Accurate numerical simulation of electrodiffusion and water movement in brain tissue

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Mathematical modelling of ionic electrodiffusion and water movement is emerging as a powerful avenue of investigation to provide new physiological insight into brain homeostasis. However, in order to provide solid answers and resolve controversies, the accuracy of the predictions is essential. Ionic electrodiffusion models typically comprise non-trivial systems of non-linear and highly coupled partial and ordinary differential equations that govern phenomena on disparate time scales. Here, we study numerical challenges related to approximating these systems. We consider a homogenized model for electrodiffusion and osmosis in brain tissue and present and evaluate different associated finite element-based splitting schemes in terms of their numerical properties, including accuracy, convergence, and computational efficiency for both idealized scenarios and for the physiologically relevant setting of cortical spreading depression (CSD). We find that the schemes display optimal convergence rates in space for problems with smooth manufactured solutions. However, the physiological CSD setting is challenging: we find that the accurate computation of CSD wave characteristics (wave speed and wave width) requires a very fine spatial and fine temporal resolution.

Keywords: electrodiffusion, osmosis, brain electrophysiology and mechanics, finite element method, splitting scheme, numerical convergence

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1. Introduction

The movement of ions and molecules in and between cellular compartments is fundamental for brain function, and importantly for neuronal excitability and activity. Vital processes such as action potential firing, transmitter release, and synaptic transmission are all driven by ionic gradients across the neuronal membrane. Regulation of the extracellular volume by cellular swelling is closely related to ionic dynamics, including potassium buffering. Several pathologies are associated with disruption to ionic homeostasis in the brain, e.g., Huntington’s disease, multiple sclerosis, migraine, epilepsy, Alzheimer’s disease, and cortical spreading depression. Recent research efforts indicate that ion concentrations in the extracellular space are not static, but vary across states such as locomotion and the sleep cycle.

In spite of these aspects, mathematical and numerical models for describing dynamics in brain tissue traditionally assume that the ion concentrations are constant in time and space. Although such models have provided valuable insight into the mechanisms underlying excitable cells, they fail to represent essential dynamics related to altered ion concentrations in brain tissue. Recently, several mathematical models also including electrodiffusive effects have been presented. However, to date little attention has been paid to the numerical solution of these models.

In this paper, we consider a mathematical framework proposed by Mori, consisting of a system of partial differential equations (PDEs) governing ionic electrodiffusion and water flow in biological tissue, coupled to a system of ordinary differential equations (ODEs) describing the temporal evolution of ionic membrane mechanisms. The system predicts the dynamics of volume fractions, ion concentrations, electrical potentials and mechanical pressure in an arbitrary number of cellular compartments and in the extracellular space (ECS). The cellular compartments can communicate with the ECS via transmembrane ion and water fluxes. This mathematical model extends on the celebrated bidomain model and both represent the tissue in a homogenized manner. Homogenized models are coarse-grained, and hence well suited for simulating phenomena on the tissue scale (mm). Importantly, the two models differ in that the classical bidomain model only predicts electrical potentials, whereas the model for ionic electrodiffusion and water flow takes into account how the movement of ions affect the excitable tissue, both in terms of electrochemical and mechanical effects.

Previously, the electrodiffusive model (in its zero flow limit) has been used to study dynamics in brain tissue, and in particular cortical spreading depression (CSD). CSD is a slowly propagating wave of depolarization of brain cells, characterized by elevated levels of extracellular potassium, calcium, and glutamate, cellular swelling and pronounced ECS shrinkage. Importantly, CSD is a fundamental pattern of brain signalling that challenges ionic homeostasis mechanisms in the brain. As such, a better understanding of the sequence of events in CSD has the
potential to provide new insight into underlying processes both in cerebral physiology and pathology. The aforementioned computational studies have focused on providing new insight into the role of glial cells in CSD, and the role of glutamate dynamics in CSD. However, in order to provide true physiological insight, the accuracy of the numerical and computational predictions is key; the difference between conflicting experimental observations may very well be within the numerical error of underresolved models.

Previously considered numerical schemes for the electrodiffusive model are based on finite difference or finite volume discretizations in space and a backward Euler scheme (with explicit treatment of the active membrane flux) in time. The spatio-temporal discretization sizes of these schemes are reported to be on the order of $\Delta x \approx 0.02 - 0.2$ mm and $\Delta t \approx 10$ ms. By applying a (comparable) finite element scheme in space and a similar discretization scheme in time, we find that the CSD wave properties change substantially during spatial and temporal refinement. In particular, we observe that the wave speed and the width of the wave increase with decreasing time resolution, and decrease with decreasing spatial resolution (Figure 1). As the Mori framework comprises a system of non-linear and highly coupled partial and ordinary differential equations, governing phenomena on disparate time scales (both fast electrotonic effects and much slower effects mediated by diffusion), theoretical analysis of the full equations is challenging. In this paper, we take a natural first step towards accurate and efficient approximation schemes for the system by comparing different schemes numerically, with an emphasis on convergence and performance for simulating CSD waves.

In the first instance, we consider a low-order finite element scheme in space for the electrodiffusive model in the zero flow limit, and numerically study the effect of: (i) different operator splitting schemes, (ii) choice of time stepping schemes for the PDEs, (iii) choice of time stepping schemes for the ODEs, and (iv) a higher order spatial discretization scheme. All schemes display optimal convergence rates during refinement in space and time for problems with smooth manufactured solutions. However, we find that the accurate computation of CSD wave characteristics (such as wave speed and wave width) requires a very fine spatial and fine temporal resolution for all schemes tested. In particular, the different splitting schemes and PDE time stepping give comparable results in terms of accuracy. We observe that higher order ODE time stepping schemes (ESDIRK4, RK4) yield slightly faster convergence than the lower order backward Euler scheme. Finally, we find that applying a higher order finite element scheme with a coarser spatial resolution gives comparable results to the lower order finite element scheme in terms of accuracy, but at a higher cost, justifying the use of a low order scheme with fine spatial resolution.

We then turn to consider the full mathematical model, where the electrochemical and mechanical dynamics described in the zero flow limit are coupled with microscopic fluid dynamics. To the best of our knowledge, the only previous study involving this model was presented by O’Connell, studying the effects of mechanical pressures and compartmental fluid flow on CSD wave characteristics in a setting...
Fig. 1. Wave properties during refinement in space ($N$) and time ($\Delta t$, ms) in a 1D domain of length 10 mm at $t = 50$ s. The PDEs are discretized in time by the previously presented first order scheme from Mori, O’Connell, and Tuttle et al.\textsuperscript{24,28,45} and the ODEs are solved using backward Euler. A: Neuron potential $\phi_n(x, 50)$ (mV) versus $x \in \Omega$ (mm). B: CSD mean wave speed $\bar{v}_{\text{CSD}}$ (mm/min) and difference $\Delta \bar{v}_{\text{CSD}}$ between consecutive refinements.

with two compartments (neurons and ECS). Here, we present a low order finite element scheme and simulation results for the full model in three compartments (neurons, glial and ECS) and study the convergence of the scheme. The scheme again displays optimal convergence rates during refinement in space and time for a problem with smooth manufactured solutions, and meets similar challenges as the zero flow limit model for the CSD case.

The paper is organized as follows. The Mori framework is summarized in Section 2. In Section 3 we present new numerical schemes for the zero flow limit version of the model, along with numerical convergence and performance studies for the suggested schemes in Section 4 and Section 5. The next sections consider the full model. We present a numerical scheme in Section 6 along with numerical convergence studies in Section 7 while in Section 8 we present results from a full model simulation of CSD including microscopic fluid dynamics. Finally, Section 9
contains a discussion and concluding remarks. The code used to obtain the simulation results presented within this work is based on FEniCS\textsuperscript{23}, and is publicly available\textsuperscript{9}.

2. Mathematical model

The tissue of interest is represented as a domain $\Omega \subset \mathbb{R}^d$, with $d \in \{1, 2, 3\}$. Moreover, the tissue is composed of $R$ compartments indexed by $r = 1, \ldots, R$. We assume that $r = R$ always denotes the ECS, and that other compartments communicate with the ECS only. Let time $t \in (0, T]$. For a self-contained exposition, we summarize the Mori framework\textsuperscript{24} below.

2.1. Governing equations

We will consider the following system of coupled, time-dependent, nonlinear partial differential equations. Find the volume fractions $\alpha_r : \Omega \times (0, T] \rightarrow [0, 1)$ such that for each $t \in (0, T]$: \begin{align}
\frac{\partial \alpha_r}{\partial t} + \nabla \cdot (\alpha_r u_r) &= -\gamma_r w_{rR}, \quad \text{for } r = 1, \ldots, R - 1, \quad (2.1a) \\
\frac{\partial \alpha_R}{\partial t} + \nabla \cdot (\alpha_R u_R) &= \sum_{r=1}^{R-1} \gamma_r w_{rR}, \quad (2.1b)
\end{align}
where $u_r : \Omega \times (0, T] \rightarrow \mathbb{R}^d$ is the fluid velocity field of compartment $r$ (m/s). The transmembrane water flux $w_{rR}$ between compartment $r$ and the ECS is driven by osmotic and oncotic pressure, and will be discussed further in Section 2.2. The coefficient $\gamma_r$ (1/m) represents the area of cell membrane between compartment $r$ and the ECS per unit volume of tissue. By definition, the volume fractions sum to 1, and hence:

$$\alpha_R = 1 - \sum_{r=1}^{R-1} \alpha_r. \quad (2.2)$$

where $\alpha_r \geq 0$. Further, for each ion species $k \in K$, find the ion concentrations $[k]_r : \Omega \times (0, T] \rightarrow \mathbb{R}$ (mol/m$^3$) and the electrical potentials $\phi_r : \Omega \times (0, T] \rightarrow \mathbb{R}$ (V) such that for each $t \in (0, T]$: \begin{align}
\frac{\partial (\alpha_r[k]_r)}{\partial t} + \nabla \cdot J^k_r &= -\gamma_r w_{rR} J^k_{rR}, \quad \text{for } r = 1, \ldots, R - 1, \quad (2.3a) \\
\frac{\partial (\alpha_R[k]_R)}{\partial t} + \nabla \cdot J^k_R &= \sum_{r=1}^{R-1} \gamma_r w_{rR} J^k_{rR}, \quad (2.3b)
\end{align}
where $J^k_r : \Omega \times (0, T] \rightarrow \mathbb{R}^d$ is the ion flux density (mol/(m$^2$s)) for each ion species $k$. Modelling the transmembrane ion flux density (mol/(m$^2$s)) $J^k_{rR}$ for each ion species $k \in K$ will be discussed further in Section 2.2. Note that (2.3) follow from first principles and express conservation of ion concentrations for the bulk of each
region. Moreover, we assume that the ion flux densities (and a fortiori the ion concentrations and electrical potentials) satisfy:

\[ \gamma_r C_r \phi_r = \sum_k z^k [k]_r, \quad r = 1, \ldots, R - 1, \]  

(2.4a)

\[ -\sum_r \gamma_r C_r \phi_r = \sum_k z^k [k]_R, \]  

(2.4b)

where \( z^k \) (dimensionless) is the valence of ion species \( k \), \( \alpha_r \) (mol/m\(^3\)) is the amount of immobile ions, \( F \) (C/mol) denotes Faraday’s constant, and \( C_R \) (F/m\(^2\)) is the membrane capacitance of the membrane between compartment \( r \) and the ECS.

