Ion Channels: A Link between Physiology and Mathematics

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Motivation

The Poisson-Nernst-Planck Model

A new Model

Analysis for new Model
What are Ion Channels?

- Ion channels are proteins with a hole down their middle.
- They regulate the movement of inorganic ions ($\text{Na}^+$, $\text{Ca}^+$, $\text{Cl}^-$, $\text{Ca}^{2+}$) through impermeable cell membranes.
- They are found in biological membranes (humans, animals, plants).
Why are Ion Channels interesting?

- ion channels play a vital role in life
- structural properties of certain channels not known so far
- defects are reason for serious diseases
- existing models have poor agreement with experimental data in some cases
The PNP Model

- describes transport of ions through a single open channel pore
- movement is mainly driven by diffusion and electrostatic interactions among ions, protein charges, and externally applied electric field
- PNP is a mean field approach (time averages of electrostatic field are computed)
- model describes average charge densities of ions
The PNP Model

PNP System in three Dimensions for Ion Densities $c_i$:

\[
\begin{align*}
\epsilon \Delta V &= -e_0 \sum_i z_i c_i + f \quad \text{Poisson equation} \\
\partial_t c_i &= -\nabla \cdot J_i \\
J_i &= -\frac{1}{k_B T} D_i c_i \nabla \mu_i \\
\mu_i &= k_B T \ln c_i + z_i e_0 V + V_i^0
\end{align*}
\]

\[
\begin{align*}
\epsilon \quad &\text{permittivity} \\
e_0 \quad &\text{unit charge} \\
z_i \quad &\text{valence of ion species } i \\
f(x, t) \quad &\text{protein charge} \\
k_B \quad &\text{Boltzmann constant} \\
T \quad &\text{absolute temperature} \\
D_i \quad &\text{diffusion coefficient} \\
J_i \quad &\text{ion flux}
\end{align*}
\]
The PNP Model

\[ \mu_i = k_B T \ln c_i + z_i e_0 V + V_i^0 \]

- \( k_B T \ln c_i + z_i e_0 V \): ideal part constituted by diffusion and mean field electrostatic interactions
- \( V_i^0 \): external forces

**Problem:**

**size effects** of ion diameter especially in small channels
Derivation of Model

**self-consistent one-dimensional hopping model:**

![Diagram of hopping model]

**Probability**

\[ c_i(x, t) = P(\text{particle of species } i \text{ is at position } x \text{ at time } t) \]
Derivation of Model

- transition rate if neighbouring sites are free:

\[ \tilde{\Pi}^+_c(x, t) = P(\text{jump of particle of species } i \text{ from position } x \text{ to } x \pm h \text{ in } (t, t + \Delta t)) \cdot \frac{1}{\Delta t} \]

\[ = \alpha_i \mp \beta_i V_{ix}(x \pm h/2, t) \]
Motivation

The Poisson-Nernst-Planck Model

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Derivation of Model

- transition rate if neighbouring sites are free:

\[ \tilde{\Pi}_i^{+/-}(x, t) = P(\text{jump of particle of species } i \text{ from position } x \text{ to } x \pm h \text{ in } (t, t + \Delta t)) \cdot \frac{1}{\Delta t} \]

\[ = \alpha_i \mp \beta_i V_{ix}(x \pm h/2, t) \]

- transition rate including finite size effects:

\[ \Pi_i^{+/-}(x, t) = \tilde{\Pi}_i^{+/-}(x, t) \cdot P(x \pm h \text{ is empty}) \]
Derivation of Model

- transition rate if neighbouring sites are free:

\[ \tilde{\Pi}_{ci}^{+/ -}(x, t) = P(\text{jump of particle of species } i \text{ from position } x \text{ to } x \pm h \text{ in } (t, t + \Delta t)) \cdot \frac{1}{\Delta t} \]

\[ = \alpha_i \mp \beta_i V_{ix}(x \pm h/2, t) \]

