeS), i.e., glial, cells. The absorbed glutamate molecules are either transferred to the pre-synaptic (PrS) neuron for reuse or metabolised. Reuptake also occurs in PrS neurons, where glutamate molecules are reused in vesicles. Finally, reuptake may occur in the PoS neuron, where glutamate molecules are either transferred to the PoS cells for processing or metabolised directly.

Many factors influence the glutamate reuptake rate, including the size of the synapse [27]. This is in accord with our current understanding of the reuptake mechanisms. The distance to the reuptake locations plays an important role since reuptake occurs mostly through the peri-synaptic cells.

The role of glutamate reuptake in the synaptic transmission has been studied before. Earlier studies consider glutamate reuptake as part of the synaptic noise [28], while there are recently emerging papers that are dedicated to the glutamate reuptake [19], [29]. While there are few experiments, the reuptake rate of change of glutamate concentration within the cleft is relatively constant [30]. Since glutamate reuptake is a slow process [31], blocking all transport molecules does not significantly impact the current transmission [32]. However, the spillover to neighbouring synaptic clefts is possible. Still, the probability of excitation of glutamatergic receptors due to the random spillover of glutamate molecules is assumed to be too small for detection [33].

There is a lack of data on the contribution of the PrS, PoS neurons and PeS cells in the glutamate reuptake. We can make good approximations if the number of transport molecules on each of these cells is known. However, the existing data is not only insufficient but also incompatible. Some of the existing values are in transporters per volume [35], some are transporters per area [36], some are the number of transporters in a certain synapse type and some are percentages [35]. The results might also show variations depending on the whether EAATs [35], [36], [37] or the mRNAs associated with EAAT production are being measured [38].

One method to alleviate the lack of data is to start with sources giving the exact numbers and then work our way through studies giving densities and comparative numbers, as done in [39]. Although this method accumulates errors in the literature, we still obtain some approximate numbers on the transport molecules. Another method is to find the limiting performance values, i.e., extrapolating the existing information to obtain the worst or best-case performance. In this work, we choose the latter.

The most cited values for EAAT1 and EAAT2 densities are 2300 EAAT1 and 8500 EAAT2 per $\mu$m$^2$ in adult rat hippocampus and 4700 EAAT1 and 7740 EAAT2 per $\mu$m$^2$ in cerebellar molecular layer [36]. We use these values as starting points in our analysis.

III. EAAT KINEMATICS

In Sec. II, we qualitatively describe the glutamate reuptake process, briefly explain how EAAT prevalence values are measured and state the numerical values we use in our simulations. In this section, we dive into the kinematic model of the glutamate reuptake.

For a simple perfectly absorbing boundary model, the kinetics of the EAAT2 glutamate transport is not needed. However, the validity of the perfectly absorbing boundary model depends on the kinetics of the EAAT2 glutamate transport. We use EAAT2 kinetics because of their availability and assume that EAAT1 cannot perform better than EAAT2, giving us the best possible reuptake performance. While there is no direct evidence that EAAT2 individually outperforms EAAT1, several works suggest that EAAT2 is responsible for 90% of the glutamate reuptake [37], [40], [41]. That is also the reason our current work exclusively focuses on reuptake from PeS, i.e., due to the extremely high prevalence of EAAT2 in PeS compared to PrS or PoS terminals.

EAAT2 kinetic model is a 15-state Markov process including all transformations of EAAT2 [34]. This model is depicted in Fig. 2. $To$ stands for the EAAT2 ready to react out of the cell and $Ti$ to react in the cell. Despite the seemingly complicated model, 12 states are needed for three Na$^+$, one H$^+$, one K$^+$ and one glutamate binding and unbinding and two states are used to denote movements into and out of the cell. The fifteenth state describes the invariability in the order of binding for H$^+$ and glutamate.

We present the transition rates of EAAT2 as described in [34] in Table 1. Note that the forward and backward rates are defined with the convention that clockwise transitions are
Figure 2. EAAT2 kinetic model, including the state transition rates as given in [34].

Table 1. State transition probabilities for EAAT2 as given in [34].