In this paper, we assume that the ion flux densities \( J_r^k \) can be expressed in terms of the ion concentrations, the electrical potentials, the volume fractions and the fluid velocity field as:

\[ J_r^k = -D_r^k \nabla [k]_r - \frac{D_r^k z^k}{\psi} [k]_r \nabla \phi_r + \alpha_r u_r [k]_r, \quad r = 1, \ldots, R. \]  

(2.5)

Here, \( D_r^k \) (m\(^2\)/s) denotes the effective diffusion coefficient of ion species \( k \) in the region \( r \) and may be a given constant or e.g. a spatially varying scalar field dependent of \( \alpha_r \). The constant \( \psi = RTF^{-1} \) combines Faraday’s constant \( F \), the absolute temperature \( T \) (K), and the gas constant \( R \) (J/(K mol)). We assume that the system is isothermal, i.e. \( T \) is constant. The ion flux density, i.e. the flow rate of ions per unit area, is thus modelled as the sum of three terms: (i) the diffusive movement of ions due to ionic concentrations \(-D_r^k \nabla [k]_r\), (ii) the ion concentrations that are transported via electrical potential gradients, i.e. the ion migration \(-D_r^k z^k \psi^{-1}[k]_r \nabla \phi_r\), where \( D_r^k \psi^{-1} \) is the electrochemical mobility and (iii) the convective movement \( \alpha_r u_r [k]_r \) of ions.

We now turn to the dynamics of the fluid velocity field \( u_r \) and the mechanical pressure \( p_r : \Omega \times (0, T] \to \mathbb{R} \) (Pa). Let the compartmental fluid velocity \( u_r \) (m/s) be expressed as:

\[ u_r = -\kappa_r \left( \nabla \tilde{p}_r + F \sum_k z^k [k]_r \nabla \phi_r \right), \quad \tilde{p}_r = p_r - RT \frac{\alpha_r}{\alpha_r} \]  

(2.6)

where \( \kappa_r \) (m\(^4\)/(N s)) is the water permeability in compartment \( r \). The fluid velocity field is thus modelled as the sum of three terms: (i) the mechanical pressure gradient \(-\kappa_r \nabla p_r\), (ii) the osmotic pressure gradient \( \kappa_r \nabla (RT \frac{\alpha_r}{\alpha_r})\), and (iii) the electrostatic forces \(-\kappa_r F \sum_k z^k [k]_r \nabla \phi_r\). The mechanical pressure \( p_r \) in compartment \( r \) and in the ECS \( p_R \) may be related as:

\[ p_r - p_R = \tau_r (\alpha_r), \quad r = 1, \ldots, R - 1, \]  

(2.7)

where the mechanical tension per unit area of the membrane \( \tau_r = \tau_r (\alpha_r) \) is to be modelled. A simple relation could be \( \tau_r = S_r (\alpha_r - \alpha_r^0) \), where \( S_r \) (Pa/m\(^3\)) denotes the stiffness of the membrane between compartment \( r \) and the ECS, and \( \alpha_r^0 \) is the
volume fraction at which the membrane has no mechanical tension. Furthermore, we assume that the volume–fraction weighted velocity is divergence free, that is:

$$\nabla \cdot \left( \sum_{r=1}^{R} \alpha_r u_r \right) = 0. \quad (2.8)$$

Upon inserting (2.6)–(2.7) into (2.8), we obtain the following equation for the extracellular mechanical pressure $p_R : \Omega \times (0,T) \to \mathbb{R}$ (Pa),

$$\nabla \cdot \left( \sum_{r=1}^{R} \kappa_r \alpha_r \left( -\nabla p_R + \nabla RT \frac{a_r}{\alpha_r} - F \sum_{k} z^k[k]_r \nabla \phi_r \right) - \sum_{r=1}^{R-1} \kappa_r \alpha_r \nabla \tau_r \right) = 0. \quad (2.9)$$

The combination of (2.1a) and (2.2)–(2.4), together with the insertion of (2.5)–(2.6) and (2.9), defines a system of $|R||K|+2|R|+1$ equations for the $|R||K|+2|R|+1$ unknown scalar fields. Appropriate initial conditions, boundary conditions, and importantly membrane mechanisms close the system.

### 2.2. Membrane mechanisms

The transmembrane water flux $w_{r,R}$ is driven by a combination of mechanical and osmotic pressure, and can be expressed as:

$$w_{r,R} = \eta_r \left( p_r - p_R + RT \left( \frac{a_r}{\alpha_r} + \sum_{k} [k]_r - \sum_{k} [k]_r \right) \right), \quad (2.10)$$

where $\eta_r \text{ (m}^4/\text{mol s})$ denotes the water permeability. The compartmental and extracellular potentials across the membrane are coupled by defining $\phi_{r,R}$ as the jump in the electrical potential across the membrane between compartment $r$ and the ECS (c.f. (2.4)),

$$\phi_{r,R} = \phi_r - \phi_R. \quad (2.11)$$

The transmembrane ion flux $J_{r,R}^k$ between compartment $r$ and the ECS of ion species $k$ is subject to modelling, and will typically take the form:

$$J_{r,R}^k = a_{r,R}^k(\phi_{r,R},[k]_r) + p_{r,R}^k(\phi_{r,R},[k]_r, s_1, \ldots, s_M). \quad (2.12)$$

Here, $a_{r,R}^k$ represents active membrane mechanisms (e.g. ionic pumps) and $p_{r,R}^k$ denotes passive membrane mechanisms (e.g. leak or voltage gated ion channels, co-transporters). The passive membrane mechanisms typically depend on (unitless) gating variables $s_m = s_m(\phi_{r,R})$ for $m \in 1, \ldots, M$ governed by an ODE system of the form:

$$\frac{\partial s_m}{\partial t} = \alpha_m (1 - s_m) - \beta_m s_m, \quad (2.13)$$

where $\alpha_m = \alpha_m(\phi_{r,R}) \text{ (1/s)}$ and $\beta_m = \beta_m(\phi_{r,R}) \text{ (1/s)}$ are rate coefficients.
2.3. Boundary conditions

The boundary conditions will strongly depend on the problem of interest. If not otherwise stated, we assume that no ion flux or fluid leaves on the boundary \( \partial \Omega \), that is,

\[
J^k_r(x,t) = 0 \quad \text{and} \quad u_r(x,t) = 0, \quad \text{on} \ \partial \Omega,
\]

for \( r = 1, \ldots, R \).

2.4. Effective diffusion coefficients

We model the effective diffusion coefficients \( D^k_r \) for each ion species \( k \in K \) by:

\[
D^k_r = \alpha_r \chi_r D^k \quad \text{and} \quad D^k_R = \alpha_R D^k,
\]

for \( r = 1, \ldots, R - 1 \), where \( D^k \ (\text{m}^2/\text{s}) \) denotes the diffusion coefficient in water and \( \chi_r \) (dimensionless) reflects the cellular gap junction connectivity.

2.5. Zero flow limit

We first consider a simplified version of the mathematical model presented in Section 2, where the compartmental fluid velocity \( u_r \) for \( r = 1, \ldots, R \) is assumed to be zero. Thus, the advective terms in (2.1a) and (2.5) vanish and (2.9) is decoupled from the rest of the system. The remaining equations, (2.1a) and (2.2)–(2.4) with the insertion of (2.5), describe the dynamics of the volume fractions \( \alpha_r \), the ion concentrations \([k]_r \) and the electrical potentials \( \phi_r \), for \( r \in \{1, \ldots, R\} \) and for each \( k \in K \).

3. Numerical schemes for the zero flow limit

Below, we present two numerical schemes for the zero flow limit model based on the finite element method.

3.1. Spatial discretization

To obtain a variational formulation, we multiply (2.1a) and (2.3)–(2.4) with suitable test functions, integrate over the domain \( \Omega \), integrate terms with higher order derivatives by parts, and insert the boundary condition (2.14). Below, we let \( \langle u, v \rangle = \int_\Omega uv \, \text{d}x \). Let \( S_r \subset L^2(\Omega), \ V^k_r \subset H^1(\Omega), \ V^k_R \subset H^1(\Omega), \ T_r \subset H^1(\Omega) \), and \( T_R \subset H^1(\Omega) \) for \( r = 1, \ldots, R - 1 \) be spaces of functions for \( k = 1, \ldots, |K| \). The resulting system reads: find \( \alpha_r \in S_r, \ [k]_r \in V^k_r, \ \phi_r \in T_r \ (r = 1, \ldots, R - 1), \ [k]_R \in V^k_R, \)
and \( \phi_R \in T_R \) such that:

\[
\begin{align*}
\langle \partial \alpha_r / \partial t, s_r \rangle + \gamma_{rR} \langle w_{rR}, s_r \rangle &= 0, \\
\langle \partial \alpha_r[k]_r / \partial t, \psi_k^r \rangle - \langle J^k_r, \nabla \psi_k^r \rangle + \gamma_{rR} \langle J^k_{rR}, \psi_k^r \rangle &= 0, \\
\langle \partial \alpha_R[k]_R / \partial t, \psi_k^R \rangle - \langle J^k_R, \nabla \psi_k^R \rangle - \sum_r \gamma_{rR} \langle J^k_{rR}, \psi_k^r \rangle &= 0, \\
\langle \gamma_{rR} C_r \phi_{rR}, t_r \rangle - \langle z^0 F a_r, t_r \rangle - \langle F \alpha_r \sum_k z^k [k]_r, t_r \rangle &= 0, \\
- \sum_r \langle \gamma_{rR} C_r \phi_{rR}, t_R \rangle - \langle z^0 F a_R, t_R \rangle - \langle F \alpha_R \sum_k z^k [k]_R, t_R \rangle &= 0,
\end{align*}
\]
φ_R ∈ T_R such that:

\[ \frac{1}{\Delta t}(\alpha_r - \frac{4}{3} \alpha^n_r + \frac{1}{3} \alpha^{n-1}_r, s_r) + \frac{2}{3} \gamma_R \langle w_R, s_r \rangle = 0, \]  
(3.2a)

\[ \frac{1}{\Delta t}(\alpha_r[k]_r - \frac{4}{3} \alpha^n_r[k]^n_r + \frac{1}{3} \alpha^{n-1}_r[k]^{n-1}_r, v^k_r) - \frac{2}{3} \langle J^{k,n}_r, \nabla v^k_r \rangle + \frac{2}{3} \gamma_R \langle J^{k,n}_r, v^k_r \rangle = 0, \]  
(3.2b)

\[ \frac{1}{\Delta t}(\alpha_R[k]_R - \frac{4}{3} \alpha^n_R[k]^n_R + \frac{1}{3} \alpha^{n-1}_R[k]^{n-1}_R, v^k_R) - \frac{2}{3} \langle J^{k,n}_R, \nabla v^k_R \rangle + \frac{2}{3} \gamma_R \langle J^{k,n}_R, v^k_R \rangle = 0, \]  
(3.2c)

\[ \langle \gamma_R G_C R \phi_R, t_r \rangle - \langle z^0 F a_r, t_r \rangle - \langle F a_r \sum_k z^k[k]_r, t_r \rangle = 0, \]  
(3.2d)

\[ - \sum_r \langle \gamma_R G_C R \phi_R, t_r \rangle - \langle z^0 F a_R, t_R \rangle - \langle F a_R \sum_k z^k[k]_R, t_R \rangle = 0, \]  
(3.2e)

for all s_r ∈ S_r, v^k_r ∈ V^k_R, v^k_R ∈ V^k_R, t_r ∈ T_r, t_R ∈ T_R. The solutions at time level 1 and 0 are given by a backward Euler step and the initial conditions, respectively. Note that the passive part of the membrane flux J^{k,n}_R is treated implicitly, whereas the active part is treated explicitly, both in the BDF2 and the BE time stepping schemes (see (2.12)).

