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Reduced model of neurotransmitter transport in the presence of generic receptors and transporters

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Abstract. We present a description of a reduction procedure for a model of glutamate transport in a synaptic cleft in the presence of a finite number of receptors and transporters with different kinetics properties. Under certain conditions a system of equations for glutamate, receptors and transporters concentrations can be substituted by a single equation for glutamate with effective diffusion and modified kinetics term. The results of model reduction are illustrated with an example showing good agreement between the behavior of the original model and the reduced model.

Keywords: model reduction, neurotransmitters, glutamate transport, synaptic cleft, effective diffusion, receptors, transporters

1. Introduction

We consider a general reduction procedure for a model of neurotransmitter transport in the presence of receptors and transporters. While the approach that we describe is applicable to a wide class of models of molecular transport in the presence of fast forward and reverse binding reactions, here we are mostly interested in a particular case related to glutamate transport.

Glutamate molecules are neurotransmitters that carry chemical signals between neurons through synaptic clefts, thin regions (≈ 20 nm) separating consecutive neurons. A certain number of glutamate molecules (≈ 3000) is released from a synaptic vesicle at the presynaptic boundary. These molecules diffuse through the cleft, activate receptors located at the postsynaptic neuron boundary, leading to the appearance of ionic currents through the postsynaptic neuron membrane. Also, glutamate is being removed from the cleft via transporters located at certain regions of the postsynaptic boundary, as well as via diffusion through the side boundaries of the synapse.

We consider a procedure that under certain conditions reduces the spatially 3-dimensional model of glutamate transport to a spatially 2-dimensional one. The ultimate goal of the analysis is to produce an adequate model for fast computation of glutamate concentration distributions (as a function of time and spatial variables) for various initial concentrations of glutamate released from the vesicles in the interior of the cleft as well as for various spatial distributions of receptors and transmitters at the postsynaptic boundary of the cleft. The resulting model will allow us to include in the computations any finite number of receptors and transmitters of different types.

Another goal in obtaining a reduced model is to produce an explicit expression for such a characteristic of glutamate transport as the effective diffusion that must change depending on
the local concentration of receptors and transporters. Analysis of various limiting cases using this expression will allow one to elucidate the effects of changing receptors and transporters concentration and positions on glutamate transport.

In this presentation we are only interested in characterizing the glutamate dynamics (and effects of receptor and transporter presence on this dynamics), and we are not going to address, e.g., the analysis of ionic currents produced by activated receptors, etc. Thus, here we are going to discuss the case of some generic (effective) receptors and transmitters with variable kinetics characteristics that affect glutamate transport properties. The derivation of more precise reduced models for some particular types of receptors and transmitters (for which the kinetic schemes are considerably more complex; see, e.g., Wadiche and Kavanaugh [11], Franks et al. [2], Larsson et al. [5]) will be performed in the near future and published elsewhere.

We note that recent numerical modeling of neurotransmitters transport (including modeling of glutamate in a synaptic cleft, with analysis of possible spill over of glutamate in the extra-synaptic regions) has attracted considerable attention (see, e.g., Rusakov and Kullman [7], Nielsen and DiGregorio [6]; for Monte Carlo simulation approaches see, e.g., Franks et al. [2], and Cogan et al. [1]). However, the reduction procedures for the models used in such numerical simulations are not addressed in the literature. Reduced models can help one to understand which parameters and parameter combinations in the system can be estimated from experiments, and which ones, in principle, cannot be estimated for given sensitivities of measuring devices.

Mathematical justifications of the procedures discussed in this paper can be performed using the methods of classical perturbation analysis (see, e.g., Vasil’eva et al. [10]), and they are not included in the current presentation.

2. Statement of the problem: geometry of the synaptic cleft region and assumptions

We initially represent the synaptic cleft as a cylindrical domain (e.g., in a Cartesian coordinate system): \((x, y) \in \Omega, 0 \leq z \leq h\). The height \(h\) of this domain is assumed to be much smaller compared to the characteristic length \(L\) of its base \(\Omega\): \(0 < h \ll L\). In what follows we will use this inequality to perform the original model simplification.

Let us formulate a set of assumptions:

(a) In the absence of receptors and transporters the diffusion coefficient for glutamate is the same (i.e., it is a constant) throughout the cleft region.

(b) When the glutamate molecules arrive at the side boundaries of the domain, \((x, y) \in \partial \Omega, 0 \leq z \leq h\), they are immediately washed out: this means that glutamate concentration at these boundaries is equal to zero (no glutamate molecules re-enter the region from outside).

(c) The receptors and transporters affect the glutamate molecules in a thin region near the postsynaptic boundary of the cleft. We denote the effective height of this near-boundary region by \(\delta\). Evidently, \(0 < \delta \ll h\).

(d) Presynaptic boundary is not permeable for glutamate molecules.

Certain additional assumptions related to glutamate binding and transport dynamics due to the presence of receptors and transporters will be specified later.

3. Statement of the problem: equations, initial and boundary conditions

The following model will correspond to the assumptions stated above.

In the interior of the cleft the glutamate concentration \(u(x, y, z, t)\) is described by the diffusion equation (\(D\) is diffusion coefficient):

\[
\frac{\partial u}{\partial t} = D \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right). \tag{1}
\]
The boundary conditions for \( u \) are formulated as follows:

\[
\begin{align*}
    u(x, y, z, t) &= 0 \quad \text{for} \quad (x, y) \in \partial \Omega, \quad 0 \leq z \leq h, \\
    \frac{\partial u}{\partial z}(x, y, h, t) &= 0 \quad \text{(impermeable presynaptic boundary)}; \\
    -D \frac{\partial u}{\partial z}(x, y, 0, t) &= \delta \frac{\partial u}{\partial t}(x, y, 0, t). 
\end{align*}
\]  

(receptors/transporters related dynamics at the post-synaptic boundary).