- transition rate including finite size effects:

\[ \Pi_{ci}^{+/ -}(x, t) = \tilde{\Pi}_{ci}^{+/ -}(x, t) \cdot P(x \pm h \text{ is empty}) \]

- closure assumption:

\[ P(\text{position } x \text{ is empty at time } t) = 1 - \sum_j c_j(x, t) \]
Derivation of Model

- **probability** that a particle of species $i$ is located at position $x$ at time $t + \Delta t$:

\[
c_i(x, t + \Delta t) =
\]
\[
c_i(x, t)(1 - \Pi^+(x, t) - \Pi^-(x, t)) +
\]
\[
c_i(x + h, t)\Pi^-(x + h, t) + c_i(x - h, t)\Pi^+(x - h, t)
\]
Derivation of Model

- **Probability** that a particle of species $i$ is located at position $x$ at time $t + \Delta t$:

\[
c_i(x, t + \Delta t) = c_i(x, t) \left(1 - \Pi^+(x, t) - \Pi^-(x, t)\right) + c_i(x + h, t)\Pi^-(x + h, t) + c_i(x - h, t)\Pi^+(x - h, t)
\]

- This is equal to (orange terms add up to zero)

\[
c_i(x, t + \Delta t) - c_i(x, t) = c_i(x, t)\Pi^+(x - h, t) + \Pi^-(x + h, t) - \Pi^+(x, t) - \Pi^-(x, t) + (c_i(x + h, t) - c_i(x, t))\Pi^-(x + h, t) + (c_i(x - h, t) - c_i(x, t))\Pi^+(x - h, t)
\]
Derivation of Model

- **Taylor-expansion** of blue terms of

\[
c_i(x, t + \Delta t) - c_i(x, t) =
\]

\[
c_i(x, t)(\Pi^+(x - h, t) + \Pi^-(x + h, t) - \Pi^+(x, t) - \Pi^-(x, t)) +
(c_i(x + h, t) - c_i(x, t))\Pi^-(x + h, t) +
(c_i(x - h, t) - c_i(x, t))\Pi^+(x - h, t)
\]
Derivation of Model

- **Taylor-expansion** of blue terms of

\[ c_i(x, t + \Delta t) - c_i(x, t) = \]
\[ c_i(x, t)(\Pi^+(x - h, t) + \Pi^-(x + h, t) - \Pi^+(x, t) - \Pi^-(x, t)) + \]
\[ (c_i(x + h, t) - c_i(x, t))\Pi^-(x + h, t) + \]
\[ (c_i(x - h, t) - c_i(x, t))\Pi^+(x - h, t) \]

- leads to

\[ c_i(x, t + \Delta t) - c_i(x, t) = \]
\[ c_i(x, t) \left( h(\Pi^-_x(x, t) - \Pi^+_x(x, t)) + \frac{h^2}{2}(\Pi^+_{xx}(x, t) + \Pi^-_{xx}(x, t)) \right) + \]
\[ hc_{ix}(\Pi^-_x(x + h, t) - \Pi^+_x(x - h, t)) + \]
\[ \frac{h^2}{2} c_{ixx}(\Pi^-_x(x + h, t) + \Pi^+_x(x - h, t)) \]
Derivation of Model

\[ \Pi^+/-(x, t) = \alpha_i \mp \beta_i V_{ix}(x \pm h/2, t) \left( 1 - \sum c_j \right) \]