We will also compare with the following Crank-Nicholson (CN) scheme in time: given α^n_r, [k]^n_r, and [k]_R^n at time level n, find at time level n + 1 the volume fractions α_r ∈ S_r, the ion concentrations [k]_r ∈ V^k_R, [k]_R ∈ V^k_R, and the potentials φ_r ∈ T_r, φ_R ∈ T_R, such that:

\[ \frac{1}{\Delta t}(\alpha_r - \alpha^n_r, s_r) + \gamma_R \langle w^{n+1/2}_R, s_r \rangle = 0, \]  
(3.3a)

\[ \frac{1}{\Delta t}(\alpha_r[k]_r - \alpha^n_r[k]^n_r, v^k_r) - \langle J^{k,n+1/2}_r, \nabla v^k_r \rangle + \gamma_R \langle J^{k,n+1/2}_r, v^k_r \rangle = 0, \]  
(3.3b)

\[ \frac{1}{\Delta t}(\alpha_R[k]_R - \alpha^n_R[k]^n_R, v^k_R) - \langle J^{k,n+1/2}_R, \nabla v^k_R \rangle - \sum_{r} \gamma_R \langle J^{k,n+1/2}_R, v^k_R \rangle = 0, \]  
(3.3c)

along with (3.2d) and (3.2e), for all s_r ∈ S_r, v^k_r ∈ V^k_R, v^k_R ∈ V^k_R, t_r ∈ T_r, t_R ∈ T_R. Here, f^{n+1/2} denotes the solution at time level n + 1/2 and is approximated by (f^n + f^{n+1})/2, for f ∈ {w_R, J^k_R, J^k_R}.

### 3.3. Strang splitting scheme

We use a second order Strang splitting scheme where we solve the coupled systems of ODEs and PDEs step-wise in the following manner:

1. Insert the previous solution of φ_R, [k]_r, [k]_R into the system of ODEs (2.13), and solve ODEs for a half timestep Δt/2;
2. Solve the system of PDEs (e.g. (3.2)) with values for the gating variables s_1, s_2, ..., s_M from step (1) for one time step Δt.
(3) Insert solution for $\phi_R$, $[k]_r$, $[k]_R$ from step (2) into the system of ODEs (2.13), and solve the ODEs for a half timestep $\Delta t/2$; and continue steps (1)–(3) until the global end time is reached. We compare the Strang splitting scheme with a first order Godunov scheme; see e.g. Sundnes et al.\textsuperscript{[10]} for a detailed description the Godunov method.

3.4. ODE solvers

We consider three different schemes for the ODE time-stepping: a fourth order Runge-Kutta (RK4) method, a fourth order explicit singly diagonal implicit Runge-Kutta (ESDIRK4) method or a second order backward Euler (BE) method. The ODEs are solved with the RK4 method unless otherwise stated. See e.g. Langtangen and Linge\textsuperscript{[22]} for details.

4. Numerical convergence study: smooth analytical solution

To evaluate the numerical accuracy of the various schemes presented above, we begin by constructing a smooth analytical solution using the method of manufactured solutions\textsuperscript{[33]}.

4.1. Problem description

We consider a two-compartment version of the model in the zero flow limit and a neuronal ($n$, $r = 1$) and an extracellular ($e$, $r = 2$) compartment. We use $1, 2$ and $n, e$ interchangeably for subscripts of our variables and model parameters. In each compartment, we model the movement of potassium ($\text{K}^+$), sodium ($\text{Na}^+$) and chloride ($\text{Cl}^-$). In the numerical experiments of this test, we consider a one dimensional domain $\Omega = [0, 1]$ uniformly meshed with $N \in \{8, 16, 32, 64, 128\}$ elements. We initially set $\Delta t = 10^{-3}$ s, and then halve the timestep with each spatial refinement. The errors are evaluated at $t = 2 \times 10^{-3}$ s. Further, we assume that the transmembrane ion flux $J_{ne}^k$ depends on the gating variables $m, h$ and $g$ governed by the following ODEs:

\begin{equation}
\frac{\partial m}{\partial t} = \phi_{ne}, \quad \frac{\partial h}{\partial t} = \phi_{ne}, \quad \frac{\partial g}{\partial t} = \phi_{ne},
\end{equation}

where $\phi_{ne} = \phi_n - \phi_e$ is the membrane potential. The analytical solution to the PDE system is given by:

$$
\begin{align*}
\alpha_n &= 0.3 - 0.1 \sin(2\pi x) \exp(-t), \\
[\text{Na}^+]_n &= 0.7 + 0.3 \sin(\pi x) \exp(-t), \\
[\text{K}^+]_n &= 0.3 + 0.3 \sin(\pi x) \exp(-t), \\
[\text{Cl}^-]_n &= 1.0 + 0.6 \sin(\pi x) \exp(-t), \\
\phi_n &= \sin(2\pi x) \exp(-t),
\end{align*}
\begin{align*}
[\text{Na}^+]_e &= 1.0 + 0.6 \sin(\pi x) \exp(-t), \\
[\text{K}^+]_e &= 1.0 + 0.2 \sin(\pi x) \exp(-t), \\
[\text{Cl}^-]_e &= 2.0 + 0.8 \sin(\pi x) \exp(-t), \\
\phi_e &= \sin(2\pi x)(1 + \exp(-t)).
\end{align*}
$$
and the solution to the system of ODEs (4.1) is

\[ m = \cos(t) \cos(\pi x), \quad h = \cos(t) \cos(\pi x), \quad g = \cos(t) \cos(\pi x). \]  

Parameter values are given in Table 1. Initial and boundary conditions are governed by the exact solutions (4.2).

| Parameter                               | Symbol | Value     | Unit       | Ref. |
|-----------------------------------------|--------|-----------|------------|------|
| Temperature                             | \( T \) | 310       | K          | –    |
| Faraday’s constant                      | \( F \) | 96485     | C/mol      | –    |
| Gas constant                            | \( R \) | 8.3144598 | J/(mol K)  | –    |
| Membr. area-to-volume neuron            | \( \gamma_{ne} \) | \( 6.3849 \times 10^5 \) | 1/m | 19 |
| Membr. capacitance neuron               | \( C_{ne} \) | \( 7.5 \times 10^{-3} \) | F/m² | 19 |
| Membr. water permeability neuron        | \( \eta_{ne} \) | \( 5.4 \times 10^{-10} \) | m³/(mol s) | 28 |
| Gap junction connectivity neuron        | \( \chi_n \) | 0         |           | 23 |
| Diffusion coefficient \( \text{Na}^+ \) | \( D_{\text{Na}} \) | \( 1.33 \times 10^{-9} \) | m²/s | 17 |
| Diffusion coefficient \( \text{K}^+ \)   | \( D_{\text{K}} \) | \( 1.96 \times 10^{-9} \) | m²/s | 17 |
| Diffusion coefficient \( \text{Cl}^- \)  | \( D_{\text{Cl}} \) | \( 2.03 \times 10^{-9} \) | m²/s | 17 |
| Valence \( \text{Na}^+ \)               | \( z_{\text{Na}} \) | 1         |           | –   |
| Valence \( \text{K}^+ \)                | \( z_{\text{K}} \) | 1         |           | –   |
| Valence \( \text{Cl}^- \)              | \( z_{\text{Cl}} \) | –1        |           | –   |

Table 1. Physical model parameters. We use SI base units, that is, Kelvin (K), Coulomb (C), mole (mol), meter (m), second (s), and Joule (J). The values are collected from Hille et al.\cite{17}, Kager et al.\cite{19}, Mori\cite{24}, and O’Connell et al.\cite{28}. – indicates that a standard value is used.

4.2. Convergence and convergence rates under refinement

Based on the approximation spaces and the time discretization, we expect the optimal theoretical rate of convergence to be 1 in the \( H^1 \)-norm and 2 in the \( L^2 \)-norm for the concentrations \([k]_n, [k]_e\), the potentials \( \phi_n, \phi_e \) and the gating variables \( m, h, g \), and 1 in the \( L^2 \)-norm for the volume fraction \( \alpha_n \). Our numerical observations are in agreement with these optimal rates, both for the BDF2 scheme (Table 2A) and for the CN scheme (Table 2B). We observe second order convergence in the \( L^2 \)-norm for the approximation of the extracellular and intracellular concentrations and potentials, and first order convergence in the \( H^1 \)-norm. The neuron potential approximated by the CN scheme displays superconvergence between \( N = 64 \) and \( N = 128 \) (Table 2B). For the volume fractions, we observe a convergence rate of 1 in the \( L^2 \)-norm.
Table 2. Selected $L^2$ (upper panel) and $H^1$-errors (lower panel) and convergence rates (in parenthesis) for the BDF2 (A) and CN (B) schemes at time $t = 0.002$ s. The test was run on the unit interval, and we initially let $\Delta t = 1 \times 10^{-3}$ s, and then halve the timestep with each mesh refinement. The spatial discretization consists of $N$ intervals.

### A

| $N$ | $||[\text{Na}] - [\text{Na}]_h||_{L^2}$ | $||\phi_n - \phi_{nh}||_{L^2}$ | $||\alpha_n - \alpha_{nh}||_{L^2}$ | $||m - m_h||_{L^2}$ |
|-----|-----------------------------------|--------------------------|--------------------------|--------------------------|
| 8   | 5.74E-03 (—–)                     | 7.66E-02 (—–)          | 1.58E-02 (—–)          | 9.99E-03 (—–)          |
| 16  | 1.45E-03 (1.99)                   | 1.90E-02 (2.01)       | 7.97E-03 (0.98)       | 2.50E-03 (2.00)       |
| 32  | 3.63E-04 (1.99)                   | 4.72E-03 (2.01)       | 4.00E-03 (1.00)       | 6.26E-04 (2.00)       |
| 64  | 9.11E-05 (2.00)                   | 1.17E-03 (2.01)       | 2.00E-03 (1.00)       | 1.56E-04 (2.00)       |
| 128 | 2.28E-05 (2.00)                   | 2.93E-04 (2.00)       | 1.00E-03 (1.00)       | 3.91E-05 (2.00)       |

### B

| $N$ | $||[\text{Na}] - [\text{Na}]_h||_{H^1}$ | $||\phi_n - \phi_{nh}||_{H^1}$ | $||\alpha_n - \alpha_{nh}||_{L^2}$ | $||m - m_h||_{L^2}$ |
|-----|-----------------------------------|--------------------------|--------------------------|--------------------------|
| 8   | 1.50E-01 (—–)                     | 1.02E+00 (—–)          |                          |                          |
| 16  | 7.53E-02 (1.00)                   | 5.05E-01 (1.02)       |                          |                          |
| 32  | 3.77E-02 (1.00)                   | 2.52E-01 (1.00)       |                          |                          |
| 64  | 1.88E-02 (1.00)                   | 1.26E-01 (1.00)       |                          |                          |
| 128 | 9.43E-03 (1.00)                   | 6.28E-02 (1.00)       |                          |                          |

### 5. Numerical convergence study: physiological CSD wave

Next, we consider the simulation of cortical spreading depression with a sharp wave front. This is a more challenging problem, with characteristics quite different from the previous smooth MMS case. We numerically study the effect of splitting scheme, time-discretization of the PDEs, and discretization of the ODEs.
5.1. Problem description

| Parameter                        | Symbol         | Value   | Unit   | Ref. |
|----------------------------------|----------------|---------|--------|------|
| Na\(^{+}\) leak conductance neuron | \(g_{Na,\text{leak}}\) | 0.2     | S/m\(^2\) | 19   |
| K\(^{+}\) leak conductance neuron | \(g_{K,\text{leak}}\) | 0.7     | S/m\(^2\) | 19   |
| Cl\(^{-}\) leak conductance neuron | \(g_{Cl,\text{leak}}\) | 2.0     | S/m\(^2\) | 25   |
| Maximum pump rate neuron         | \(I_n\)       | 0.1372  | A/m\(^2\) | 35   |
| Threshold for pump [Na\(^{+}\)] \(r\) | \(m_{Na}\)    | 7.7     | mol/m\(^3\) | 48   |
| Threshold for pump [K\(^{+}\)] \(R\) | \(m_{K}\)     | 2.0     | mol/m\(^3\) | 48   |

Table 3. Physical parameters for the neuron membrane mechanisms. We use SI base units, i.e. meter (m), mole (mol), Siemens (S) and ampere (A). The values are collected from Kager et al\(^{19}\), O’Connell et al\(^{28}\) and Yao et al\(^{48}\).