Here

\[
\frac{\partial u}{\partial t}(x, y, 0, t) = \sum_{i=1}^{n} f_i(u(x, y, 0, t), v_i, x, y) + \sum_{j=1}^{m} g_j(u(x, y, 0, t), w_j, x, y). 
\]  

(5)

For different receptor concentrations \( v_i \) \( (i = 1, \ldots, n) \), and different transporter concentrations \( w_j \) \( (j = 1, \ldots, m) \), we have the equations

\[
\begin{align*}
    \frac{\partial v_i}{\partial t}(x, y, t) &= f_i(u(x, y, 0, t), v_i, x, y), \quad (i = 1, \ldots, n), \\
    \frac{\partial w_j}{\partial t}(x, y, t) &= G_j(u(x, y, 0, t), w_j, x, y), \quad (j = 1, \ldots, m). 
\end{align*}
\]  

Equation (5) describes glutamate dynamics (forward/reverse binding, loss, etc.) in a thin layer (of effective depth \( \delta \)) near the postsynaptic boundary of the cleft due to the presence of receptors and transporters \( (f_i \text{ with } i = 1, \ldots, n \text{ describe the kinetics associated with } n \text{ different types of receptors, and } g_j \text{ with } j = 1, \ldots, m \text{ describe the kinetics associated with } m \text{ different types of transporters distributed over the postsynaptic boundary surface}).

A particular form of the right hand side of the boundary condition (4) at \( z = 0 \), which is proportional to the right hand side of (5), as well as the right hand sides of the equations (6), (7) for surface receptor concentration \( v_i \) and surface transporter concentration \( w_j \), respectively, will be specified later after additional assumptions on receptor and transporter kinetics are introduced. We note that in our model \( G_j \neq g_j \) (see discussion in Section 5 below).

The initial conditions have the form:

\[
\begin{align*}
    u(x, y, z, 0) &= U^*(x, y, z) \quad \text{(initial glutamate distribution in the cleft)}; \\
    v_i(x, y, 0) &= V_i^*(x, y) \quad (i = 1, \ldots, n) \\
    w_j(x, y, 0) &= W_j^*(x, y) \quad (j = 1, \ldots, m)
\end{align*}
\]  

(initial spatial distribution of receptors);

(initial spatial distribution of transporters).
4. Step 1 of model reduction: derivation of spatially 2-dimensional equation for glutamate concentration

Let us average the equation for glutamate concentration \( u \) over the height of the synaptic cleft. To do so we integrate both sides of the equation (1) with respect to \( z \) from 0 to \( h \), and divide the result by \( h \):

\[
\frac{\partial \bar{u}}{\partial t} = D \left( \frac{\partial^2 \bar{u}}{\partial x^2} + \frac{\partial^2 \bar{u}}{\partial y^2} + \frac{1}{h} \int_0^h \frac{\partial^2 u}{\partial z^2} dz \right)
\]

(11)

Here we use notation

\[
\bar{u}(x, y, t) = \frac{1}{h} \int_0^h u(x, y, z, t) dz
\]

(12)

for the values of \( u \) averaged over \( z \).

Substituting conditions (3) and (4) in the right hand side of (11), we obtain:

\[
\frac{\partial \bar{u}}{\partial t} = D \left( \frac{\partial^2 \bar{u}}{\partial x^2} + \frac{\partial^2 \bar{u}}{\partial y^2} \right) + \frac{\delta}{h} \frac{\partial u}{\partial z}(x, y, h, t) - \frac{1}{h} \frac{\partial u}{\partial z}(x, y, 0, t)
\]

(13)

where we also used relation (5).

From (12) it follows that

\[
\bar{u}(x, y, t) = \frac{1}{h} \int_0^h (u(x, y, 0, t) + \partial u/\partial z(x, y, 0, y) z + ...) dz
\]

(14)

Assuming that \( h \) is sufficiently small (compared to \( L \)), \( \partial u/\partial z(x, y, 0, t) \) is moderate, \( \delta/h \) is finite, \( f_i \), \( g_j \) are sufficiently smooth, and introducing the new notation

\[
\tilde{u}(x, y, t) = u(x, y, 0, t),
\]

(15)

we arrive at the approximate equation

\[
\frac{\partial \tilde{u}}{\partial t} = D \left( \frac{\partial^2 \tilde{u}}{\partial x^2} + \frac{\partial^2 \tilde{u}}{\partial y^2} \right) + \frac{\delta}{h} \left( \sum_{i=1}^n f_i(\tilde{u}, v_i, x, y) + \sum_{j=1}^m g_j(\tilde{u}, w_j, x, y) \right)
\]

(16)

It follows from (2) and (8) that we must solve (16), together with the system (6) and (7) for \( v_i (i = 1, \ldots, n) \) and \( w_j (j = 1, \ldots, m) \), with the following boundary and initial conditions for \( \tilde{u} \):
\( \ddot{u}(x, y, t) = 0 \) for \( (x, y) \in \partial \Omega, \)

\( \ddot{u}(x, y, 0) = \frac{1}{h} \int_0^h U^*(x, y, z) dz = \tilde{U}^*(x, y), \)

and initial conditions (9), (10) for \( v_i, w_j \), respectively.

### 5. Receptor and transporter kinetics

Let us use the notation \( U \) for a molecule of glutamate. We consider the following generic reaction scheme for \( i \)-th receptor:

\[
U + V_i \xrightarrow{k^+} C_i, \quad C_i \xrightarrow{k^-} U + V_i. \tag{19}
\]

Here \( V_i \) denotes the free \( i \)-th receptor, and \( C_i \) denotes the corresponding occupied receptor (in what follows we use the notation \( v_i \) and \( c_i \) for concentrations of \( V_i \) and \( C_i \), respectively); \( k_i^+ \) and \( k_i^- \) are the rate constants of the forward and reverse receptor binding reactions.

Also, we assume the following generic reaction kinetics for the \( j \)-th transporter:

\[
U + W_j \xrightarrow{K_j^+} E_j, \quad E_j \xrightarrow{\lambda_j} W_j + U_{\text{removed}}, \quad E_j \xrightarrow{K_j^-} U + W_j. \tag{20}
\]

Here \( W_j \) denotes the free \( j \)-th transporter, and \( E_j \) denotes the corresponding occupied transporter (in what follows we use the notation \( w_j \) and \( e_j \) for concentrations of \( W_j \) and \( E_j \), respectively); \( U_{\text{removed}} \) represents glutamate molecules that are removed from the cleft via transporters; \( K_j^+ \) and \( K_j^- \) are the rate constants of the forward and reverse transporter binding reactions; \( \lambda_j \) are the rate constants of glutamate removal reactions.