| Initial State | Final State | Forward Rate | Unit | Backward Rate | Unit | Binding Ion |
|---------------|-------------|--------------|------|---------------|------|-------------|
| To            | ToNa        | 1 × 10^4     | M⁻¹s⁻¹ | 1 × 10^2      | s⁻¹  | Na⁺         |
| ToNa          | ToNa₂       | 1 × 10^4     | M⁻¹s⁻¹ | 5 × 10^2      | s⁻¹  | Na⁺         |
| ToNa₂         | ToNa₂G      | 6 × 10^6     | M⁻¹s⁻¹ | 500          | s⁻¹  | Glu         |
| ToNa₂         | ToNa₂H      | 6 × 10^6     | M⁻¹s⁻¹ | 700          | s⁻¹  | H⁺          |
| ToNa₂G        | ToNa₂GH     | 6 × 10^11    | M⁻¹s⁻¹ | 700          | s⁻¹  | H⁺          |
| ToNa₂H        | ToNa₂GH     | 6 × 10^6     | M⁻¹s⁻¹ | 500          | s⁻¹  | Glu         |
| ToNa₂GH       | ToNa₂GH     | 1 × 10^4     | M⁻¹s⁻¹ | 1 × 10^3      | s⁻¹  | Na⁺         |
| ToNa₂GH       | TiNa₂GH     | 2000         | s⁻¹   | 1900         | s⁻¹  |
| TiNa₂GH       | TiNa₂GH     | 1000         | s⁻¹   | 4 × 10^4      | M⁻¹s⁻¹ | Na⁺ |
| TiNa₂GH       | TiNa₂G      | 3000         | s⁻¹   | 9 × 10^10     | M⁻¹s⁻¹ | H⁺ |
| TiNa₂G        | TiNa₂      | 3000         | s⁻¹   | 1 × 10^5      | M⁻¹s⁻¹ |
| TiNa₂         | TiNa       | 1 × 10⁵      | s⁻¹   | 2 × 10⁷       | M⁻¹s⁻¹ | Na⁺ |
| TiNa          | Ti         | 1 × 10⁵      | s⁻¹   | 1 × 10⁸       | M⁻¹s⁻¹ | Na⁺ |
| Ti            | TiK        | 1 × 10⁶      | M⁻¹s⁻¹ | 1000         | s⁻¹  | K⁺          |
| TiK           | ToK        | 40           | s⁻¹   | 10           | s⁻¹  |
| ToK           | To         | 2 × 10⁴      | s⁻¹   | 1 × 10⁶      | M⁻¹s⁻¹ | K⁺ |
| TiNa₂         | TiNa₂      | 1.4         | s⁻¹   | 0.01         | s⁻¹  |

desired, i.e., absorbs glutamate into the PeS, while anticlockwise transitions remove glutamate molecules out of the PeS into the synaptic cleft. The numerical values next to the state names in Table 1 are the assigned numbers to those stated to be used in numerical calculations. The “binding ion” is the ion whose concentration is important for the rate calculations, which has a unit of M⁻¹s⁻¹, i.e., it might bind in the forward or backward reaction.

IV. PERFECTLY ABSORBING BOUNDARIES

In this section, first, we derive an analytical expression for the probability of a glutamate molecule released at the center of the PrS terminal to be in the cleft at time \( t \). Then, we explore the possible uses of our approach in other problems in MC.

A. PERFECTLY ABSORBING PERISYNAPTIC BOUNDARIES

As we state in Sec. II and Sec. III, peri-synaptic cells surrounding the neuron, i.e., glial cells, do the heavy lifting in glutamate reuptake. Therefore, we start with the assumption that all glutamate molecules reaching the glial cells are absorbed. Until they are absorbed, the motion of glutamate molecules is approximated by Brownian Motion.

A common approach to calculate the expected number of molecules remaining in the channel with perfectly absorbing boundaries, \( V \), is to integrate the molecular concentration [42], [43], [44], [45]. Thus, the expected number of molecules becomes

\[
\mathbb{E}(N(t)) = \int_V \rho(\vec{r})d\vec{r},
\]

(1)

where \( \rho \) in 1D is given by

\[
\rho(\vec{r}) = \frac{1}{\sqrt{4\pi D t}} \exp\left(-\frac{-r^2}{4Dt}\right),
\]

(2)

where \( D \) is the diffusion constant.

However, there is a probability that although these molecules are within \( V \) at time \( t \), they might have crossed one of the boundaries and returned to \( V \) at a time \( t' < t \). Therefore, the simple approach outlined with (1) and (2)
overestimates the number of molecules within the boundaries and only works for infinite dimensions [46, 47].

Since any molecule reaching the lateral boundaries is absorbed, the number of glutamate molecules never reached the lateral boundaries of the synaptic cleft at time \( t \) gives the number of stray molecules at time \( t \).

Assume that \( S \) is a 1-D Brownian Motion with either -1 or 1 jump at each time interval. The probability of \( S \) hitting a one-sided boundary stationed at \( c > 0 \), within \( m \) time intervals is equal to

\[
Pr[T < m] = Pr[S_m > c] + \int_{-\infty}^{-c} Pr[T < m | S_m = \xi]Pr[S_m = d\xi],
\]

where \( Pr[T < m] \) is the probability of hitting time being less than \( m \). The first term of (3) gives the probability that \( S \) is already outside the boundary at time step \( m \), i.e., hit the boundary at \( c \) at some \( T < m \). The second term gives the probability that \( S \) is within the boundary at time step \( m \) but exceeded \( c \) at one point \( T \in [0, m) \) and then crossed the boundary again. (3) is a very well-known result in the field of statistics [48], [49].