We define a more physiological version of the mathematical model considered in Section 4.1 (two compartments, zero flow limit, and a neuronal \((n, r = 1)\) and an extracellular compartment \((e, r = 2)\)). In each compartment, we again model the movement of potassium (K\(^{+}\)), sodium (Na\(^{+}\)) and chloride (Cl\(^{-}\)). We consider a 1D domain of length 0.01 m (10 mm), and now apply physiologically relevant neuronal membrane mechanisms as described below, notably including a system of ODEs describing the gating variables of voltage-gated sodium and potassium channels. The domain and the transmembrane ion flux densities are taken from the original Mori study\(^{24}\).

Concretely, the transmembrane ion flux densities \(J_{ne}^k\) for \(k = \{\text{Na}^{+}, \text{K}^{+}, \text{Cl}^{-}\}\) in \(^{23}\) are modelled as:

\[
J_{ne}^{Na} = \frac{1}{F z_{Na}} (I_{n,\text{leak}}^{Na} + I_{NaP} + 3I_{n,\text{ATP}} + I_{ex}^{Na}),
\]  
\[
J_{ne}^{K} = \frac{1}{F z_{K}} (I_{n,\text{leak}}^{K} + I_{KDR} + I_{KA} - 2I_{n,\text{ATP}} + I_{ex}^{K}),
\]  
\[
J_{ne}^{Cl} = \frac{1}{F z_{Cl}} (I_{n,\text{leak}}^{Cl} + I_{ex}^{Cl}),
\]

where \(I_{n,\text{leak}}^{Na}, I_{n,\text{leak}}^{K}, I_{n,\text{leak}}^{Cl}, I_{NaP}, I_{KDR}, I_{KA},\) and \(I_{n,\text{ATP}}\) denote the sodium leak current, the potassium leak current, the chloride leak current, the persistent sodium current, the potassium delayed rectifier current, the transient potassium current, and the Na/K/ATPase current, respectively. Further, \(I_{ex}^{Na}, I_{ex}^{K},\) and \(I_{ex}^{Cl}\) are excitatory fluxes used to trigger a cortical spreading depression wave and whose expressions are given by \(^{5.5}\) in Section 5.1.1 below. Note that the currents (A/m\(^2\)) are converted to ion fluxes (mol/(m\(^2\)s)) by dividing by Faraday’s constant \(F\) times the valence \(z^k\).

The leak currents (A/m\(^2\)) of ion species \(k\) over the membrane between compart-
membrane permeability and conductance. The gating variables ODEs: the proportion of open voltage–gated ion channels, and are governed by the following

\[ I^{k}_{\text{leak}} = g^{k}_{\text{leak}}(E^{k}_{r} - E^{k}_{r}), \quad E^{k}_{r} = \frac{RT}{Fz^{k}} \ln \left( \frac{[k]_{R}}{[k]_{r}} \right), \] (5.2)

where \( E^{k}_{r} \) (V) denotes the Nernst potential. The values for the neuronal leak conductances \( g^{k}_{\text{leak}} \) are listed in Table 3.

The current-voltage relation for the voltage-gated currents \( I_{\text{NaP}}, I_{\text{KDR}} \) and \( I_{\text{KAP}} \) (A/m²) are described by the Goldman-Hodgkin-Katz (GHK) current equation:

\[ I^{k}_{\text{GHK}} = g^{k}_{m}p hq \frac{F\mu ([k]_{e} - [k]_{n}e^{-\mu})}{1 - e^{-\mu}}. \]

Here, \( \mu = F\phi_{ne}/(RT) \) is dimensionless, while \( g^{k} \) (m/s) denotes the product of membrane permeability and conductance. The proportion of open voltage–gated ion channels, and are governed by the following ODEs:

\[ \frac{\partial m}{\partial t} = \alpha_{m}(\phi_{ne})(1 - m) - \beta_{m}(\phi_{ne})m, \] (5.3a)
\[ \frac{\partial h}{\partial t} = \alpha_{h}(\phi_{ne})(1 - h) - \beta_{h}(\phi_{ne})h, \] (5.3b)

where the activation rate functions \( \alpha_{m} : \mathbb{R} \to \mathbb{R} \) and \( \beta_{m} : \mathbb{R} \to \mathbb{R} \), and the inactivation rate functions \( \alpha_{h} : \mathbb{R} \to \mathbb{R} \) and \( \beta_{h} : \mathbb{R} \to \mathbb{R} \), are specified for each current in Table 4. The initial conditions are given in Table 12A (Supplementary Tables).

| Current      | Permeability | Gates | Voltage dependent rate constants |
|--------------|--------------|-------|----------------------------------|
| \( I_{\text{NaP}} \) | 2.0 × 10⁻⁷   | m² h  | \( \alpha_{m} = 1/(6 + 6 \exp(-0.143\phi_{ne} - 5.67)) \)
|              |              |       | \( \beta_{m} = 1/6 - \alpha_{m} \)
|              |              |       | \( \alpha_{h} = 5.12 \times 10^{-8} \exp(-0.056\phi_{ne} - 2.94) \)
|              |              |       | \( \beta_{h} = 1.6 \times 10^{-6}/(1 + \exp(-0.2\phi_{ne} - 8)) \) |
| \( I_{\text{KDR}} \) | 1.0 × 10⁻⁵   | m     | \( \alpha_{m} = 0.016 \frac{-\phi_{ne} - 34.9}{\exp(-0.20\phi_{ne} - 6.98) - 1} \)
|              |              |       | \( \beta_{m} = 0.25 \exp(-0.025\phi_{ne} - 1.25) \) |
| \( I_{\text{KAP}} \) | 2.0 × 10⁻⁶   | m² h  | \( \alpha_{m} = 0.02 \frac{-\phi_{ne} - 56.9}{\exp(-0.10\phi_{ne} - 56.9) - 1} \)
|              |              |       | \( \beta_{m} = 0.0175 \frac{\phi_{ne} + 29.9}{\exp(0.1\phi_{ne} + 29.9) - 1} \) |
|              |              |       | \( \alpha_{h} = 0.016 \exp(-0.05\phi_{ne} - 4.61) \)
|              |              |       | \( \beta_{h} = 0.5/(\exp(-0.2\phi_{ne} - 11.98) + 1) \) |

Table 4. Permeability, gates and voltage dependent expressions for the activation rates (\( \alpha \)) and the inactivation rates (\( \beta \)) for the persistent sodium current (\( I_{\text{NaP}} \)), the potassium delayed rectifier current (\( I_{\text{KDR}} \)) and the transient potassium current (\( I_{\text{KAP}} \)) in the neuron membrane. The values are collected from Kager et al.\(^{179}\) and Yao et al.\(^{38}\)
The Na/K/ATPase pump exchanges 2 potassium ions for 3 sodium ions, and the pump current $I_{r, \text{ATP}}$ (A/m$^2$) over the membrane between compartment $r$ (here with $r = n$) and $R$ is modelled as:

$$I_{r, \text{ATP}} = \frac{\dot{I}_r}{(1 + \frac{m_K}{[K^+]_r})^2(1 + \frac{m_{Na}}{[Na^+]_r})^3},$$

(5.4)

where $\dot{I}_r$ is the maximum pump rate, and $m_{Na}$ and $m_K$ denote the sodium and potassium pump threshold, respectively. The values for the neuron pump parameters are listed in Table 3.

5.1.1. Initiation of the CSD wave

Following the original Mori study $^{24}$, we initiate a CSD wave by adding excitatory fluxes to the transmembrane fluxes defined by (5.1) in the following manner:

$$I^{k}_{\text{ex}} = G_{\text{ex}}(E^{k}_r - \phi_{nR}),$$

$$G_{\text{ex}}(x,t) = \begin{cases} G_{\text{max}} \cos^2(\pi x/2L_{\text{ex}}) \sin(\pi t/T_{\text{ex}}) & \text{if } x \leq L_{\text{ex}} \text{ and } t \leq T_{\text{ex}}, \\ 0 & \text{otherwise}, \end{cases}$$

(5.5)

for $k = \{Na^+, K^+, Cl^-\}$. We set $L_{\text{ex}} = 2.0 \times 10^{-5}$ m, $T_{\text{ex}} = 2$ s, and $G_{\text{max}} = 5.0$ S/m$^2$.

5.2. CSD wave characteristics

The excitatory flux stimulation leads to a wave of neuronal depolarization, ionic concentration changes and neuronal swelling spreading through the tissue domain (Figure 2). We observe a dramatic depolarization of the neuron potential: from $-71$ mV to $-8.7$ mV, accompanied by a small drop in the extracellular potential: from 0 to $-3.9$ mV. This latter drop is known as the DC shift, a key characteristic associated with cortical spreading depression $^{31}$. The neuronal depolarization wave is followed by a complete break-down of the ionic homeostasis: a substantial increase in the concentrations of extracellular potassium, and decreases in extracellular sodium and chloride. In response to the ionic shifts, the neurons swell with an increase in volume fraction of up to 10%, while the extracellular space shrinks correspondingly. We observe that although we have not enforced positivity of $\alpha_r$ explicitly, $\alpha_r \geq 0$ holds throughout our numerical experiments.

Experimental studies typically focus on the speed and duration of the CSD wave. We thus define the following quantities of interest to be studied further quantitatively in terms of numerical convergence.

- The point of $x_{\text{peak},50}$ of peak neuron potential $\phi_n$ at $t = 50$ s.
- The mean CSD wave speed $\bar{v}_{\text{CSD}}$ is computed by the distance between the peak neuronal potential at two points (as long as $\phi_n > -20$ mV) divided by the time elapsed to cover that distance.
Fig. 2. Snapshot of a CSD wave spreading through the tissue domain – extracellular sodium (Na\(^+\)), potassium (K\(^+\)) and chloride (Cl\(^-\)) concentrations (A, B, C), neuron and extracellular potentials (D, E, F), and neuron and extracellular changes in volume fractions (G, H, I) – at, from left to right, t = 10, 30, 50 s. Numerical scheme and resolutions: BDF2, Strang, RK4 with N = 32000 and \(\Delta t = 0.195\) s.