Using the Law of Mass Action, we write the equations (at the postsynaptic boundary) for \( v_i(x, y, t), c_i(x, y, t), w_j(x, y, t) \), and \( e_j(x, y, t) \):

\[
\frac{\partial v_i}{\partial t} = -k_i^+ \dot{u} v_i + k_i^- c_i; \tag{21}
\]

\[
\frac{\partial c_i}{\partial t} = +k_i^+ \dot{u} v_i - k_i^- c_i; \tag{22}
\]

\[
\frac{\partial w_j}{\partial t} = -K_j^+ \dot{w}_j + K_j^- e_j + \lambda_j e_j; \tag{23}
\]

\[
\frac{\partial e_j}{\partial t} = +K_j^+ \dot{w}_j - K_j^- e_j - \lambda_j e_j. \tag{24}
\]

Corresponding initial conditions describe the initial spatial distribution of \( v_i, c_i, w_j, \) and \( e_j \) at the postsynaptic boundary:

\[
v_i(x, y, 0) = V_i^*(x, y), \quad c_i(x, y, 0) = 0, \tag{25}
\]

\[
w_j(x, y, 0) = W_j^*(x, y), \quad e_j(x, y, 0) = 0. \tag{26}
\]

Equations (21), (22) with corresponding conditions from (25) can be used to eliminate \( c_i \):

\[
\frac{\partial v_i}{\partial t} = -k_i^+ \dot{u} v_i + k_i^- (V_i^*(x, y) - v_i) := f_i(\dot{u}, v_i, x, y). \tag{27}
\]
Similarly, equations (23), (24) with corresponding conditions from (26) can be used to eliminate $e_j$:

$$\frac{\partial w_j}{\partial t} = -K_j^+ \tilde{u} w_j + K_j^- (W_j^*(x, y) - w_j) + \lambda_j (W_j^*(x, y) - w_j)$$

(28)

We note that the functions $f_i$ and $g_j$ defined in (27) and (28), respectively, are exactly the ones that enter (5) (and thus, equation (16) for $\tilde{u}$) and (6), the functions $G_j$ are the ones that enter (7).

So, now our model consists of a quasi-linear parabolic equation (16), with conditions (17), (18), and equations (27), (28), with conditions (9), (10).

6. Step 2 of model reduction: making use of fast receptor and transporter kinetics

Let us make additional assumptions related to receptor and transporter kinetics that will allow us to further simplify the model. First, we assume that

(c) distributions of various types of receptors and transporters at the postsynaptic boundary are uniform (i.e., $V_i^*(x, y) = V_i^{*\text{const}}$ and $W_j^*(x, y) = W_j^{*\text{const}}$). This assumption is only needed to clarify the relations between various characteristic time scales in the model. After the derivation, the reduced model may be used for non-uniform spatial receptor and transporter distributions as well. However, we will then need to take into account the fact that in the regions without receptors and/or transporters corresponding values of $V_i$ and/or $W_j$ will be zero, and local transport in these regions will only be associated with the original glutamate diffusion.

Let us introduce several time scales characteristic of our problem:

- characteristic diffusion time $\tau_D = L^2/D$;
- characteristic times of forward and reverse binding reactions for receptors, $\tau_{k_i^+} = 1/(k_i^+ V_i^*)$ and $\tau_{k_i^-} = 1/(k_i^-)$;
- characteristic times of forward and reverse binding reactions for transporters, $\tau_{K_j^+} = 1/(K_j^+ W_j^*)$ and $\tau_{K_j^-} = 1/(K_j^-)$;
- characteristic times of glutamate loss via transporters, $\tau_{\lambda_j} = 1/\lambda_j$.

Next, we formulate the assumptions that will allow us to reduce the system of equations for concentrations of glutamate, receptors and transporters to one equation for glutamate with an effective diffusion coefficient that depends nonlinearly on the concentration of free glutamate. If only a portion of conditions formulated below is satisfied for a certain number of receptors and transporters, then only this number of equations can be eliminated, and the reduced system will have fewer equations compared to the original one. If none of the conditions formulated below is satisfied, then further reduction of the system (16), (27), (28) is not possible.

(f) We assume that the forward and reverse receptor binding reactions are fast compared to diffusion, i.e., $\tau_{k_i^\pm} \ll \tau_D$. Also, we assume that the ratios $\tau_{k_i^-}/\tau_{k_i^+}$ are moderate.

(g) We assume that the forward and reverse transporter binding reactions are fast compared to diffusion, i.e., $\tau_{K_j^\pm} \ll \tau_D$. We also assume that the ratios $\tau_{K_j^-}/\tau_{K_j^+}$ are moderate.

(h) In addition, we consider the case where $\tau_{\lambda_j}/\tau_D$ are moderate.

In the Appendix we present the non-dimensionalization procedure (needed for the rigorous construction of the asymptotic approximation of the solution), as well as the details of mathematical model reduction algorithm. Here we only mention characteristic model reduction steps written in terms of the original variables and parameters, and present the final reduced model formulation.
Substituting expressions (27) and (28) for \( f_i \) and \( g_i \),

\[
f_i(\tilde{u}, v_i, x, y) = \frac{\partial v_i}{\partial t},
\]

\[
g_j(\tilde{u}, w_j, x, y) = \frac{\partial w_j}{\partial t} - \lambda_j(W_j^* - w_j),
\]

into (16), we obtain:

\[
\frac{\partial \tilde{u}}{\partial t} = D \left( \frac{\partial^2 \tilde{u}}{\partial x^2} + \frac{\partial^2 \tilde{u}}{\partial y^2} \right)
\]

\[
+ \frac{\delta}{h} \left( \sum_{i=1}^{n} \frac{\partial v_i}{\partial t} + \sum_{j=1}^{m} \left[ \frac{\partial w_j}{\partial t} - \lambda_j(W_j^* - w_j) \right] \right).
\]

In the quasi-steady state (or, in the leading order approximation following from the asymptotic algorithm; see Appendix), from (27), (28), we have

\[
0 = -k_i^+ \tilde{u} v_i + k_i^- (V_i^* - v_i).
\]