For a double-sided symmetric boundary of a region of length \( 2c \) with boundaries at \( \pm c \), starting with (3), we obtain

\[
Pr[T < m] = Pr[S_m > c] + Pr[S_m < c] + \int_{-c}^c Pr[T < m | S_m = \xi]Pr[S_m = d\xi],
\]

where the first and second terms are the probability that \( S \) is already outside the upper and lower boundaries respectively and the third term is the probability that \( S \) is within the boundaries at time step \( m \) but left one of the boundaries before \( m \). Since backtracking a Brownian Motion itself is a Brownian Motion, using the reflection principle, the probability of a particle hitting the lower boundary \( c \) and returning to the region \([−c, c]\) before time step \( m \) is equal to the particle reaching \([−3c, −c]\) region at time step \( m \), i.e.,

\[
P^m_l = Pr[S_m \in [−3c, −c]],
\]

where \( P^m_l \) is the probability of hitting the lower boundary before time step \( m \). Reflection principle for (5) is and the region to be integrated is visualised in Fig. 3. Note that, thanks to the symmetry, \( P^m_u = Pr[S_m \in [c, 3c]] \), where \( P^m_u \) is the probability of hitting the upper boundary before time step \( m \). Hence, we reach

\[
Pr[T < m] \approx P^m_u + P^m_l.
\]

By extending the reflection principle, we find that

\[
P^m_{lu} = Pr[S_m \in [−5c, −3c]],
\]

\[
P^m_{ul} = Pr[S_m \in [3c, 5c]],
\]

where \( P^m_{lu}(P^m_{ul}) \) is the probability of first hitting the lower(upper) and than the upper(lower) boundary. However, \( P^m_{lu} \) and \( P^m_{ul} \) are included both in \( P^m_u \) and in \( P^m_l \). As a result, (6) sums \( P^m_{lu} \) and \( P^m_{ul} \) twice, i.e., we need to subtract them to refine (6).

\[
Pr[T < m] \approx P^m_u + P^m_l - P^m_{lu} - P^m_{ul}.
\]

Since \( P^m_{lu} \) and \( P^m_{ul} \) are included both in \( P^m_u \) and \( P^m_l \), we need to continue this alternating summation indefinitely. To generalise, probability of hitting \( i \) opposite boundaries is calculated as

\[
P^m_{l_1 \ldots l_i \ldots u} = Pr[S_m \in [(−2i + 1)c, −(2i − 1)c]].
\]

Hence, (4) becomes

\[
Pr[T < m] = \sum_{i=-\infty}^\infty (-1)^{i+1} \times \left[ \Phi \left( \frac{(2i + 1)c}{\sqrt{m}} \right) - \Phi \left( \frac{(2i - 1)c}{\sqrt{m}} \right) \right]
\]

where \( \Phi(x) \) is the standard normal cumulative probability distribution and expressed as

\[
\Phi(x) = \frac{1}{2} \left[ 1 + \text{erf} \left( \frac{x}{\sqrt{2}} \right) \right].
\]

To move from \( S \) to modelling molecular dispersion with Brownian motion, we need to express \( D \) and \( t \) in terms of \( m \). Since \( m \) is the number of time steps, \( t \) is defined as

\[
m \rightarrow \frac{t}{\Delta t}.
\]
Similarly, $D$ is defined by the Einstein-Smoluchowski equation and is equal to
\[ D = \frac{l^2}{2\Delta t} = \frac{1}{2\Delta t}. \] (14)
due to the jump length, $l$ being 1. Hence,
\[ c \to \frac{c}{\sqrt{2D\Delta t}}. \] (15)
Substituting (15) and (13) into (11), we reach
\[ Pr\{T < t\} = \sum_{i=-\infty}^{\infty} (-1)^{i+1} \times \left[ \Phi\left(\frac{(2i+1)c}{\sqrt{2Dt}}\right) - \Phi\left(\frac{(2i-1)c}{\sqrt{2Dt}}\right) \right]. \] (16)

where $Pr\{T > t\}$ is the probability that the particle hit a wall before time $t$. Thus, the probability that the particle is still in the system at time $t$ is
\[ Pr\{T > t\} = 1 - Pr\{T < t\}. \] (17)

A result remarkably similar to (17) is also obtained in [16] for infinite dimensions, i.e., $c = \infty$. However, since particles crossing the boundary located at the infinity cannot cross back to the volume of interest, the result in [16] is not directly applicable to finite boundaries.

Due to the isotropy of the medium and the independence of the dimensions, the probability of not hitting a wall in different directions is independent. Therefore, we use (16) separately for each dimension.

Not hitting any wall at time $t$ is therefore the product of the probability of not hitting a wall at time $t$, obtained in (16), in either direction. Thus, for a base of $2c \times 2c$, the probability of absorption is given by
\[ Pr_{2D}\{T < t\} = 1 - (1 - Pr\{T < t\})^2. \] (18)

We can easily extend (18) to rectangular bases. For a rectangular cleft base of $2c_1 \times 2c_2$, $Pr_{2D}$ becomes
\[ Pr_{2D}\{T < t\} = 1 - (1 - Pr_{c_1}\{T < t\})(1 - Pr_{c_2}\{T < t\}). \] (19)

where $Pr_{c}\{T < t\}$ is calculated by substituting $x$ for $c$ in (16). Similarly, we can extend (19) if all surfaces enclosing the cleft contribute to glutamate reuptake. For a cleft of size $2c_1 \times 2c_2 \times 2c_3$, the probability that the glutamate is still within the cleft is
\[ Pr_{3D}\{T < t\} = 1 - \prod_{i=1}^{3} (1 - Pr_{c_i}\{T < t\}). \] (20)

Fig. 4 shows the equivalence of absorption probability calculated by (18) and the 2D grid-free Brownian Motion generated through the Monte Carlo simulations as outlined in [50].