- The (temporal) duration \(d_{\text{CSD}}\) of the CSD wave in terms of elevated extracellular potassium levels at \(x = 1\) mm, where

\[
T = \{ t \mid [\text{K}^+]_R(1, t) > k_{\text{thres}} \}
\]

\[
d_{\text{CSD}} = \max T - \min T
\]

with \(k_{\text{thres}} = 10\) mM for \(t \in (0, T]\).
• The (spatial) width $w_{CSD}$ of the extracellular potassium wave at $t = 50$ s, where

$$X = \{ x \mid [K^+]_R(x, 50) > k_{\text{thres}} \}$$

$$w_{CSD} = \max X - \min X$$

with $k_{\text{thres}} = 10$ mM for $x \in \Omega$.

5.3. Convergence of the CSD wave characteristics

We begin by considering a reference scheme – based on Strang splitting, a BDF2 method for the PDE time-discretization, and ESDIRK4 for the ODE time-stepping – to compute the mean speed, the (spatial) width, and the (temporal) duration of the CSD wave (cf. Section 5.2) during temporal and spatial refinement, before discussing how variations in terms of splitting scheme, time-stepping and higher order spatial discretization affect accuracy and convergence. Specifically, we apply the reference scheme and calculate the quantities of interest for different mesh resolutions and time steps: $\Delta x_N = 10/N$ mm for $N = 1000, 2000, 4000, 8000, 16000, 32000$ and $\Delta t_i = 12.5/i$ s for $i = 1, 2, 4, 8, 16, 32, 64$. The results are presented in Figure 3.

Wave speeds are converted from the native m/s to mm/min for interpretability. In general, the computed mean wave speed and width increases with decreasing $\Delta t$, and decreases with decreasing $\Delta x$: the smaller the time step, the faster and wider the wave, while the smaller the mesh size, the slower and narrower the wave (Figure 3A). Regarding the mean wave speed (Figure 3B), we observe that the computed values vary substantially, ranging from 5.063 to 10.090 mm/min. We observe that the spatial errors, estimated by proxy by the difference between consecutive spatial refinements, dominate the temporal errors/differences. In particular, the differences $\Delta \bar{v}_{CSD}$ in wave speed between the coarsest mesh sizes $N = 1000$ and 2000 are in the range $1.70 - 2.45$ mm/min. Conversely, the differences in wave speed between the coarsest time steps $\Delta t = 12.5$ and 6.25 are in the range $0.51 - 0.64$ mm/min. For the ultimate spatial and temporal refinement level, we observe a difference of 0.012 and 0.008 mm/min, respectively. Finally, we observe that the wave speed seems to converge in space and time with an estimated wave speed of 5.1 mm/min: the differences $\Delta \bar{v}_{CSD}$ reduce as $\Delta x$ and $\Delta t$ is reduced. There is however no clear rate of convergence.

Similarly, we observe large variations in the computed (spatial) CSD wave width, ranging from 1.121 to 4.420 mm (Figure 3C). The difference $(\Delta w_{CSD})$ varies in the range $0.755 - 1.07$ mm and $0.062 - 0.280$ mm between respectively the coarsest mesh sizes $N = 1000$ and 2000 and the coarsest time steps $\Delta t = 12.5$ and 6.25 s. For the finest time and mesh discretizations, we observe differences of 0.005 mm and 0.002 mm, respectively. Moreover, the differences $\Delta w_{CSD}$ reduce as the mesh size and time step are reduced. As with the mean wave speed, there is no clear rate of convergence. In contrast, the (temporal) duration $d_{CSD}$ of the CSD wave does not change substantially during refinement in space and time: we observe a duration of elevated extracellular potassium levels of $17 - 18$ s for all the spatial
and temporal resolutions considered (results not shown). Finally, we observe that
this implicit higher-order (reference) scheme behaves qualitatively similar to the
implicit lower-order scheme – based on Godunov splitting, a BE method for the
PDE time-discretization, and BE for the ODE time-stepping as shown in Figure 1.

5.4. Choice of discretizations

We turn to evaluate the effect of discretization choices in terms of splitting scheme,
time-stepping, and higher order spatial discretization.

Splitting scheme

To evaluate the second order Strang splitting scheme, we compared the computed
CSD wave characteristics, peak neuron potentials, and wave speeds with those com-
puted using a first order Godunov splitting scheme (cf. Section 3.3). The computed
wave speeds are comparable at given resolutions, and we observe a similar differ-
ence decay ($\Delta \bar{v}$) for the Strang and Godunov splitting schemes (see Table 10 in
Supplementary Tables).

Time stepping

To assess how the choice of PDE time stepping affects the convergence of the nu-
merical schemes, we repeat the convergence study presented above in Section 5.3
replacing the BDF2 scheme by a Crank-Nicolson (CN) scheme and ESDIRK4 by
RK4 for the ODE time stepping (Table 5). We note that choosing an explicit ODE
time stepping scheme (RK4) here is based on the observation that CN for the PDE
time stepping in combination with implicit ODE time stepping schemes results in
a diverging (non-linear) ODE solver.

Importantly, we note that the PDE Newton solver fails to converge for $\Delta t \geq$
1.563 ms for this scheme. Again, we observe that the computed speed and width of
the wave decreases with decreasing $\Delta x$, and is essentially constant with decreasing
$\Delta t$ (likely due to the already fine timestep required for convergence of the PDE
Newton solver). The spatial errors, estimated by proxy by the difference between
consecutive spatial refinements, are comparable to those reported for BDF2, and
again we obtain an estimated wave speed of 5.1 mm/min for this model scenario.

To assess how the choice of ODE time stepping affects the convergence of the
numerical schemes, we repeat the convergence study presented above in Section 5.3
replacing ESDIRK4 by a first-order Backward Euler (BE) scheme or an explicit
4th order Runge-Kutta (RK4) method. For the RK4 method, we observe nearly
indistinguishable results as for ESDIRK4 with the important distinction that the
RK4 solvers fail to converge for $\Delta t \geq 3.125$ ms (see Supplementary Tables, Ta-
ble 11A). Also for the BE scheme, the computed wave speed values are similar,
Fig. 3. CSD wave characteristics and quantities of interest under refinement in space (rows) and
time (columns). A: Neuron potential \( \phi_n(x, 50) \) (mV) versus \( x \in \Omega \) (mm), where green, yellow, and
red represent wave speeds differing by respectively \( \pm 5\% \), \( \pm 15\% \), and more than \( \pm 15\% \) from our
estimated wave speed of \( 5.1 \text{ mm/min} \). B: CSD mean wave speed \( \mathring{v}_{\text{CSD}} \) (mm/min) and difference
\( \Delta \mathring{v}_{\text{CSD}} \) between consecutive refinements. C: Wave width \( w_{\text{CSD}} \) (mm) at \( t = 50 \text{ s} \) and difference
\( \Delta w_{\text{CSD}} \) between consecutive refinements. Numerical scheme: Strang splitting, BDF2, ESDIRK4.
Table 5. CSD wave characteristics and quantities of interest under refinement in space (rows) and time (columns). A: CSD mean wave speed $\bar{v}_{\text{CSD}}$ (mm/min) and difference $\Delta \bar{v}_{\text{CSD}}$ between consecutive refinements. B: Wave width $w_{\text{CSD}}$ (mm) at $t = 50$ s and difference $\Delta w_{\text{CSD}}$ between consecutive refinements. Numerical scheme: Strang splitting, CN, RK4. * indicates that the solver failed to converge.

Higher order spatial discretization

To assess how the polynomial degree of the finite elements affects the convergence of the numerical schemes, we repeat the convergence study presented in Section 5.3 replacing the lowest order finite element pairings by higher order pairings. We consider the model described in Section 2 discretized with discontinuous piecewise linear polynomials ($P_1$) for the volume fractions $\alpha_r$ and continuous piecewise linear polynomials of degree 2 ($P_2^e$) for the ion concentrations and potentials. The finite element software used within this work (FEniCS) has automated functionality for solving coupled PDE-ODE systems via the PointIntegralSolver class. The
PointIntegralSolver solves the ODEs at the vertices of the elements and only supports the use of elements with degrees of freedom located at the vertices. Higher order elements are thus not supported. To assess the accuracy and convergence of the higher order scheme, we here consider an alternative implementation where the ODEs are solved at each degree of freedom of the spatial discretization using a backward Euler scheme and a Newton solver.

| $P_0$-$P_1^{c}$ | $P_1$-$P_2^{c}$ |
|-----------------|-----------------|
| $N$             | $\bar{v}_{CSD}$ | $\Delta \bar{v}_{CSD}$ | $\bar{v}_{CSD}$ | $\Delta \bar{v}_{CSD}$ |
| 1000            | 7.585           | -                   | 6.415           | -                  |
| 2000            | 6.346           | 1.239               | 5.416           | 0.999              |
| 4000            | 5.412           | 0.934               | 5.005           | 0.411              |
| 8000            | 5.005           | 0.407               | 4.987           | 0.018              |
| 16000           | 4.988           | 0.017               | 4.989           | -0.002             |
| 32000           | 4.989           | -0.001              | -               | -                  |

| $P_0$-$P_1^{c}$ | $P_1$-$P_2^{c}$ |
|-----------------|-----------------|
| $N$             | $w_{CSD}$       | $\Delta w_{CSD}$ | $w_{CSD}$       | $\Delta w_{CSD}$ |
| 1000            | 3.330           | -                   | 2.800           | -                  |
| 2000            | 2.785           | 0.545               | 2.380           | 0.420              |
| 4000            | 2.380           | 0.405               | 2.210           | 0.170              |
| 8000            | 2.210           | 0.170               | 2.202           | 0.008              |
| 16000           | 2.203           | 0.007               | 2.203           | -0.001             |
| 32000           | 2.203           | 0.000               | -               | -                  |

Table 6. Comparison of CSD wave characteristics and quantities of interest under refinement in space between the $P_0$-$P_1^{c}$ spatial discretization described in Section 3.1 and a $P_1$-$P_2^{c}$ discretization (both solved using the implementation allowing for higher order elements). A: CSD mean wave speed $\bar{v}_{CSD}$ (mm/min) and difference $\Delta \bar{v}_{CSD}$ between consecutive refinements. B: Wave width $w_{CSD}$ (mm) at $t = 50$ s and difference $\Delta w_{CSD}$ between consecutive refinements. Numerical scheme: Strang splitting, BDF2, BE using $\Delta t = 3.125$ ms.

In Table 6, we compare the CSD wave characteristics (wave speed $\bar{v}_{CSD}$ and wave width $w_{CSD}$) computed after solving the system with the two different spatial discretizations: $P_0$-$P_1^{c}$ and $P_1$-$P_2^{c}$. The numerical scheme consists of a second order Strang splitting, together with a BDF2 time-stepping scheme for the PDE and a backward Euler (BE) scheme for the system of ODEs, with a timestep of $\Delta t = 3.125$ ms. We observe that the wave speed and wave width computed using a second order $P_1$-$P_2^{c}$ spatial discretization with a mesh of $N$ elements (where
Fig. 4. Left: Neuron potential $\phi_n$ (blue) together with its polynomial approximation of degree 100 (red) computed using the Chebfun software. Right: Magnitude of the Chebyshev coefficients of the polynomial approximation to $\phi_n$.

$N \in \{1000, 2000, 4000, 8000, 16000\}$) are similar to the quantities obtained by a $P_0$-$P_1^c$ discretization with $2N$ elements (i.e. the same number of degrees of freedom).

We also study the approximation of the neuron potential by arbitrary higher-order polynomials to compare low-degree finite element spatial discretization against higher order discretizations or global spectral methods. First, the system of equations is solved using a $P_0$-$P_1^c$ finite element scheme with a large spatial discretization of $N = 32000$. We then use the Chebfun software to approximate the neuron potential with Chebyshev polynomials.