Thus, from (32), we can express \( v_i \) in terms of \( \tilde{u} \) as follows:

\[
v_i = \frac{k_i^- V_i^*}{k_i^- + k_i^+ \tilde{u}}.
\]

Similarly, in the quasi-steady state (or, in the leading order approximation), from (28), we get

\[
0 = -K_j^+ \tilde{u} w_j + K_j^- (W_j^* - w_j).
\]

Thus, from (34), we can express \( w_j \) in terms of \( \tilde{u} \) as follows:

\[
w_j = \frac{K_j^- W_j^*}{K_j^- + K_j^+ \tilde{u}}.
\]

Differentiating (33) and (35) with respect to \( t \), we obtain:

\[
\frac{\partial v_i}{\partial t} = -\frac{k_i^- k_i^+ V_i^*}{(k_i^- + k_i^+ \tilde{u})^2} \frac{\partial \tilde{u}}{\partial t},
\]

\[
\frac{\partial w_j}{\partial t} = -\frac{K_j^- K_j^+ W_j^*}{(K_j^- + K_j^+ \tilde{u})^2} \frac{\partial \tilde{u}}{\partial t}.
\]

Substituting (35), (36), (37) into (31), and re-arranging terms, we write:

\[
\frac{\partial \tilde{u}}{\partial t} \left\{ 1 + \frac{\delta}{h} \left( \sum_{i=1}^{n} \frac{k_i^- k_i^+ V_i^*}{(k_i^- + k_i^+ \tilde{u})^2} + \sum_{j=1}^{m} \frac{K_j^- K_j^+ W_j^*}{(K_j^- + K_j^+ \tilde{u})^2} \right) \right\}
\]

\[
= D \left( \frac{\partial^2 \tilde{u}}{\partial x^2} + \frac{\partial^2 \tilde{u}}{\partial y^2} \right) - \frac{\delta}{h} \sum_{j=1}^{m} \lambda_j \left( W_j^* - \frac{K_j^- W_j^*}{K_j^- + K_j^+ \tilde{u}} \right).
\]

Finally, from (38), after some more re-arrangement of terms, we obtain the reduced equation for \( \tilde{u}(x, y, t) \):
\[
\begin{align*}
\frac{\partial \tilde{u}}{\partial t} &= D \left( \frac{\partial^2 \tilde{u}}{\partial x^2} + \frac{\partial^2 \tilde{u}}{\partial y^2} \right) \\
&= \left\{ 1 + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{(k_i^+/k_i^-) V_i^*}{(1 + (k_i^+/k_i^-) \tilde{u})^2} + \sum_{j=1}^{m} \frac{(K_j^+/K_j^-) W_j^*}{(1 + (K_j^+/K_j^-) \tilde{u})^2} \right) \right\} \\
&- \frac{\delta}{\hbar} \sum_{j=1}^{m} \lambda_j W_j^* \left( \frac{(K_j^+/K_j^-) \tilde{u}}{1 + (K_j^+/K_j^-) \tilde{u}} \right) \\
&\quad \times \left\{ 1 + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{(k_i^+/k_i^-) V_i^*}{(1 + (k_i^+/k_i^-) \tilde{u})^2} + \sum_{j=1}^{m} \frac{(K_j^+/K_j^-) W_j^*}{(1 + (K_j^+/K_j^-) \tilde{u})^2} \right) \right\}.
\end{align*}
\] (39)

This equation must be solved with boundary conditions (17) and initial condition (18); see the detailed discussion about the choice of asymptotically correct initial conditions in the Appendix. When \(u(x, y, t)\) is known, \(v_i(x, y, t)\) \((i = 0, \ldots, n)\) and \(w_j(x, y, t)\) \((j = 0, \ldots, m)\) are found from (33) and (35), respectively.

We note that the actual number of parameters (or parameter combinations) that enter (39) is smaller compared to the system (16), (27), (28): e.g., \(k_i^\pm (i = 0, \ldots, n)\) appear only in combinations \((k_i^+/k_i^-)_j\), \(K_j^\pm (j = 0, \ldots, m)\) appear as the combinations \((K_j^+/K_j^-)\). If the conditions for which the reduction is possible are satisfied, and if the time sensitivity of measuring devices is of the order of the (slow) characteristic diffusion time, \(\tau_D\), then \(k_i^\pm, K_j^\pm\) cannot be independently identified from an experiment, and only combinations \((k_i^+/k_i^-)\) and \((K_j^+/K_j^-)\) can, in principle, be determined.

Another important observation: it follows from (39) that glutamate transport in the presence of receptors and transporters is characterized by the new effective diffusion coefficient that is not now constant (it depends on \(\tilde{u}(x, y, t)\) and the original distribution of free receptors \(V_i^*\) and free transporters \(W_j^*)\):

\[
D_{\text{effective}} = \frac{D}{\left\{ 1 + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{(k_i^+/k_i^-) V_i^*}{(1 + (k_i^+/k_i^-) \tilde{u})^2} + \sum_{j=1}^{m} \frac{(K_j^+/K_j^-) W_j^*}{(1 + (K_j^+/K_j^-) \tilde{u})^2} \right) \right\}}. \tag{40}
\]

It can be easily seen from (40) that for any value of \(\tilde{u}\) we have \(D_{\text{effective}} \leq D\). Also, as \(\tilde{u} \to \infty\), the effective diffusion coefficient \(D_{\text{effective}} \to D\). Finally, the minimal value of \(D_{\text{effective}}\) is observed when \(\tilde{u} \to 0\):

\[
D_{\min}^{\text{effective}} = \frac{D}{\left\{ 1 + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{(k_i^+/k_i^-) V_i^*}{(1 + (k_i^+/k_i^-) \tilde{u})^2} + \sum_{j=1}^{m} \frac{(K_j^+/K_j^-) W_j^*}{(1 + (K_j^+/K_j^-) \tilde{u})^2} \right) \right\}}. \tag{41}
\]

Remark. The asymptotic procedure described in the Appendix is based on the Boundary Function Method algorithm (see Vasil’eva et al. [10]). Our results are also related to those presented in Haario and Kalachev [3], Keener and Sneyd [4], Smith et al. [8], and Sneyd et al. [9].