To find the probability of $n$ glutamate molecules remaining in the cleft at time $t$ out of the $N$ glutamate molecules released to the center of the cleft at time $t = 0$, we use binomial distribution, i.e.,
\[ Pr(N, n, t) = \binom{N}{n} [Pr\{T > t\}]^n [1 - Pr\{T > t\}]^{N-n}, \] (21)
where we used 1D $Pr()$. For 2D calculations, (21) works with $Pr_{2D}$, calculated through (18).

Since $N$ is a large number, usually around $10^4 - 10^5$, $\binom{N}{n}$ is also large. Logarithmic expression of (21) offers computational ease, i.e.,
\[ \ln(Pr(N, n, t)) = \ln \left[ \binom{N}{n} \right] + 2n \ln(Pr\{T > t\}) + (N-n) \ln(1 - Pr\{T > t\}). \] (22)

where \[ \log \binom{N}{n} \] is expressed through Stirling Approximation of the form
\[ \log(N!) = \frac{1}{2} \ln(2\pi N) + N \ln(N) - N + \ln \left( 1 + \frac{1}{12N} \right). \] (23)

B. EXTENSION TO OTHER MC APPLICATIONS

The equations we derive in Sec. IV-A are easily extendable to all rectangular volumes, as long as the medium is isotropic and each surface is either perfectly reflective or perfectly absorbing.

As a demonstration, we solve the one-sided boundary problem depicted in Fig. 5 using the same approach as (16). Instead of solving the boundary value problems as in [18], we realise that movements in the reflecting dimension do not contribute to absorption. Thus, the problem becomes a 1D Brownian Motion problem with $D_{1D} = D_{2D}/2$. We also know that two factors contribute to the one-sided absorption: molecular flux reaching the absorbing boundary before reaching the reflective boundary and molecular flux reaching
FIGURE 5. Equivalence of double-sided rectangular volume problem with single sided rectangular volume in 2D for \( c = 5, D = 4, \Delta t = 0.5 \) and \( t = 40 \). The movement is created by the same random seed. Blue movements are reflected over the \( x = 0 \) due to an odd number of reflections at the \( x = 0 \) boundary, while black movements are not reflected due to an even (or zero) number of reflections. The Brownian Motion step size, \( l = \sqrt{2D\Delta t} \), does not satisfy the Brownian Motion simulation requirement of \( l \ll c \). We deliberately kept \( l \) large for visualisation purposes.

By treating the two fluxes separately, we convert the one-sided absorption problem to a two-sided absorption problem. Adjusting (16) for the boundaries located at \(-3c\) and \( c\), we reach

\[
\Pr\{T < t\} = \sum_{i=-\infty}^{\infty} (-1)^{i+1} \times \left[ \Phi \left( \frac{(4i + 1)c}{\sqrt{2Dt}} \right) - \Phi \left( \frac{(4i - 3)c}{\sqrt{2Dt}} \right) \right].
\]

(24)

We can find the first incidence rate by taking the time derivative of (24) as well.

As we demonstrated with (24), we can modify our results to reflect any starting point for the molecule. Also, similar to (19), we can easily extend this approach to 3D as long as the medium is isotropic.

Our approach is especially valuable when the exact concentration within the volume is not needed or for large \( t \), for which we assume that concentration is relatively homogeneous within the volume.

V. NUMERICAL RESULTS

In Sec. IV-A, we derive an analytical expression for the number of glutamate molecules within the synaptic cleft. In this section, we display our numerical results.

We show the literature values of relevant variables in Table 2, from which we choose appropriate numerical parameters. Note that we use \( d = 40 \text{nm} \), twice the value of the accepted synaptic width, as a limiting value, i.e., worst-case performance. The cleft base area is usually the independent variable in our analysis, and we explicitly express the assumed value in each analysis.

![FIGURE 6. Finding concentration values through normal distribution simplification. The solid black lines are impenetrable walls while the dotted lines are for segmenting the forbidden region limited by the impenetrable walls. The left is the concentration plot of a molecule as if the boundaries are fully permeable, and the right is the folded concentration plot, according to (27).](image)

TABLE 2. Base parameters for numerical calculations and simulations.

| Variable                             | Value   | Unit  | Ref. |
|--------------------------------------|---------|-------|------|
| Diffusion Coefficient (\( D \))      | \( 0.46 \times 10^{-9} \) | \( \text{m}^2 \text{s}^{-1} \) | [51] |
| Cleft Width (\( d \))                | \( 20 \times 10^{-9} \)  | \( \text{m} \) | [52] |
| Cleft Base Area (\( (4c^3) \))      | \( 0.632 \times 10^{-12} \) | \( \text{m}^3 \) | [53, 54] |
| Quantal Size (\( N \))               | \( 4000 \) |       | [54, 55] |
| Na⁺ Cleft Concentration              | \( 0.15 \) | \( \text{M} \) | [56, 57] |
| Na⁺ Cell Concentration               | \( 0.015 \) | \( \text{M} \) | [56, 57] |
| K⁺ Cleft Concentration               | \( 0.004 \) | \( \text{M} \) | [57] |
| K⁺ Cell Concentration                | \( 0.14 \) | \( \text{M} \) | [57] |
| H⁺ Cleft Concentration               | \( 631 \times 10^{-9} \) | \( \text{M} \) | [58] |
| H⁺ Cell Concentration                | \( 562 \times 10^{-9} \) | \( \text{M} \) | [59] |
| Glu Cleft Concentration              | \( 1.32 \) | \( \text{M} \) |[
| Glu Cell Concentration               | \( 0.0013 \) | \( \text{M} \) | |