In Figure 4 (left), we display the original function $\phi_n$ (in blue), together with its polynomial approximation of degree 100 (in red). We see that the approximation has large oscillating errors near the wave front located at $x = 4$ mm, which is likely due to the Wilbraham–Gibbs phenomenon. On the right panel of Figure 4 we report the coefficients of the polynomial approximation to $\phi_n$ of degree 100 constructed by Chebfun. The magnitude of the Chebyshev coefficients seems to decay algebraically at a rate of $-1.2$, suggesting that a very large polynomial degree (of order $10^4 - 10^5$) would be required to approximate the solution to (2.1a) and (2.3)-(2.4) accurately.

5.5. Numerical performance for the zero flow limit

So far, we have investigated the convergence of the different schemes via studying key functionals of the solution. To evaluate the performance and scalability of the implementation of the schemes for the model in the zero flow limit, we consider an additional set of experiments measuring the memory usage and CPU timings.

Timings were performed on a Lenovo ThinkPad 2.70GHz x 4 Intel Core i7-7500U CPU using FEniCS 2019.1.0 without parallelization.
respectively, and compare the performance of Godunov and Strang splitting. For the implementation allowing for higher order finite elements we consider simulations with Strang splitting, BDF2 time PDE stepping, BE time ODE stepping, and compare performance of using $P_0-P_1^c$ and $P_1-P_2^c$ elements.

For both the Godunov and Strang splitting schemes and the standard implementation, we observe that the memory usage increases linearly with the number of degrees of freedom: doubling the number of degrees of freedom leads to an increase in memory of a factor 2 (see Table 7A and B). We observe that the CPU time for the simulations grows linearly with the number of degrees of freedom: doubling the number of degrees of freedom leads to an increase in total simulation time of a factor 2. In the Strang splitting scheme, the ODEs are solved twice for each PDE step and we thus expect the total ODE stepping time to be greater than for the Godunov splitting scheme (where the ODEs are only solved once per PDE step). Indeed, the total ODE stepping time is about twice as large for Strang splitting as for Godunov splitting (Table 7). Conversely, the time required for finite element assembly and LU solves is comparable for Godunov splitting and Strang splitting. In total, the simulation time is higher for Strang splitting than Godunov (11 – 18%). Moreover, the total simulation time is dominated by the cost of finite element assembly and LU solves (84% for Godunov splitting, 72% for Strang splitting). Finally, the time required for finite element assembly is comparable to that of the LU solves for both splitting schemes.

The simulation time of the higher order $P_1-P_2^c$ discretization (with the implementation allowing for higher order schemes) is reported in Table 7D. For a given number of mesh elements $N \in \{4000, 8000, 16000\}$, we compare the timings with the $P_0-P_1^c$ discretization with a mesh of $2N$ elements (Table 7C) so that the underlying systems have the same number of degrees of freedom as well as approximately the same accuracy, following the linear convergence of the $P_1-P_2^c$ discretization as observed in Section 5.4. We then see that the total time needed to run the full simulation is approximately 21 – 40% higher for the $P_1-P_2^c$ discretization. This difference is explained by the higher density of the finite element matrices resulting from the $P_1-P_2^c$ discretization compared to the choice of $P_0-P_1^c$.

In conclusion, Strang and Godunov splitting yield comparable accuracy and memory usage. We observe that Strang splitting yields higher total CPU time than Godunov. When varying (ODE and PDE) time stepping schemes we observe minor variations in terms of accuracy. The higher order element scheme ($P_1-P_2^c$) has both a higher total CPU time and memory usage than the lower order spatial scheme ($P_0-P_1$), whereas the accuracy is comparable. We find that the accurate computation of CSD wave characteristics (wave speed and wave width) requires a very fine spatial and fine temporal resolution for all schemes tested.
Table 7. CPU timings and memory usage for approximating solutions in the zero flow limit.

| N  | Dofs  | M (MiB) | $T_A$ (s) | $T_{LU}$ (s) | $T_{PDE}$ (s) | $T_{ODE}$ (s) | $T_{tot}$ (s) |
|----|-------|---------|-----------|-------------|-------------|-------------|-------------|
| 8000 | 72008 | 117     | 329       | 350         | 679         | 129         | 813         |
| 16000 | 144008 | 199     | 659       | 707         | 1366        | 258         | 1632        |
| 32000 | 288008 | 396     | 1438      | 1520        | 2958        | 559         | 3526        |

| N  | Dofs  | M (MiB) | $T_A$ (s) | $T_{LU}$ (s) | $T_{PDE}$ (s) | $T_{ODE}$ (s) | $T_{tot}$ (s) |
|----|-------|---------|-----------|-------------|-------------|-------------|-------------|
| 8000 | 72008 | 118     | 333       | 352         | 685         | 259         | 954         |
| 16000 | 144008 | 199     | 677       | 719         | 1396        | 536         | 1932        |
| 32000 | 288008 | 396     | 1367      | 1451        | 2818        | 1086        | 3916        |

| N  | Dofs  | M (MiB) | $T_A$ (s) | $T_{LU}$ (s) | $T_{PDE}$ (s) | $T_{ODE}$ (s) | $T_{tot}$ (s) |
|----|-------|---------|-----------|-------------|-------------|-------------|-------------|
| 8000 | 72008 | 130     | –         | –           | 696         | 253         | 953         |
| 16000 | 144008 | 223     | –         | –           | 1411        | 506         | 1922        |
| 32000 | 288008 | 446     | –         | –           | 3076        | 1115        | 4198        |

| N  | Dofs  | M (MiB) | $T_A$ (s) | $T_{LU}$ (s) | $T_{PDE}$ (s) | $T_{ODE}$ (s) | $T_{tot}$ (s) |
|----|-------|---------|-----------|-------------|-------------|-------------|-------------|
| 4000 | 72008 | 165     | –         | –           | 1017        | 309         | 1331        |
| 8000 | 144008 | 285     | –         | –           | 1693        | 511         | 2209        |
| 16000 | 288008 | 567     | –         | –           | 3902        | 1182        | 5091        |

Dofs: number of degrees of freedom in the linear (PDE) system, M: Maximal memory usage of simulation relative to baseline. $T_A$: CPU time for finite element assembly, $T_{LU}$: CPU time for LU solver, $T_{ODE}$: CPU time for ODE stepping, $T_{PDE}$: CPU time for PDE stepping (in A and B this equals the sum of $T_A$ and $T_{LU}$), $T_{tot}$: Total CPU time for simulation. $T_A$ and $T_{LU}$ are not reported for C and D. All simulations have $\Delta t = 3.125$ ms and final time $T = 5$ s (i.e. 1600 timesteps). Results from simulations with the standard implementation with BDF2, ESDIRK4, $P_0-P_1^\gamma$, and either A: Godunov splitting; or B: Strang splitting. Results from simulations with the implementation allowing for higher order elements with BDF2, BE, Strang splitting, and either C: $P_0-P_1^\gamma$ elements; or D: $P_1-P_2^\gamma$ elements.
6. Numerical solution of model including fluid dynamics

The previous schemes and experiments considered only the zero flow limit. Here, we present a numerical scheme for the full mathematical model. The variational formulation (6.1) is obtained by multiplying (2.1), (2.4) and (2.8) by suitable test functions, integrating over the domain $\Omega$, integrating terms with higher order derivatives by parts, and inserting the boundary conditions (2.14). Further, we use a backward Euler scheme for the PDE time discretization. Let $S_r \subset H^1(\Omega)$, $V^k_r \subset H^2(\Omega)$, $V^k_R \subset H^1(\Omega)$, $T_r \subset H^1(\Omega)$, $T_R \subset H^1(\Omega)$, and $Q \subset H^1(\Omega)$ be spaces of functions for $r = 1, \ldots, R - 1$ and $k = 1, \ldots, |K|$. Given $\alpha^n_r$, $[k]^n_r$, and $[k]^k_R$ at time level $n$, at each time level $n + 1$ find the volume fractions $\alpha_r \in S_r$, the potentials $\phi_r \in T_r$, $\phi_R \in T_R$, and the extracellular mechanical pressure $p_R \in Q$ such that:

\[
\frac{1}{\Delta t} \langle \alpha_r - \alpha^n_r, s_r \rangle - \langle \alpha_r u_r, \nabla s_r \rangle + \gamma_r R \langle w_{rR}, s_r \rangle = 0, \quad (6.1a)
\]

\[
\frac{1}{\Delta t} \langle \alpha_r [k]_r - \alpha^n_r [k]_R, z^k_R \rangle - \langle J^{k}_{R}, \nabla z^k_R \rangle + \gamma_r R \langle J^{k}_{R}, v^k_R \rangle = 0, \quad (6.1b)
\]

\[
\frac{1}{\Delta t} \langle \alpha_R [k]_R - \alpha^n_R [k]_R, v^k_R \rangle - \langle J^{k}_{R}, \nabla v^k_R \rangle - \sum_{r} \gamma_{rR} \langle J^{k}_{rR}, v^k_R \rangle = 0, \quad (6.1c)
\]

\[
\langle r R C_R \alpha_R, t_r \rangle - \langle z^0 F_R, t_r \rangle - \langle F \alpha_R \sum_{k} z^k [k]_R, t_r \rangle = 0, \quad (6.1d)
\]

\[
- \sum_{r} \langle r R C_R \phi_{rR}, t_r \rangle - \langle z^0 F_R, t_R \rangle - \langle F \alpha_R \sum_{k} z^k [k]_R, t_R \rangle = 0, \quad (6.1e)
\]

\[
- \langle \sum_{r} \alpha_r u_r, \nabla q \rangle = 0, \quad (6.1f)
\]

for all $s_r \in S_r$, $v^k_R \in V^k_R$, $v^k_R \in V^k_R$, $t_r \in T_r$, $t_R \in T_R$, $q \in Q$. The compartmental ion flux $J^k_R$ is given by (2.5), the compartmental fluid velocity $u_r$ is given by (2.6), the transmembrane water flux $w_{rR}$ is given by (2.10), while the transmembrane ion fluxes $J^k_{rR}$ are subject to modelling. As before, the potentials $\phi_r$ for $r = 1, \ldots, R$ and the extracellular mechanical pressure $p_R$ are only determined up to a constant. We employ continuous piecewise linear elements for all variables. Note that $\alpha_r \in L^1(\Omega)$ is sufficient for the weak formulation of the zero flow limit model to be well-defined, whereas in the full model, the gradient of $\alpha_r$ appears via the expression for the compartmental fluid velocities $u_r$ in (2.6), thus suggesting $\alpha_r \in H^1(\Omega)$. For the ODE time stepping, we apply an ESDIRK4 scheme and first order Godunov splitting.