Next, we consider an illustrative example where for some particular choice of parameter values we compare a solution of a model system consisting of a radially symmetric (and thus, spatially 1-dimensional) equation for free glutamate concentration coupled with a transporter equation and a solution of the corresponding reduced model consisting of one equation for free glutamate.
7. Illustrative example

Let us consider the case where one transporter is uniformly distributed throughout the postsynaptic boundary of the cleft, region $\Omega$ has the shape of a disk with radius $R = 2 \mu m$, and the problem is radially symmetric (the glutamate vesicle opens in the center of the disk, and the initial shape of the released glutamate concentration is radially symmetric). For the radially symmetric case the Laplace operator $(\partial^2 \hat{u}/\partial x^2 + \partial^2 \hat{u}/\partial y^2)$ will have the form $(\partial^2 \hat{u}/\partial r^2 + (1/r)\partial \hat{u}/\partial r)$, where $r$ is the radial distance from the center of the disk.

We will call the system for concentrations $\hat{u}$ and $w_1$ averaged over the height of the cleft ($h = 20 \text{ nm}$) and the corresponding additional conditions the original model. It consists of the following equations:

\[
\begin{align*}
\frac{\partial \hat{u}}{\partial t} &= D \left( \frac{\partial^2 \hat{u}}{\partial r^2} + \frac{1}{r} \frac{\partial \hat{u}}{\partial r} \right) + \frac{\delta}{h} [-K_1^+ \hat{u} w_1 + K_1^- (W_1^* - w_1)]; \tag{42} \\
\frac{\partial w_1}{\partial t} &= -K_1^+ \hat{u} w_1 + K_1^- (W_1^* - w_1) + \lambda_1 (W_1^* - w_1). \tag{43}
\end{align*}
\]

The boundary and initial conditions are written as follows:

\[
\hat{u}(R, t) = 0, \tag{44}
\]

\[
\hat{u}(r, 0) = \hat{U}^*(r) = 0.0004 \times \exp(-5r^2), \tag{45}
\]

\[
w_1(r, 0) = W_1^* = 0.0001. \tag{46}
\]

All concentrations are measured in moles per liter (M), and time is measured in msec. Other sample parameter values are chosen as follows: $D = 0.2 \mu M^2/\text{msec}$; $K_1^+ = 1.8 \times 10^4 \text{ M/msec}$; $K_1^- = 1.8 \text{ 1/msec}$; $\lambda_1 = 0.18 \text{ 1/msec}$; $\delta = 2 \text{ nm}$.

For the above choice of parameter values the characteristic times defined in the previous section are: $\tau_D = 20 \gg \tau_{K_1^+} = \tau_{K_1^-} \approx 0.55, \tau_{\lambda_1} \approx 5.55$. The conditions for which the reduction of the model is possible are (approximately) satisfied.

The reduced model will consist of the equation

\[
\frac{\partial \hat{u}}{\partial t} = \frac{(1 + (K_1^+ / K_1^-) \hat{u})^2 D}{(1 + (K_1^+ / K_1^-) \hat{u})^2 + (\delta/h)(K_1^+ / K_1^-) W_1^*} \left( \frac{\partial^2 \hat{u}}{\partial r^2} + \frac{1}{r} \frac{\partial \hat{u}}{\partial r} \right) - \frac{(\delta/h)\lambda_1 (K_1^- / K_1^+) W_1^* (1 + (K_1^+ / K_1^-) \hat{u}) \hat{u}}{(1 + (K_1^+ / K_1^-) \hat{u})^2 + (\delta/h)(K_1^+ / K_1^-) W_1^*} \hat{u}, \tag{47}
\]

and additional conditions (44), (45).

When $\hat{u}$ is known, we also know (see (35)):

\[
w_1 = \frac{K_1^- W_1^*}{K_1^- + K_1^+ \hat{u}}. \tag{48}
\]

Solutions for the original model and for the reduced model were obtained numerically using the method of lines (programs were written in MATLAB). The radially symmetric concentration profiles obtained by numerical computations for $t = 0, 0.5, 1.0 \text{ msec}$ are shown in Figures 1 (a), (b), (c), respectively.

At $t = 0$ the initial conditions for both models are the same. We note that for $t = 0.5$ and $t = 1.0$ the curves representing concentrations of free glutamate obtained for the original and the reduced models are almost undistinguishable.
Figure 1. Example: comparison of (radially dependent) concentration profiles of free glutamate for the original and the reduced models. The concentration of free transporters and bound glutamate for the original model are also shown; (a) initial instant of time \( t = 0 \) msec (initial conditions are the same for the original and for the reduced model); (b) instant of time \( t = 0.5 \) msec; (c) instant of time \( t = 1.0 \) msec.

Remark. The numerical results shown in Figures 1 (a), (b) and (c) qualitatively stay the same for the set of parameter values found in the literature (see, e.g., Rusakov and Kullman [7]): \( K_1^+ = 6.0 \times 10^3 \) M/msec; \( K_1^- = 0.1 \) 1/msec; \( \lambda_1 = 0.02 \) 1/msec.
8. Conclusion
We presented a general model reduction procedure for neurotransmitter transport in the presence of a finite number of generic receptors and transporters. It is important to emphasize that here we did not perform numerical experiments for various distributions of receptors and transporters to elucidate the details of glutamate transport in a synaptic cleft. Such numerical experiments as well as experimental data fitting using a set of reduced models of the type presented above will be done in the near future and published elsewhere. Our main goal was to illustrate the reduction procedure and specify conditions under which various steps of the reduction can be performed.

Comparison of the solutions of the original model and the reduced model for an example with a particular sample choice of parameter values that satisfied the conditions imposed shows good agreement between the two models.

Appendix
Here we present the asymptotic reduction algorithm for a spatially 2-dimensional model in the case where forward/reverse binding reactions involving receptors and transmitters are assumed to be fast in comparison with diffusion and trans-membrane neurotransmitter transport. In what follows to simplify the explanation of the reduction procedure, we assume that receptors and transporters are uniformly distributed, i.e., $V_i^* = W_j^* = \text{const} \ (i = 1, \ldots, n; j = 1, \ldots, m)$.