We obtain after Taylor-expansion:

\[ \Pi^-(x, t) - \Pi^+_x(x, t) = 2\beta_i \frac{\partial}{\partial x} \left( V_{ix} \left( 1 - \sum c_j \right) \right) + 2h\alpha_i \sum c_{jxx} + O(h^2) \]
\[ \Pi^+_x(x, t) + \Pi^-_{xx}(x, t) = -2\alpha_i \sum c_{jxx} + O(h) \]
\[ \Pi^-(x + h, t) - \Pi^+(x - h, t) = 2\beta_i V_{ix} \left( 1 - \sum c_j \right) + O(h^2) \]
\[ \Pi^-(x + h, t) + \Pi^+(x - h, t) = 2\alpha_i \left( 1 - \sum c_j \right) + O(h) \]
Derivation of Model

\[
c_i(x, t + \Delta t) - c_i(x, t) = \\
\partial_x \left( h^2 \alpha_i \left( \left( 1 - \sum c_j \right) c_{ix} + c_i \sum c_{jx} \right) + 2h\beta_i c_i \left( 1 - \sum c_j \right) V_{ix} \right)
\]

Scaling: \(\Delta t = 2h^2\)

\[
D_i \approx \frac{\alpha_i}{2} \quad \text{diffusion coefficient}
\]

\[
\mu_i = \frac{2\beta_i}{\alpha_i h}
\]

mass density: \(m = \sum_j c_j\)

asymptotic limit \(\Delta t \to 0\):

\[
\partial_t c_i = D_i \partial_x \left( (1 - m) \partial_x c_i + c_i \partial_x m + \mu_i c_i (1 - m) \partial_x V_i \right)
\]

1D \(\Rightarrow\) **single file** movement
Derivation of Model

\[ V_i = z_i e_0 V + V_i^0, \]

\( e_0 \) unit charge, \( z_i \) valence, \( V_i^0 \) electro-chemical interactions

\( V \) computed self-consistently from Poisson equation:

\[ \epsilon \Delta V = -e_0 \sum_i z_i c_i + f \]

\( f(x, t) \) protein charge patterns

▶ Multidimensional Model

\[ \partial_t c_i = \nabla \cdot ( D_i ((1 - m) \nabla c_i + c_i \nabla m + \mu_i c_i (1 - m) \nabla V_i)) \]

ion flux \( J_i \)
Boundary Condition

concentration: \( c_i(x, t) = \gamma_i(x) \quad x \in \Gamma_D \)

remaining part of system: \( J_i(x, t) \cdot n = 0 \quad x \in \Gamma_N \)

charge neutrality: \( \sum z_i \gamma_i(x) = 0 \) in bathes

electrical potential: \( V(x, t) = V_D^0(x) + UV_D^1(x) \quad x \in \Gamma_D \)

remaining part of system: \( \nabla V(x, t) \cdot n = 0 \quad x \in \Gamma_N \).
Equilibrium Solution

ionic fluxes equal zero in equilibrium case:

\[ J_{i\infty} = (1 - m_{\infty}) \nabla c_{i\infty} + c_{i\infty} \nabla m_{\infty} + \mu_i c_{i\infty} (1 - m_{\infty}) \nabla V_{i\infty} = 0 \]

this is equal to

\[ \frac{\nabla c_{i\infty}}{c_{i\infty}} + \frac{\nabla m_{\infty}}{1 - m_{\infty}} + \mu_i \nabla V_{i\infty} = 0 \iff \nabla (\log c_{i\infty} - \log (1 - m_{\infty}) + \mu_i V_{i\infty}) = 0 \iff \log c_{i\infty} - \log (1 - m_{\infty}) + \mu_i V_{i\infty} = K_i \]

\[ \Rightarrow c_{i\infty} = (1 - m_{\infty}) k_i \exp (\mu_i V_{i\infty}) \quad \text{with } k_i = \exp K_i \]

we arrive at **Generalized Boltzmann Distributions:**

\[ c_{i\infty} = \frac{k_i \exp (\mu_i V_{i\infty})}{1 + \sum_j k_j \exp (-\mu_j V_{j\infty})} \quad k_i \geq 0 \]
Equilibrium Solution

\[ c_{i\infty} = \frac{k_i \exp(-\mu_i V_{i\infty})}{1 + \sum_j k_j \exp(-\mu_j V_{j\infty})} \]