7. Numerical convergence study with fluid dynamics: smooth analytical solution

To evaluate the numerical accuracy of the scheme presented above in Section 6, we construct an analytical solution using the method of manufactured solutions[10]. We
consider the full model with three compartments, namely a neuronal \((n, r = 1)\), a glial \((g, r = 2)\) and an extracellular compartment \((e, r = 3)\). We use \(1, 2, 3\) and \(n, g, e\) interchangeably for subscripts of our variables and model parameters. In each compartment, we model the movement of potassium \((K^+)\), sodium \((Na^+)\) and chloride \((Cl^-)\). The transmembrane ion fluxes \(J^k_{rR}\) are taken to be passive leak fluxes, i.e.:

\[
J^k_{rR} = \frac{1}{Fz^k} I^k_{r,\text{leak}},
\]

(7.1)

where \(I^k_{r,\text{leak}}\) is defined by (5.2) for compartment \(r\) and ion species \(k\). The neuronal leak conductances \(g^k_{n,\text{leak}}\) are given in Table 3, and the glial leak conductances \(g^k_{g,\text{leak}}\) for \(Na^+\) and \(Cl^-\) are given in Table 8 whereas the glial \(K^+\) conductance is given by (8.1). We consider a one dimensional domain \(\Omega = [0, 1]\) uniformly meshed with \(N \in \{8, 16, 32, 64, 128\}\) elements. We initially set \(\Delta t = 10^{-3}\) s, and then halve the timestep with each spatial refinement. The errors are evaluated at \(t = 2 \times 10^{-3}\) s. The analytical solutions are given by (4.2)–(4.3) for the neuronal and extracellular tissue variables, and by the following for the glial tissue variables and the extracellular mechanical pressure:

\[
\alpha_g = 0.2 - 0.1 \sin(2\pi x) \exp(-t), \quad [Na]_g = 0.5 + 0.6 \sin(\pi x) \exp(-t),
\]

\[
[K]_g = 0.5 + 0.2 \sin(\pi x) \exp(-t), \quad [Cl]_g = 1.0 + 0.8 \sin(\pi x) \exp(-t),
\]

\[
\phi_g = \sin(2\pi x) \exp(-t), \quad p_R = \sin(2\pi x) \exp(-t).
\]

(7.2)

Parameters values are given in Table 3 and Table 8. Initial and boundary conditions are governed by the exact solutions (4.2) and (7.2).

Based on properties of the approximation spaces and the time discretization, we expect the optimal rate of convergence to be 1 in the \(H^1\)-norm and 2 in the \(L^2\)-norm for the volume fractions \(\alpha_n, \alpha_g, \alpha_e\), the ion concentrations \([k]_n, [k]_g, [k]_e\), the potentials \(\phi_n, \phi_g, \phi_e\) and the mechanical pressure \(p_e\). Our numerical observations are in agreement with the theoretically optimal rates (Table 9).

8. Numerical convergence study: physiological CSD model with microscopic fluid mechanics

8.1. Problem description

Finally, we consider the full model with a neuronal \((n, r = 1)\), glial \((g, r = 2)\) and extracellular compartment \((e, r = 3)\) and three ion species, namely potassium \((K^+)\), sodium \((Na^+)\) and chloride \((Cl^-)\). Cortical spreading depression is triggered by applying excitatory fluxes to the neurons as described in (5.5) in the one-dimensional domain of length 10 mm. The physiological parameters values are given in Table 1 and Table 8 whereas the initial conditions are given in Table 12B (Supplementary Tables).

The neuronal membrane mechanisms are as described in Section 5.1. For the glial membrane mechanisms we follow O’Connell and consider leak currents modelled as in (5.2) (with \(r = g\)) for sodium \((Na^+)\) and chloride \((Cl^-)\), and a potassium
Table 8. Physical parameters for the glial membrane and mechanical pressure. We use SI base units, that is, meter (m), mole (mol), Siemens (S) and ampere (A). The values are collected from O’Connell et al.\textsuperscript{28}, Østby et al.\textsuperscript{29}, Steinberg et al.\textsuperscript{38}, and Yao et al.\textsuperscript{48}. The symbol – indicates that the value is chosen by the authors, as we could not find any relevant values in the literature. * The neuronal water permeability is set to zero as we assume no gap junctions connecting the neurons.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Parameter & Symbol & Value & Unit
\hline
Na\textsuperscript{+} leak conductance glial & \(g_{Na,\text{leak}}\) & 0.072 & S/m\textsuperscript{2} \textsuperscript{29}
\hline
Cl\textsuperscript{−} leak conductance glial & \(g_{Cl,\text{leak}}\) & 0.5 & S/m\textsuperscript{2} \textsuperscript{29}
\hline
KIR resting conductance glial & \(g_{0,\text{KIR}}\) & 1.3 & S/m\textsuperscript{2} \textsuperscript{38}
\hline
Maximum NaKCl rate glial & \(g_{\text{NaKCl}}\) & 8.13 \times 10^{-4} & A/m\textsuperscript{2} \textsuperscript{28}
\hline
Maximum pump rate glial & \(I_g\) & 0.0372 & A/m\textsuperscript{2} \textsuperscript{28}
\hline
Membr. area-to-volume glial & \(\gamma_{ge}\) & 6.3849 \times 10^5 & 1/m \textsuperscript{19}
\hline
Membr. capacitance glial & \(C_{ge}\) & 7.5 \times 10^{-3} & F/m\textsuperscript{2} \textsuperscript{19}
\hline
Membr. water permeability glial & \(\eta_{ge}\) & 5.4 \times 10^{-10} & m\textsuperscript{4}/(mol s) \textsuperscript{28}
\hline
Membrane stiffness neuron & \(S_{ne}\) & 2.85 \times 10^3 & Pa/m\textsuperscript{3} –
\hline
Membrane stiffness glial & \(S_{ge}\) & 2.85 \times 10^3 & Pa/m\textsuperscript{3} –
\hline
Gap junction connectivity glial & \(\chi_g\) & 0.05 & –
\hline
Neuronal water permeability & \(\kappa_n\) & 0 & m\textsuperscript{4}/(N s) *
\hline
Glia water permeability & \(\kappa_g\) & 5.0 \times 10^{-16} & m\textsuperscript{4}/(N s) –
\hline
ECS water permeability & \(\kappa_e\) & 5.0 \times 10^{-16} & m\textsuperscript{4}/(N s) –
\hline
\end{tabular}
\caption{Physical parameters for the glial membrane and mechanical pressure.}
\end{table}

\begin{equation}
\begin{split}
g_{\text{KIR}} &= g_{0,\text{KIR}} \sqrt{\frac{[K^+]_R}{3}} \frac{1 + \exp(\frac{18.5}{42.3})}{1 + \exp(\frac{\phi_{ge} - E_g^{K^+}}{42.3})} \frac{1 + \exp(-\frac{118.6 - 85.2}{44.1})}{1 + \exp(-\frac{118.6 + \phi_{ge}}{44.1})},
\end{split}
\end{equation}

where \(g_{0,\text{KIR}}\) (S/m\textsuperscript{2}) is the resting membrane conductance, and corresponds to the conductance when \(\phi_{ge} = E_g^{K^+}\) and \([K^+]_c = [K^+]_c^0\). The Na/K/ATPase pump (ATP) occurs in both the neuron and glial membrane, and is modelled as in (5.4). Finally, the current through the NaKCl cotransporter \(I_{\text{NaKCl}}\) (A/m\textsuperscript{2}) is modelled as:

\begin{equation}
I_{\text{NaKCl}} = g_{\text{NaKCl}} \ln \left( \frac{[Na^+]_g[K^+]_g[Cl^-]_g^2}{[Na^+]_e[K^+]_e[Cl^-]_e^2} \right).
\end{equation}

In summary, the total currents over the glial membrane are modelled by (8.3) (with the currents (A/m\textsuperscript{2}) are converted to ion fluxes (mol/(m\textsuperscript{2}s)) by dividing by...
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| $n$  | $\|\text{[Na]} c - \text{[Na]} c_h\|_{L^2}$ | $\|\phi - \phi_h\|_{L^2}$ | $\|\alpha - \alpha_h\|_{L^2}$ | $\|p - p_h\|_{L^2}$ |
|------|---------------------------------|-----------------|-----------------|-----------------|
| 8    | 2.47E-03(2.05)                  | 7.19E-02(1.94)  | 1.73E-03(2.14)  | 1.31E+01(3.40)  |
| 16   | 6.11E-04(2.02)                  | 1.81E-02(1.99)  | 4.13E-04(2.06)  | 2.26E+00(2.53)  |
| 32   | 1.52E-04(2.00)                  | 4.54E-03(2.00)  | 1.02E-04(2.02)  | 4.79E-01(2.24)  |
| 64   | 3.80E-05(2.00)                  | 1.14E-03(2.00)  | 2.54E-05(2.00)  | 1.15E-01(2.06)  |
| 128  | 9.51E-06(2.00)                  | 3.15E-04(1.85)  | 6.35E-06(2.00)  | 2.41E-02(2.25)  |

| $n$  | $\|\text{[Na]} c - \text{[Na]} c_h\|_{H^1}$ | $\|\phi - \phi_h\|_{H^1}$ |
|------|---------------------------------|-----------------|
| 8    | 1.51E-01(1.00)                  | 1.02E+00(1.01)  |
| 16   | 7.55E-02(1.00)                  | 5.05E-01(1.02)  |
| 32   | 3.77E-02(1.00)                  | 2.52E-01(1.01)  |
| 64   | 1.89E-02(1.00)                  | 1.26E-01(1.00)  |
| 128  | 9.42E-03(1.00)                  | 6.28E-02(1.00)  |

Table 9. Selected $L^2$-errors (upper panel) and $H^1$-errors (lower panel) and convergence rates (in parenthesis) for the full scheme at time $t = 0.002$ s. The test was run on the unit interval, and we initially let $\Delta t = 0.001$ s, and then halve the timestep in each series. The spatial discretization consists of $N$ intervals.

Faraday’s constant $F$ times the valence $z^k$:

$$J_g^{Na} = \frac{1}{F z^{Na}} \left( I_{g, \text{leak}}^{Na} + 3 I_{g, \text{ATP}}^{Na} + I_{NaKCl}^{Na} + I_{\text{ex}}^{Na} \right),$$  \hspace{1cm} (8.3a)

$$J_g^K = \frac{1}{F z^K} \left( I_{K, \text{leak}} - 2 I_{g, \text{ATP}} + I_{NaKCl}^{K} + I_{\text{ex}}^{K} \right),$$  \hspace{1cm} (8.3b)

$$J_g^{Cl} = \frac{1}{F z^{Cl}} \left( I_{g, \text{leak}}^{Cl} + 2 I_{NaKCl}^{Cl} + I_{\text{ex}}^{Cl} \right).$$  \hspace{1cm} (8.3c)

Here, $I_{\text{ex}}^{Na}$, $I_{\text{ex}}^{K}$, and $I_{\text{ex}}^{Cl}$ are excitatory fluxes used to trigger a cortical spreading depression wave, see (5.5) in Section 5.1.1.

### 8.2. CSD wave characteristics

As in the zero flow limit scenario, excitatory flux stimulation leads to a CSD wave traveling through the tissue: we observe neuronal depolarization, neuronal and ECS ionic concentration changes, and neuronal swelling (Figure 5). Moreover, we observe that the glial potential depolarizes: from $-81$ to $-31$ mV, accompanied by a small drop in the extracellular potential from 0 to $-5$ mV. Substantial alterations in the intra- and extracellular ion compositions follow the depolarization wave: we observe an increase in the concentrations of extracellular potassium, and decreases in extracellular sodium and chloride. In response to the ionic shifts, the neurons and glial cells swell with an increase in volume fractions of respectively 12.5% and 6.8%, while the extracellular space shrinks correspondingly. We note that the neural and extracellular dynamics are qualitatively similar to those in the case of two...
compartments (neurons, ECS) in the zero flow limit (c.f. Figure 2), which is in accordance with the (numerical) findings reported by O’Connell et al. The CSD wave is accompanied by a decrease in the mechanical pressures, from the baseline of 0 kPa down to \(-288, -334\) and \(-389\) kPa in the neuronal, glial and extracellular compartments, respectively (Figure 5F). The pressure gradients (mechanical and osmotic) drive microscopic fluid flow within the glial and the extracellular compartments. We observe flow rates of up to \(1.1\) and \(-0.03\) \(\mu\)m/s in the glial and extracellular compartments, respectively; i.e. fluid flows in opposite directions (Figure 5B,C). During glial swelling, water moves across the glial membrane from the ECS into the glial cells. In response, water within the glial cell network will be pushed away from this area. Indeed, we observe a positive flow rate to the right of the swelling, and a negative flow rate left of the swelling in the glial cells and vice versa in the ECS. We observe no flow in the neuronal compartment, which is expected as the neuronal water permeability is set to zero (Figure 6A).