Earlier, we have introduced the following characteristic time scales: characteristic diffusion time $\tau_D = L^2/D$; characteristic times of forward and reverse binding reactions for receptors, $\tau_{k_i^+} = 1/(k_i^+ V_i^*)$ and $\tau_{k_i^-} = 1/(k_i^-)$; characteristic times of forward and reverse binding reactions for transporters, $\tau_{K_j^+} = 1/(K_j^+ W_j^*)$ and $\tau_{K_j^-} = 1/(K_j^-)$; characteristic times of glutamate loss via transporters (i.e., trans-membrane transport), $\tau_{\lambda_j} = 1/\lambda_j$. Let us introduce the following re-scaled quantities and auxiliary notations: we define non-dimensional time $\hat{t} = t/\tau_D$, non-dimensional spatial variables $\hat{x} = x/L, \hat{y} = y/L$, where $L$ is characteristic lateral dimension of the synaptic cleft region. We define re-scaled concentrations ($i = 1, \ldots, n; j = 1, \ldots, m$):

$$\hat{u} = \frac{\tilde{u}}{\max_{(x,y) \in \Omega} U^*(x,y)}; \quad \hat{U}^* = \frac{\tilde{U}^*(x,y)}{\max_{(x,y) \in \Omega} U^*(x,y)} \leq 1;$$

$$\hat{v}_i = \frac{\tilde{v}_i}{V_i^*} \leq 1; \quad \hat{w}_j = \frac{\tilde{w}_j}{W_j^*} \leq 1; \quad \hat{\lambda}_j = \lambda_j \cdot \tau_D.$$

Let us re-formulate assumptions (f), (g), (h) introduced in Section 6 using a small parameter $0 < \varepsilon \ll 1$. Without loss of generality, we define

$$\varepsilon = \frac{\tau_{k_i^+}}{\tau_D}.$$

Then assumptions (f), (g), (h) are equivalent to the following set of asymptotic relations:

$$\frac{\tau_D \max_{(x,y) \in \Omega} \tilde{U}^*(x,y)}{\tau_{k_i^+}} \frac{V_i^*}{a_i} \varepsilon = O \left( \frac{1}{\varepsilon} \right); \quad \frac{\tau_D}{\tau_{k_i^-}} \frac{b_i}{\varepsilon} = O \left( \frac{1}{\varepsilon} \right);$$

$$\frac{\tau_D \max_{(x,y) \in \Omega} \tilde{U}^*(x,y)}{\tau_{K_j^+}} \frac{W_j^*}{A_j} \frac{1}{\varepsilon} = O \left( \frac{1}{\varepsilon} \right); \quad \frac{\tau_D}{\tau_{K_j^-}} \frac{B_j}{\varepsilon} = O \left( \frac{1}{\varepsilon} \right); \quad \hat{\lambda}_j = O(1).$$
Here $a_i$, $b_i$, $A_j$, $B_j = O(1) \ (i = 1, \ldots, n; \ j = 1, \ldots, m)$.

Using the new notation introduced above, we re-write the problem for (16), (27), (28) with corresponding conditions in the form:

\[
\begin{align*}
\varepsilon \frac{\partial \hat{u}}{\partial t} &= \varepsilon \left( \frac{\partial^2 \hat{u}}{\partial x^2} + \frac{\partial^2 \hat{u}}{\partial y^2} \right) + \frac{\delta}{\varepsilon} \left( \sum_{i=1}^{n} [-a_i \hat{u} \hat{v}_i + b_i (1 - \hat{v}_i)] + \sum_{j=1}^{m} [-A_j \hat{u} \hat{w}_j + B_j (1 - \hat{w}_j)] \right), \\
\varepsilon \frac{\partial \hat{v}_i}{\partial t} &= -a_i \hat{u} \hat{v}_i + b_i (1 - \hat{v}_i); \\
\varepsilon \frac{\partial \hat{w}_j}{\partial t} &= -A_j \hat{u} \hat{w}_j + B_j (1 - \hat{w}_j) + \varepsilon \hat{\lambda}_j (1 - \hat{w}_j); \\
\hat{u}(\hat{x}, \hat{y}, 0) &= \hat{U}^*(\hat{x}, \hat{y}) \quad \text{for} \quad (\hat{x}, \hat{y}) \in \hat{\Omega}, \\
\hat{v}_i(\hat{x}, \hat{y}, 0) &= 1, \quad \hat{w}_j(\hat{x}, \hat{y}, 0) = 1 \quad \text{for} \quad (\hat{x}, \hat{y}) \in \hat{\Omega}; \\
\hat{u}(\hat{x}, \hat{y}, t) &= 0 \quad \text{for} \quad (\hat{x}, \hat{y}) \in \partial \hat{\Omega}.
\end{align*}
\]

where \( \hat{\Omega} \) is re-scaled \( \Omega; \hat{U}^*(\hat{x}, \hat{y}) = 0 \) for \( (\hat{x}, \hat{y}) \in \partial \hat{\Omega} \).

To simplify the notation, let us omit hats (\(^\hat{}\)) in (50) – (55).

According to the Boundary Function Method algorithm (see Vasil’eva et al. [10]), we seek approximate solution to (50) – (55) in the form of an asymptotic expansion

\[
u(x, y, t) = \tilde{u}_0(x, t) + \varepsilon \tilde{v}_1(x, t) + \ldots + \Pi_0 u(x, \tau) + \varepsilon \Pi_1 u(x, \tau) + \ldots,
\]

with similar expressions for \( v_i \) and \( w_j \). Here \( \tilde{u}_0, \tilde{v}_1 \) are the functions that describe the, so-called, regular part of the asymptotic expansion and are important for \( t > 0 \) away from the initial layer; \( \Pi_0 u, \Pi_1 u \) are the boundary layer functions important in the initial layer near \( t = 0 \) (for \( \tau \geq 0 \), where \( \tau = t/\varepsilon \) is the, so-called, stretched variable).

Substituting (56) and similar expressions for \( v_i \) and \( w_j \) into (50) – (55), and equating at every order of \( \varepsilon \) terms of the asymptotic expansions separately for regular and boundary functions, we obtain the problems for \( \tilde{u}_0, \tilde{v}_1, \) etc.