A. GLUTAMATE POPULATION WITHIN THE SYNAPTIC CLEFT

First, we compare the normal distribution simplification, as outlined with (1), (2), with the results we reach with (11), (18), (21). For a square cleft base with a side \( 2c \), (1) becomes

\[
\begin{align*}
\mathbb{E}(N(t)) &= \frac{1}{4\pi D t} \exp \left( -\frac{r^2}{4Dt} \right) d\vec{r} \\
&= \int_{-\infty}^{\infty} \int_{-c}^{c} \int_{-c}^{c} \frac{1}{(2\pi D t)^{3/2}} \exp \left( -\frac{x^2 + y^2 + z^2}{4Dt} \right) \, dx \, dy \, dz \\
&= \left[ \text{erf} \left( \frac{c}{\sqrt{4Dt}} \right) - \text{erf} \left( \frac{-c}{\sqrt{4Dt}} \right) \right]^2.
\end{align*}
\]

(25)

(26)

(27)

Fig. 6 illustrates how concentration values are calculated via the normal distribution simplification in 2D. Since molecules cannot penetrate the boundaries, the \( i^{th} \) segments for \( i \neq 0 \) are folded onto \( 0^{th} \) segment, i.e., the synaptic cleft
which constitutes the volume of interest for SMC. During this folding, odd-numbered segments are reflected over the boundaries due to the odd number of reflections, i.e., even-numbered segments are reflected twice and return to their original form. After the appropriate reflections of the segments, the concentration values of all segments are summed accordingly.

Fig. 7 gives the difference between the normal distribution simplification and perfectly absorbing PeS boundaries for the expected number of molecules within the cleft. Note that the cleft width is unimportant for this calculation and PrS and PoS terminals are perfect reflectors. As evident from the huge difference, any MC framework with absorbing boundaries calculating molecular concentration through normal distribution approximation grossly overestimates the concentration values.

As we describe in Sec. IV-A, absorbing boundaries do not let molecules move back to the volume of interest. However, if the perfectly absorbing boundaries are replaced with permeable boundaries or narrow holes, which allow movement of molecules back to the cleft, the overall concentration in the cleft increases at a given time. However, even in this case, (27) is an underperforming estimator for the molecular concentration. The reason for this underperforming behaviour is as follows. Since all concentration values from all segments are summed, the outgoing flux from the 0\textsuperscript{th} segment is equal to the flux crossing the \(x = 0\) line, whereas, the flux into the \(0\textsuperscript{th}\) segment cannot cross the impenetrable boundaries. As a result, the normal distribution simplification overestimates the concentration in the cleft and causes an abrupt concentration change across the \(x = 0\) boundary. Hence, even if the boundary is not absorbing, (27) overestimates the molecular concentration. We will offer a detailed look into the fully permeable boundaries problem in a future study.

B. CLEFT CLEARANCE RATE

Another important result for our work is the probability of full cleft clearance at time \(t\), which is given by (21) for \(n = 0\), as illustrated in Fig. 8.

One thing that immediately attracts our attention is that cleft clearance time is only loosely depend on the quantal size. The time it takes for the cleft to be completely clear of the previous transmission with a probability of 99.9\% is approximately 1.78 ms, 2.24 ms and 2.59 ms for a quantum of 30, 500 and 4000 respectively. In other words, clearing the channel from more than 100 fold more molecules increases the clearance time by merely 30\%. The relative independence of the channel clearance time from the quantal size is due to the assumption that all molecules reaching the boundaries are absorbed, regardless of their rate of incidence, i.e., reuptake mechanisms are never congested. Thus, increasing the quantal size only affects the probability of outlier molecules that are not incident on the PeS for a longer period. We discuss the biological requirements of the no congestion assumption in Sec. VI.

The implication of the loose dependence of cleft clearance rate and the quantal size is that intersymbol interference (ISI) cannot be successfully mitigated through modulating the quantal size. Since modulating the quantal size is ineffective to mitigate ISI, we hypothesize that the evolutionary process lead to the glutamatergic receptors requiring two glutamate molecules for activation.