Next, we (quantitatively) evaluate the numerical convergence of the full model scheme presented in Section 6. To this end, we consider the quantities of interest defined in Section 5.2 in addition to the (spatial) width \(w_{CSD,p}\) of the extracellular mechanical pressure wave at \(t = 50\) s, given by

\[
X = \{x \mid p_R(x, 50) > p_{\text{thres}}\}
\]

\[
w_{CSD,p} = \max X - \min X
\]

with \(p_{\text{thres}} = -10\) kPa.

8.3. Convergence of CSD wave characteristics during refinement

Drawing on the findings in Section 6, here, we consider the implicit lower-order scheme based on Godunov splitting, a BE method for the PDE time-discretization, and ESDIRK4 for the ODE time-stepping – to compute the mean speed (cf. Section 5.2) and the (spatial) width of the extracellular mechanical pressure wave (cf. Section 8.2) for different mesh resolutions and time steps: \(\Delta x_N = 10/N\) mm for \(N = 1000, 2000, 4000, 8000, 16000, 32000\) and \(\Delta t_i = 12.5/i\) s for \(i = 1, 2, 4, 8, 16, 32, 64\). The results are presented in Figure 7. Wave speeds are converted from the native m/s to mm/min for interpretability.

As in the zero flow limit, the computed mean wave speed and the extracellular mechanical pressure wave width increases with decreasing \(\Delta t\), and decreases with decreasing \(\Delta x\): the smaller the time step, the faster and wider the wave, while the smaller the mesh size, the slower and narrower the wave (Figure 7A–C). The behavior of the mean wave speed is qualitatively similar to that in the schemes for the zero flow limit (cf. 1). The computed extracellular mechanical pressure wave width vary substantially, ranging from \(2.409\) to \(4.67\) mm.

The differences \(\Delta w_{CSD,p}\) in the extracellular mechanical pressure wave width between the coarsest mesh sizes \(N = 1000\) and \(2000\) are in the range \(2.96 - 4.67\) mm, while \(\Delta w_{CSD,p}\) between the coarsest time steps \(\Delta t = 12.5\) and \(6.25\) are in the
Fig. 5. Full model simulation of a CSD wave. Snapshots at $t = 50$ s of neuronal, glial and extracellular ion concentrations (A, B, C), electrical potentials (D), change in volume fractions (E) and mechanical pressure (F).

Fig. 6. Full model simulation of a CSD wave: fluid velocities. Snapshots at $t = 50$ s of compartmental fluid velocities in the neurons (A), the glial cells (B), and the ECS (C).

Range $2.409 - 3.910$ mm. For the finest time and mesh resolutions, we observe that $\Delta w_{\text{CSD,p}} = 0.005$ and $0.344$ mm, respectively; thus the spatial error continues to dominate. Finally, we observe that $\Delta w_{\text{CSD,p}}$ decreases as we refine the discretizations in time and space. There is however no clear convergence rate (Figure 7A, B).
Fig. 7. Full model simulation: CSD wave properties during refinement in space (N) and time (\(\Delta t\), ms) in a 1D domain of length 10 mm at \(t = 50\) s. 

A: Extracellular mechanical pressure \(p_R(x, 50)\) (kPa) versus \(x \in \Omega\) (mm). B: Extracellular mechanical pressure wave width (mm) and difference \(\Delta w_{\text{CSD}, p}\) between consecutive refinements. C: CSD mean wave speed \(\bar{v}_{\text{CSD}}\) (mm/min) and difference \(\Delta \bar{v}_{\text{CSD}}\) between consecutive refinements.
9. Discussion and concluding remarks

We have presented and analyzed finite element-based splitting schemes for a mathematical framework modelling ionic electrodiffusion and water movement in biological tissue in general, and brain tissue in particular. We have evaluated the schemes in terms of their numerical properties, including accuracy, convergence, and computational efficiency, for idealized scenarios as well as for challenging, physiologically realistic problem settings.

The schemes display optimal convergence rates in space for problems with smooth manufactured solutions. However, the physiological CSD setting is challenging: we find that the accurate computation of CSD wave characteristics (wave speed and wave width) requires a very fine spatial and fine temporal resolution for all schemes tested. Indeed, different splitting and time stepping schemes and lower and higher order finite element schemes give comparable results in terms of accuracy. Overall, the error associated with the spatial discretization dominates. Explicit PDE and/or ODE time stepping schemes easily fail to converge even for only moderately coarse time steps, but yield accurate results for very fine timesteps. In light of the long time scale associated with CSD (seconds to minutes), the small time steps imposed by the explicit schemes (less than a millisecond) represent a severe restriction.

The mathematical framework studied here was presented by Mori in 2015 and has been used to simulate cortical spreading depression in a three-compartment setting (including neurons, glial cells and extracellular space) and in multiple spatial dimensions. However, little has been reported on numerical properties of discretizations of this model. The aforementioned studies have used time steps of the order 10 ms and mesh sizes of the order 0.156–0.02 mm (corresponding to $N = 64 - 500$ cf. Figure 1). Our findings indicate that high resolution is required to accurately compute CSD wave properties and that low-to-moderate resolutions can substantially overestimate (or, but more rarely, underestimate) the CSD wave speed. We expect our finite element findings to extend also to comparable finite difference or finite volume discretizations.

In terms of limitations, we have here compared different numerical schemes in terms of accuracy, with less emphasis on computational complexity or cost. We consider these numerical investigations as a starting point and guide for future theoretical studies. Another research direction would be the extension of this study to the two-dimensional CSD model studied by O’Connell and Tuttle, where the development of multigrid solvers seems crucial to reach the high spatial resolution needed to obtain accurate solutions.

This paper focuses on numerical challenges related to approximating systems for ionic electrodiffusion and microscopic water movement. We remark that the full model simulation, including extracellular mechanical pressure, yields pressure differences far greater than what one might expect in this setting ($\sim 6$ times atmospheric pressure). It seems natural to reevaluate whether the current compartmental fluid
velocity model best represents the physiology, in particular the fluid velocity component driven by electrostatic forces. On the other hand, it is well-established that large osmotic pressure gradients indeed are present in the brain environment.

In conclusion, our findings show that numerical simulation of ionic electrodiffusion and water movement in brain tissue is feasible, but requires care numerically and substantial computational resources. Numerical schemes or solution approaches that retain accuracy at a lower computational expense would enable the study of a wide array of phenomena in brain physiology, including in the context of pathological conditions.

Appendix A. Supplementary Tables

| $N$ | 12.5 | 6.25 | 3.125 | 1.563 | 0.781 | 0.391 | 0.195 | $\Delta \bar{v}_{\text{CSD}}$ |
|-----|------|------|-------|-------|-------|-------|-------|------------------|
| 1000| 8.000| 8.631| 9.385 | 9.738 | 9.938 | 10.046| 10.092| –                |
| 2000| 6.262| 6.862| 7.223 | 7.431 | 7.538 | 7.600 | 7.638 | 2.454           |
| 4000| 5.138| 5.636| 5.938 | 6.096 | 6.181 | 6.227 | 6.246 | 1.392           |
| 8000| 4.798| 4.978| 5.128 | 5.242 | 5.311 | 5.349 | 5.366 | 0.880           |
| $\Delta \bar{v}_{\text{CSD}}$ | –    | 0.180| 0.150 | 0.114 | 0.069 | 0.038 | 0.017 |                  |

Table 10. CSD mean wave speed $\bar{v}_{\text{CSD}}$ (mm/min) and difference in CSD mean wave speed $\Delta \bar{v}_{\text{CSD}}$ between consecutive refinements in space (rows) and time (columns). Numerical scheme: Godunov splitting, BDF2, ESDIRK4.
Table 11. CSD mean wave speed $\bar{v}_{CSD}$ (mm/min) and difference in CSD mean wave speed $\Delta \bar{v}_{CSD}$ between consecutive refinements in space (rows) and time (columns). Numerical scheme: Strang, BDF2, and RK4 (A) or BE (B). * indicates that the solver failed to converge.
### A

| Parameter                        | Symbol | Value | Unit  |
|---------------------------------|--------|-------|-------|
| neuron volume fraction          | $\alpha_n^0$ | 0.8   |       |
| $\text{Na}^+$ concentration neuron | $[\text{Na}]_n^0$ | 9.3   | mol/m$^3$ |
| $\text{K}^+$ concentration neuron | $[\text{K}]_n^0$ | 132   | mol/m$^3$ |
| $\text{Cl}^-$ concentration neuron | $[\text{Cl}]_n^0$ | 8.0   | mol/m$^3$ |
| $\text{Na}^+$ concentration ECS | $[\text{Na}]_e^0$ | 137   | mol/m$^3$ |
| $\text{K}^+$ concentration ECS | $[\text{K}]_e^0$ | 4     | mol/m$^3$ |
| $\text{Cl}^-$ concentration ECS | $[\text{Cl}]_e^0$ | 114   | mol/m$^3$ |
| potential neuron                | $\phi_n^0$ | -0.070 | V     |
| potential ECS                   | $\phi_e^0$ | 0.0   | V     |

### B

| Parameter                        | Symbol | Value | Unit  |
|---------------------------------|--------|-------|-------|
| neuron volume fraction          | $\alpha_n^0$ | 0.5   |       |
| glial volume fraction           | $\alpha_g^0$ | 0.3   |       |
| $\text{Na}^+$ concentration neuron | $[\text{Na}]_n^0$ | 9.3   | mol/m$^3$ |
| $\text{K}^+$ concentration neuron | $[\text{K}]_n^0$ | 132   | mol/m$^3$ |
| $\text{Cl}^-$ concentration neuron | $[\text{Cl}]_n^0$ | 8.0   | mol/m$^3$ |
| $\text{Na}^+$ concentration glial | $[\text{Na}]_g^0$ | 13   | mol/m$^3$ |
| $\text{K}^+$ concentration glial | $[\text{K}]_g^0$ | 128   | mol/m$^3$ |
| $\text{Cl}^-$ concentration glial | $[\text{Cl}]_g^0$ | 8.0   | mol/m$^3$ |
| $\text{Na}^+$ concentration ECS | $[\text{Na}]_e^0$ | 137   | mol/m$^3$ |
| $\text{K}^+$ concentration ECS | $[\text{K}]_e^0$ | 4     | mol/m$^3$ |
| $\text{Cl}^-$ concentration ECS | $[\text{Cl}]_e^0$ | 114   | mol/m$^3$ |
| potential neuron                | $\phi_n^0$ | -0.070 | V     |
| potential glial                 | $\phi_g^0$ | -0.082 | V     |
| potential ECS                   | $\phi_e^0$ | 0.0   | V     |
| mechanical pressure ECS         | $p_e^0$   | 0.0   | V     |

Table 12. Initial values for state variables in the zero flow limit (A) and in the full model (B). We use SI base units; that is, meter (m), and mole (mol).
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