In the leading order approximation, for \( \tilde{u}_0, \tilde{v}_0, \tilde{w}_0 \), we have

\[
\begin{align*}
0 &= -a_i \tilde{u}_0 \tilde{v}_i + b_i (1 - \tilde{v}_i); \\
0 &= -A_j \tilde{u}_0 \tilde{w}_j + B_j (1 - \tilde{w}_j).
\end{align*}
\]

From (57) and (58) we write expressions for \( \tilde{v}_i, \tilde{w}_j \) in terms of \( \tilde{u}_0 \):

\[
\begin{align*}
\tilde{v}_i &= \frac{b_i}{b_i + a_i \tilde{u}_0}; \\
\tilde{w}_j &= \frac{B_j}{B_j + A_j \tilde{u}_0}.
\end{align*}
\]

In the first order approximation we have the following equations for the regular functions \( \tilde{u}_1, \tilde{v}_1, \tilde{w}_1 \):
\[
\frac{\partial \bar{u}_0}{\partial t} - \left( \frac{\partial^2 \bar{u}_0}{\partial x^2} + \frac{\partial^2 \bar{u}_0}{\partial y^2} \right) = \frac{\delta}{h} \left( \sum_{i=1}^{n} \left[ -a_i \bar{u}_1 \bar{v}_i - a_i \bar{u}_0 \bar{v}_i - b_i \bar{v}_i \right] \right) \\
+ \sum_{j=1}^{m} \left[ -A_j \bar{u}_1 \bar{w}_{j0} - A_j \bar{u}_0 \bar{w}_{j1} - B_j \bar{w}_{j1} \right] ;
\]
\[
-a_i \bar{u}_1 \bar{v}_i - a_i \bar{u}_0 \bar{v}_i - b_i \bar{v}_i = \frac{\partial \bar{v}_0}{\partial t} ,
\]
\[
-A_j \bar{u}_1 \bar{w}_{j0} - A_j \bar{u}_0 \bar{w}_{j1} - B_j \bar{w}_{j1} = \frac{\partial \bar{w}_{j0}}{\partial t} - \lambda_j (1 - \bar{w}_{j0}) .
\]

The solvability condition for the linear algebraic system (61) – (63) is written in the form:

\[
\frac{\partial \bar{u}_0}{\partial t} - \left( \frac{\partial^2 \bar{u}_0}{\partial x^2} + \frac{\partial^2 \bar{u}_0}{\partial y^2} \right) = \frac{\delta}{h} \left( \sum_{i=1}^{n} \frac{\partial \bar{v}_0}{\partial t} \right) \\
+ \sum_{j=1}^{m} \left[ \frac{\partial \bar{w}_{j0}}{\partial t} - \lambda_j (1 - \bar{w}_{j0}) \right] .
\]

From (59), (60), for the derivatives of \( \bar{v}_i, \bar{w}_{j0} \), we have

\[
\frac{\partial \bar{v}_i}{\partial t} = -\frac{a_i b_i}{(b_i + a_i \bar{u}_0)^2} \frac{\partial \bar{u}_0}{\partial t} ;
\]
\[
\frac{\partial \bar{w}_{j0}}{\partial t} = -\frac{A_j B_j}{(B_j + A_j \bar{u}_0)^2} \frac{\partial \bar{u}_0}{\partial t} .
\]

Substituting (60), (65), and (66) into (64), we obtain the equation for \( \bar{u}_0 \):

\[
\frac{\partial \bar{u}_0}{\partial t} - \left( \frac{\partial^2 \bar{u}_0}{\partial x^2} + \frac{\partial^2 \bar{u}_0}{\partial y^2} \right) = \frac{\delta}{h} \left( \sum_{i=1}^{n} \left[ -\frac{a_i b_i}{(b_i + a_i \bar{u}_0)^2} \frac{\partial \bar{u}_0}{\partial t} \right] \right) \\
+ \sum_{j=1}^{m} \left[ -\frac{A_j B_j}{(B_j + A_j \bar{u}_0)^2} \frac{\partial \bar{u}_0}{\partial t} - \lambda_j \left( 1 - \frac{B_j}{B_j + A_j \bar{u}_0} \right) \right] .
\]

From the above equation, after moving all the terms containing derivatives of \( \bar{u}_0 \) to the left hand side of (67), we obtain:

\[
\left[ 1 + \frac{\delta}{h} \sum_{i=1}^{n} \frac{a_i b_i}{(b_i + a_i \bar{u}_0)^2} + \frac{\delta}{h} \sum_{j=1}^{m} \frac{A_j B_j}{(B_j + A_j \bar{u}_0)^2} \right] \frac{\partial \bar{u}_0}{\partial t}
\]
\[
- \left( \frac{\partial^2 \bar{u}_0}{\partial x^2} + \frac{\partial^2 \bar{u}_0}{\partial y^2} \right) = -\frac{\delta}{h} \sum_{j=1}^{m} \lambda_j \left( 1 - \frac{B_j}{B_j + A_j \bar{u}_0} \right) .
\]

Dividing both sides of equation (68) by the term in the square brackets, we arrive at the partial differential equation for \( \bar{u}_0 \) with effective diffusion and effective kinetics term:
\[
\frac{\partial \bar{u}_0}{\partial t} - \frac{1}{1 + \frac{\delta}{h} \sum_{i=1}^{n} (a_i b_i + b_i a_i \bar{u}_0)^2 + \frac{\delta}{h} \sum_{i=1}^{m} (B_j + A_j \bar{u}_0)^2} \left( \frac{\partial^2 \bar{u}_0}{\partial x^2} + \frac{\partial^2 \bar{u}_0}{\partial y^2} \right)
\]

\[
= \frac{\delta}{h} \sum_{j=1}^{m} \lambda_j \left( 1 - \frac{B_j}{B_j + A_j \bar{u}_0} \right)
\]

(69)

Returning to the original variables in (69), we immediately reproduce (39).