Another implication of the relative independence of cleft clearance rate from the quantal size is that cleft clearance process of enclosed clefts with perfectly absorbing boundaries cannot be approximated as a linear system. The mathematical reasoning is that (21) is not a linear function. Thus, the impulse response of cleft clearance has very limited usefulness, especially to estimate the outlier behaviour.
Another way to examine ISI is to compare the probability of having two or more glutamate molecules in the cleft for a large quanta and having one glutamate molecule for a small quanta. Consider Fig. 9. The probability of having 1 glutamate out of a quanta of 30 is smaller than having 2 out of 4000 for all $t$. However, since glutamatergic receptors require 2 glutamate molecules for activation, the probability of having 2 glutamates in the vicinity of the same receptor is much smaller than having 1 glutamate in the vicinity of a receptor. This fact also supports our hypothesis that the 2-glutamate glutamatergic receptors act as an ISI mitigator for SMC.

VI. VALIDITY OF NO CONGESTION ASSUMPTION

No congestion assumption is a widely used assumption, both in MC and SMC domains. It implies that all molecules incident on the boundaries find a transporter to serve them [42], [43]. No congestion assumption is used not only for the models with perfectly absorbing boundaries but also for models with boundaries that absorb a constant percentage of the incident molecules [60]. This is due to the fact that in case of a congestion, the number of absorbed molecules cannot increase proportionally as the number of incident molecules increases, the number of available transport molecules has to be much greater than the number of incident molecules at all times.

To test the no congestion assumption, we need to calculate the rate of the first incidence of the glutamate molecules on the border and the average time the transporter spends to absorb a single molecule, i.e., the turnover time.

A. RATE OF THE FIRST INCIDENCE

With (18), we calculate the probability that a molecule is not incident on the perisynaptic boundary at time $t$. Since the difference between the probability of incidences at time $t$ and $t + \Delta t$ gives the number of incidences within $t \in [t, t + \Delta t]$, to compute the rate of incidence on the boundary, we first take the time derivative of (18), i.e.,

$$R(t) = 2 \left(1 - \text{Pr}(T < t)\right) \frac{d\text{Pr}(T < t)}{dt},$$  \hspace{1cm} (28)

where derivative of $\text{Pr}(T < t)$ is expressed as

$$\frac{d\text{Pr}(T < t)}{dt} = \sum_{i = -\infty}^{\infty} (-1)^{i+1} \left[\frac{(2i + 1)c}{\sqrt{4\pi Dt^3}} \exp\left(-\frac{(2i + 1)^2c^2}{4Dt}\right) - \frac{(2i - 1)c}{\sqrt{4\pi Dt^3}} \exp\left(-\frac{(2i - 1)^2c^2}{4Dt}\right)\right],$$  \hspace{1cm} (29)

where we used $D_{1D} = D_{3D}/3$. A very similar result for infinite $c$ is also obtained in [16], [17]. However, for finite $c$, this result gives the change in concentration, which is the difference between the rate of incidences from two sides of a boundary situated at $c$, rather than the rate of incidence from one side of the boundary. Therefore, [16] overstates the rate of first incidence for $c \neq \infty$.

We present the simulation results verifying (29) in Fig. 10. The Brownian Motion is created grid-free according to [50] and the behaviour of the particles hitting the upper and lower boundaries are modelled according to the rules of elastic collision. We clearly see that the simulation results are perfectly in line with the theoretical results.

Since (29) cannot be expressed in a more compact form, we could not obtain a close form expression. Accordingly, we plot the cleft area vs maximum incidence rate in Fig. 11. Note that the incidence rate is dominated by the short side of the cleft base. The cleft area, which is $4c^2$ for the square cleft, does not have a direct impact on the incidence rate. To show this, we use a rectangular base with a long side of $2c_1$ and a short side of $2c_2$, satisfying $2c_1 \times 2c_2 = 4c^2$, to keep the area constant. We observe that, more rectangular bases, i.e., bases with a higher $c_1/c_2$ ratio, have a higher incidence rate than square bases of the same area. Hence, we use the square cleft base as it provides the lowest incidence rate for a given cleft area.

Note that (29) provides the rate of first incidence rather than the rate of incidence. For a partially absorbing boundary, molecules incident on the boundary but reflected back to the cleft might coincide again on the boundary, thus increasing the incidence rate. Such molecules are not included in (29). As a result, (29) provides a loose lower bound for the actual incidence rate.

As evident from Fig. 11, the number of incident molecules shows huge variations depending on the synaptic size. However, for a typical synapse with a square cleft of 0.5 $\mu m^2$ area, the incidence rate is ~2500 per second per molecule in the quanta. For a large synapse of 1 $\mu m^2$ area, the incidence rate becomes ~1000 per second per molecule in the quanta. In other words, for a quantal size of 4000, the first incidence rate is easily on the order of $10^6$ s$^{-1}$. 

![FIGURE 9. Probability of having at least $k$ molecules out of a quanta size of $N$ in a cleft with an area of 0.5 $\mu m^2$.](image-url)
Let $G = \sum \lambda_i |\psi_i\rangle \langle \psi_i|$, be the eigendecomposition of $G$, where $\lambda_i$ is an eigenvector and $|\psi_i\rangle$ is the corresponding eigenvalue of $G$, written in *braket* notation. Then, the state probability distribution at time $t$ becomes

$$P(t) = e^{Gt} = \sum_i e^{\lambda_i t} |\psi_i\rangle \langle \psi_i|. \quad (31)$$

Note that EAAT2 operates during the repolarisation of PrS and PoS terminals. Therefore, none of the relevant ion concentrations is constant during the period of interest. Regardless, we can still choose ion concentrations that ensure the highest rate of intake, i.e., maximum(minimum) $Na^+$, $H^+$ and glutamate and minimum(maximum) $K^+$ concentration outside(inside) of the cell. Apart from the glutamate concentration, the concentration values satisfying the maximum intake rate are the resting potential values.