Modified Poisson-Boltzmann Equation:

\[ -\epsilon \Delta V_{\infty} = \frac{-e_0 \sum_j z_j k_j \exp(-\mu_j (V_j^0 + z_j V_{\infty}))}{1 + \sum_j k_j \exp(-\mu_j (V_j^0 + z_j V_{\infty}))} + f \]
Numerical Results for Equilibrium for two Species

The black line corresponds to $\epsilon = 0.01$, the red line to $\epsilon = 0.1$ and the blue line to $\epsilon = 0.25$. $\epsilon$ denotes permittivity in Poisson equation.
**Entropy**

Entropy for this Process:

\[ E = \int \sum (c_i \log c_i + (1 - m) \log(1 - m) + \mu_i c_i V_i) \, dx \]

We introduce mobilities \( \eta_i \):

\[ \eta_i = \log c_i - \log (1 - m) + \mu_i V_i, \]

especially

\[ \eta_i = \partial c_i E + \text{const} \]

The system can be written as

\[ \partial_t c_i = \nabla \cdot (D c_i (1 - m) \nabla \eta_i) \]
Entropy Dissipation

\[
\partial_t E = \int \sum_i \left( \partial_t c_i \log c_i - \partial_t m \log (1 - m) + \mu_i \partial_t c_i V_i \right) dx
\]

\[
= \int \sum_i \partial_t c_i \eta_i dx
\]

\[
= \int \sum_i \nabla \cdot \left( D c_i (1 - m) \nabla \eta_i \right) \eta_i dx
\]

\[
= - \int \sum_i D c_i (1 - m) |\nabla \eta_i|^2 dx
\]

⇒ Entropy is **decreasing**
In equilibrium, entropy is **minimal** at fixed total mass.
**Transformation to Slotboom Variables**

**Stationary Model**

\[ 0 = \nabla \cdot (D_i((1 - m)\nabla c_i + c_i \nabla m + \mu_i c_i (1 - m) \nabla V_i)) \]

This system is not easy to solve. Hence we try to transform the variables to obtain a simplified system. In classical semiconductor theory, the variables after the transformation are called **Slotboom-Variables**.

- **transformation function** \( F_i(c_1, \ldots, c_n) = \log c_i - \log(1 - m) \)
- **transformation variable** \( u_i = F_i^{-1}(F_i(c_1, \ldots, c_n) + \mu_i V_i) \)
- \( c_i = F_i^{-1}(F_i(u_1, \ldots, u_n) - \mu_i V_i) = \frac{u_i \exp(-\mu_i V_i)}{1 + \sum_j u_j (\exp(-\mu_j V_j) - 1)} \)
Slotboom Transformation

System after Transformation

$$0 = \nabla \cdot \left( \frac{\exp(-\mu_i V_i)}{(1 + \sum_j u_j(\exp(-\mu_j V_j)-1))^2} \left( \nabla u_i (1 - \sum_j u_j) + u_i \sum_j \nabla u_j \right) \right)$$

$\Rightarrow$ no convective terms

linearization $u_i = u_{i\infty} + \epsilon \tilde{u}_i$ around $u_{i\infty} = \frac{k_i}{1 + \sum_j k_j}$:

System after Linearization

$$0 = \nabla \cdot \left( \frac{\exp(-\mu_i V_{i\infty})(1 + \sum_j k_j)}{(1 + \sum_j k_j \exp(-\mu_j V_{j\infty}))^2} \left( \nabla \tilde{u}_i + k_i \sum_j \nabla \tilde{u}_j \right) \right)$$
Motivation

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A new Model

Analysis for new Model

Current

Current: \( I = e_0 \sum \int_{\Gamma_0} z_i J_i \cdot d\nu \)

\( \Gamma_0 \in \Gamma_B \)

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Universität Münster
Problems in the Analysis

We consider a system of two equations from now on. We consider red and blue particles. Density of red particles is labelled $r$, respectively for blue particles. Only difference: Response to potential $V$.