The boundary condition for (69) follows from (55):

\[\bar{u}_0(x, y, t) = 0 \quad \text{for} \quad (x, y) \in \partial \hat{\Omega}.\]  

(70)

The initial conditions for (69) are found in the process of the construction of the boundary functions. For \(\Pi_0 u, \Pi_0 v, \Pi_0 w\) we have the following system of equations:

\[
\frac{\partial \Pi_0 u}{\partial \tau} = \frac{\delta}{h} \left( \sum_{i=1}^{n} [-a_i \bar{u}_0(x, y, 0) \Pi_0 v - a_i \bar{v}_0(x, y, 0) \Pi_0 u - a_i \Pi_0 u \Pi_0 v - b_i \Pi_0 v_i] \right) + \sum_{j=1}^{m} [-A_j \bar{u}_0(x, y, 0) \Pi_0 w - A_j \bar{w}_0(x, y, 0) \Pi_0 u - A_j \Pi_0 u \Pi_0 w - B_j \Pi_0 w] \right). 
\]

(71)

\[
\frac{\partial \Pi_0 v}{\partial \tau} = -a_i \bar{u}_0(x, y, 0) \Pi_0 v - a_i \bar{v}_0(x, y, 0) \Pi_0 u - a_i \Pi_0 u \Pi_0 v - b_i \Pi_0 v_i; 
\]

\[
\frac{\partial \Pi_0 w}{\partial \tau} = -A_j \bar{u}_0(x, y, 0) \Pi_0 w - A_j \bar{w}_0(x, y, 0) \Pi_0 u - A_j \Pi_0 u \Pi_0 w - B_j \Pi_0 w. 
\]

(72)

(73)

Together with the leading order regular functions the boundary functions \(\Pi_0 u, \Pi_0 v, \Pi_0 w\) must satisfy the initial conditions (see (53), (54)):

\[\bar{u}_0(x, y, 0) + \Pi_0 u(x, y, 0) = U^*,\]

\[\bar{v}_0(x, y, 0) + \Pi_0 v(x, y, 0) = 1,\]

\[\bar{w}_0(x, y, 0) + \Pi_0 w(x, y, 0) = 1,\]

(74)

for \((x, y) \in \Omega.\)

Also, the boundary functions at any order must decay to zero as \(\tau \to \infty:\)

\[\Pi_0 u(x, y, \infty) = 0, \quad \Pi_0 v(x, y, \infty) = 0, \quad \Pi_0 w(x, y, \infty) = 0.\]

(75)

It follows from (71), (72), (73) that
\[
\frac{\partial \Pi_0 u}{\partial \tau} = \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{\partial \Pi_0 v}{\partial \tau} + \sum_{j=1}^{m} \frac{\partial \Pi_0 w}{\partial \tau} \right) .
\] (76)

Integrating (76) with conditions (75), we arrive at the relation:

\[
\Pi_0 u = \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \Pi_0 v + \sum_{j=1}^{m} \Pi_0 w \right) .
\] (77)

Substituting (59), (60), and (77) into the system describing initial conditions in the leading order approximation (74), we obtain:

\[
\bar{u}_0(x, y, 0) + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{\Pi_0 v(x, y, 0)}{b_i} + \sum_{j=1}^{m} \frac{\Pi_0 w(x, y, 0)}{B_j} \right) = U^* ,
\] (78)

\[
\frac{b_i}{b_i + a_i \bar{u}_0(x, y, 0)} + \Pi_0 v(x, y, 0) = 1 ,
\]

\[
\frac{B_j}{B_j + A_j \bar{u}_0(x, y, 0)} + \Pi_0 w(x, y, 0) = 1 .
\]

This is a system of \((n + m + 1)\) equations for \((n + m + 1)\) unknowns, the initial conditions for the regular function \(\bar{u}_0\) and the boundary functions \(\Pi_0 v, \Pi_0 w\).

From (78) we express

\[
\Pi_0 v(x, y, 0) = 1 - \frac{b_i}{b_i + a_i \bar{u}_0(x, y, 0)} = \frac{a_i \bar{u}_0(x, y, 0)}{b_i + a_i \bar{u}_0(x, y, 0)} ,
\]

\[
\Pi_0 w(x, y, 0) = 1 - \frac{B_j}{B_j + A_j \bar{u}_0(x, y, 0)} = \frac{A_j \bar{u}_0(x, y, 0)}{B_j + A_j \bar{u}_0(x, y, 0)} .
\] (79)

Substituting (79) into the first equation of (78), we obtain one equation for \(\bar{u}_0(x, y, 0)\):

\[
\bar{u}_0(x, y, 0) + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{a_i \bar{u}_0(x, y, 0)}{b_i + a_i \bar{u}_0(x, y, 0)} + \sum_{j=1}^{m} \frac{A_j \bar{u}_0(x, y, 0)}{B_j + A_j \bar{u}_0(x, y, 0)} \right) = U^* ,
\] (80)

which we re-write for convenience as

\[
F(\bar{u}_0(x, y, 0)) = U^* ,
\] (81)

where the expression for \(F\) corresponds to the left hand side of equation (80).

The function \(F(u)\) has the following properties: \(F(0) = 0, \lim_{u \to \infty} F(u) \to \infty\). Also,

\[
F'(u) = 1 + \frac{\delta}{\hbar} \left( \sum_{i=1}^{n} \frac{a_ib_i}{(b_i + a_iu)^2} + \sum_{j=1}^{m} \frac{A_jB_j}{(B_j + A_ju)^2} \right) > 0
\] (82)

for all \(u\).

It follows from the above properties of \(F\) that equation (81) has a unique solution \(\bar{u}_0(x, y, 0)\) for any choice of \(U^* \geq 0\) (geometrically this means that the increasing function \(F(u)\) intersects the horizontal line with the ordinate \(U^* \geq 0\) only at one point).
Now the initial condition for $\bar{u}_0$ is known. The problem for $\bar{u}_0$ is completely defined. It consists of the equation (69), boundary condition (70), and the initial condition that solves (81) (which is equivalent to (80)).

When $\bar{u}_0(x, y, 0)$ is known, the initial conditions for the boundary functions are found from (79). It can be shown that the equations (72), (73) for $\Pi_{0i}\bar{v}, \Pi_{0j}\bar{w}$, where the expression (77) is substituted for $\Pi_0\bar{u}$, with corresponding initial conditions have solutions exponentially decaying to zero as $\tau \to \infty$.

Remark. If $\delta/h \ll 1$, then equation (80) for $\bar{u}_0(x, y, 0)$ may be replaced by its approximation

$$\bar{u}_0(x, y, 0) \approx U^*.$$  \hfill (83)

So, in this case the initial condition for $\bar{u}_0$ is approximated by the original initial condition value $U^*$. Such an approximation was used in the illustrative example discussed in this paper.

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