We present the ion concentrations outside (cleft) and inside of the cell in Table 2. We calculate $H^+$ concentrations using the pH values of the cleft and cells available in the literature. Glutamate cleft concentration is calculated for a quantal size of 4000 in a cleft of size 0.25 $\mu m^2$ and width of 20 nm. We choose these values to ensure high cleft concentration, i.e., the highest possible reuptake rate. The glutamate concentration in the PeS cells is not available in the literature, thus we assume it to be one-thousandth of the glutamate concentration in the cleft.

State probability distribution, $P(t)$, does not divulge much information about the rate of uptake. We are interested in the clockwise transitions according to the illustration given in Fig. 2. Therefore, among the three pathways crossing the cell membrane, we are only interested in the ToNa$_3$G to TiNa$_3$G transition for the reuptake operation. However, the reverse transition, i.e., from TiNa$_3$GH to ToNa$_3$GH, is also possible. To find the average time a glutamate molecule is absorbed, we need to find the net transition rate. Thus, we formulate state transition currents. Let $P_i(t)$ be the probability that EAAT2 is at state $i$ at time $t$, obtained through (31). Then, for a time discretisation of $\Delta t$, we can count the expected number of transitions from $i$ to $j$ from $t = 0$ to $t = \Delta t$ as

$$\omega_{ij}(t) = \lim_{\Delta t \to 0} \left[ \frac{1}{\Delta t} \int_0^{\Delta t} P_i(t') dt' \right] \int_0^{\Delta t} \exp(-T_{ij} t') dt'. \quad (32)$$

Qualitatively, the limit term of (32) is the number of $\Delta t$-long time periods EAAT2 spends at state $i$. The integration following the limit term is the probability that it jumps to $j$ within $\Delta t$.

$\omega_{ij}(t)$ is a dimensionless parameter, which counts the average number of transitions from $i$ to $j$ from $t = 0$ to $t = t$. However, due to the conservation of probability in the system, i.e., $\sum_i P_i(t) = 1 \forall t$, it obeys Kirchhoff’s current law, whence we prefer the term *current*.

We define the net state transition current from $i$ to $j$ as

$$\bar{\omega}_{ij}(t) = \omega_{ij}(t) - \omega_{ji}(t). \quad (34)$$
We verify (33) and (34) via Monte Carlo simulations and recursive methods. Recursive methods, unlike Monte Carlo methods, give exact results rather than approximations powered by large numbers. Thus, we use both of these approaches for verification.

In both methods, we use a time step, $\Delta t$ to convert the Markov process into a Markov chain. While Monte Carlo simulations are straightforward, we present the recursive algorithm we use to verify in Algorithm 1. Our simulation results are given in Fig. 12.

Here, we choose the transition from TiNa$_2$G to TiNa$_2$, to describe the absorption process. This transition corresponds to the transition from state 10 to state 11 in Algorithm 1, according to our numbering in Table 1. We choose this transition because it actually marks the separation of glutamate in the PeS cell, however we can use any clockwise state transition, or transitions if we choose a state with a connectivity higher than two.

In Algorithm 1, $W[p, r]$ gives the expected number of absorptions in exactly $p$ time steps if the current state is $r$. Since absorption only occurs during the transitions from 10 to 11, absorption within a single time step is possible only if the state is at 10. The expected number of absorption is equal to the 10-11 transition probability, $T_{10-11} \Delta t$. Then, we recursively calculate the number of expected absorptions, exactly within $i$ time steps for all possible states $j$. The final summation gives us $N_{10-11}^a$ the expected absorptions for $i \leq n$ starting at state $a$.

The release algorithm can be set similarly to the absorption algorithm, for 11 to 10 transitions. The expected net transitions, i.e., $N_{10-11}^a - N_{11-10}^a$ is the expected net number of glutamates transferred from the synaptic cleft into the PeS.

Net currents between states are zero when the system is in the steady state distribution, $\pi$, satisfying $\pi G = 0$.

Algorithm 1 Expected Number of Absorption Within the Next $n$ Time Steps, Starting at State $a$

1: Inputs: $n, a, \Delta t$
2: Initialise:
5: while $i \leq n$ do
8: end while
10: end while

\[ N_{10-11}^a = \sum_{k=0}^{n} W[k, a] \]

However, EAAT2 is never in its steady state distribution due to the constant changes in the ion concentrations. The discrepancy between the net reuptake obtained through recursive methods and (34) is the choice of the starting state, $a$ for the recursive methods, while (34) assumes the steady-state distribution, $\pi$. If $a$ is chosen as one of the Ti states rather than a To state, we expect a sharp decrease at the start, rather than a sharp increase as we see in Fig. 12. After the assigned initial state disperses through all states, i.e., the state distribution approaches $\pi$, recursive methods output becomes aligned with (34).

After verifying (34), we define $\tau_o$ as the time it takes for one net transition, i.e.,

\[ \tau_o \triangleq \lim_{t \to \infty} \frac{t}{W[10-11]} \]  

(35)

Fig. 13 depicts the definition of $\tau_o$, where we assume that EAAT2 starts at state 2, ToNa$_2$. However, for small $t$, the initial state has a huge impact on the result. To correct this, we can sum over the net transition currents for all possible
initial states with weights reflecting their prevalence and find $\tau_o$, as demonstrated on Fig. 13. Alternatively, we can take a large $t$ to filter out the transitory behaviour, as described in (35). We calculate $\tau_o = 76.94$ ms with (35). Our result is perfectly aligned with the experimentally measured reuptake rate of $\sim 14$ Hz, which indicates $\tau_o \sim 70$ ms [31], [61], and similar to other reported simulation results [62], [63].

C. DISCUSSION
Given the rate of incidence that we obtain in Sec. VI-A and the $\tau_o$ that we calculate in Sec. VI-B, it is clear that no congestion assumption is not valid.

For the given kinetic model of EAAT2, only to equate the available EAAT2 number with the incident glutamate count for a cleft area of 0.5 $\mu$m$^2$, we need 1700 EAAT2 per glutamate in the vesicle, so for a typical quantal size of 4000 glutamates, we need $\sim 7 \times 10^6$ EAAT2 around the cleft. For the EAAT2 density values given in Sec. II, a synaptic cleft with a square base of 0.5 $\mu$m$^2$ and a width of 40 nm has $\sim 900$ EAAT2 and $\sim 600$ EAAT1. Considering the assumption that EAAT2 is the more robust transporter, even if all transport molecules are EAAT2, this value is three orders lower than the necessary number of transport molecules for the available transporter number to be equal to the incident molecule number. Alternatively, $\tau_o$ should be around 60 $\mu$s for the available EAAT2 number to be equal to the incident glutamate count for the same cleft and quanta.

Since the number of available transporters at any instant cannot be higher than the incident glutamate molecules, no congestion assumption, which requires the number of available transporters to be much higher than the number of incident glutamate molecules cannot hold. As a result, we conclude that no congestion assumption is plainly wrong.

Note that we use the conditions creating the lowest rate of incidence in Sec. VI-A and the highest rate of absorption in Sec. VI-B. Even without considering the secondary and tertiary incidences and change in the ion concentration through the reuptake process, it is impossible that all incident molecules can be reuptaken.

Furthermore, even if the glutamate molecules queue behind each EAAT2 patiently to be processed, using the average processing time, $\tau_o = 77$ ms, it would take 510 ms to clear the cleft. 510 ms is far too long for synapses that operate faster than 2 Hz.

The implications of the failure of the no congestion assumption are as follows.

- Synaptic reuptake models assuming a certain percentage of the glutamate molecules are removed per incidence on the boundaries or per a fixed time period are wrong. It is very clear that within a fully encapsulated synaptic cleft, transport molecules are saturated, at least at the beginning of the synaptic transmission.

- The existing literature on the kinetic model and the number of EAAT2 on the PrS boundary might be underestimating the EAAT2 performance.

- The importance of the transport molecules on the PrS and PoS terminals may be understated.

Since we know that some experiments predict a relatively constant rate of change in the concentration [30], [54], we conclude that cleft models which encapsulate the cleft entirely might not be accurate. We believe that neurotransmitters operating within the active part of the synaptic cleft, also named apposition zone, spill out of this region to an outer volume through fully permeable boundaries [64]. This outer volume is connected to the active part through the sides of the apposition zone, each with an area of $2c \times d$, where $2c$ is the side length of the cleft base as described in Sec IV-A and $d$ is the cleft width. Since there is no physical absorption, these molecules might return to the apposition zone via the fully permeable boundaries. The transporters on the surface of this outer volume perform reuptake operation without being constrained by the transmission period, i.e., the cleft will be ready for the next transmission as long as glutamate molecules are not in the vicinity of the apposition region.

VII. CONCLUSION
In this work, we derived an analytical expression for the molecule concentration within a closed volume. We showed that the normal distribution assumption widely used in MC works in the literature overestimates the concentration within a closed volume.

We introduced state transition currents and obtain an analytical expression for the average reuptake time of EAAT2 for the first time in the literature.

We proved that cleft clearance in SMC with the numerical values for EAAT2 in the literature cannot be fast enough to achieve full cleft clearance for transmission rates above 2 Hz. These results challenge the common assumptions both in MC and SMC about channel clearance.

Our results offer approximate analytical expressions for the clearance rates of cuboid channels. Thus, with this work, we paved the way for the design and implementation of more realistic MC setups that do not require a constant flow.

Besides our mathematical contributions to the field, we also challenged the no congestion assumption, an implicit assumption used in many synaptic works. Our results indicate that unless the existing numerical values given in the literature are wrong, clearance of the fully encapsulated synaptic clefts should take a much longer time than the transmission period.

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