System of Equations

$$\partial_t r = \nabla \cdot ((1 - m) \nabla r + r \nabla m + \mu r (1 - m) \nabla V)$$

$$\partial_t b = \nabla \cdot (D((1 - m) \nabla b + b \nabla m - \mu b (1 - m) \nabla V))$$

nonlinear cross diffusion $\Rightarrow$ few literature available

- existence and uniqueness of a solution?
- no a-priori estimates
- no maximum principle (only $0 \leq r, b, m \leq 1$)
**Entropy**

Entropy

\[ E(r, b) = \int (r \log r + b \log b + (1 - m) \log (1 - m) + \mu r V - \mu b V) \, dx \]

\( E \) is decreasing during the process and **minimal** in equilibrium state

**Equilibrium Solutions**

\[ r_\infty = \frac{k_1 \exp(-\mu V_\infty)}{1 + k_1 \exp(-\mu V_\infty) + k_2 \exp(\mu V_\infty)} \]

\[ b_\infty = \frac{k_2 \exp(\mu V_\infty)}{1 + k_1 \exp(-\mu V_\infty) + k_2 \exp(\mu V_\infty)} \]

special case \( b \equiv 0 \):

\[ \Rightarrow \partial_t r = \nabla \cdot (\nabla r - r(1 - r)\nabla V) \Rightarrow r_\infty = \frac{k_1 \exp(-\mu V_\infty)}{1 + k_1 \exp(-\mu V_\infty)} \]
Linear Stability in Case $V(x) = 0$

System of Equations:
\[ \partial_t r = \nabla \cdot ((1 - m)\nabla r + r\nabla m) \]
\[ \partial_t b = \nabla \cdot (D((1 - m)\nabla b + b\nabla m)) \]

equilibrium solutions: constants $r_\infty, b_\infty$
small perturbations $u$ and $v$

linearization around $r_\infty + \epsilon u$ and $b_\infty + \epsilon v$:

First Order Linearization
\[ \partial_t u = (1 - b_\infty)\Delta u + r_\infty\Delta v \]
\[ \partial_t v = D((1 - r_\infty)\Delta v + b_\infty\Delta u) \]
Linear Stability in Case $V(x) = 0$

Combine first order linearizations to one equation for $w = u + \alpha_{1/2}v$:

$$\partial_t w = ((1 - b_\infty) + \alpha Db_\infty) \Delta u + (r_\infty + \alpha D(1 - r_\infty)) \Delta v.$$ 

Choosing $\alpha$ such that

$$\alpha((1 - b_\infty) + \alpha Db_\infty) = r_\infty + \alpha D(1 - r_\infty)$$

Explicitly $\alpha_{1/2} = \frac{D(1-r_\infty)-(1-b_\infty)\pm\sqrt{((1-b_\infty)-D(1-r_\infty))^2+4Dr_\infty b_\infty}}{2Db_\infty}$
Linear Stability in Case $V(x) = 0$

$\Rightarrow$ heat equation

$$\partial_t w = k_{1/2} \Delta w$$

with

$$k_{1/2} = \frac{1}{2} \left( (1 - b_\infty) + D(1 - r_\infty) \pm \sqrt{((1 - b_\infty) - D(1 - r_\infty))^2 + 4Dr_\infty b_\infty} \right)$$

$k_1 > 0$ and $k_2 \geq 0$ ($k_2 = 0$ if $r_\infty + b_\infty = 1$)

$\Rightarrow$ stability around equilibria
Linear Stability

System can be written as

$$\partial_t r = \nabla \cdot (r(1 - m) \nabla \eta)$$
$$\partial_t b = \nabla \cdot (Db(1 - m) \nabla \xi)$$

with mobilities

$$\eta = \partial_r E(r, b) = \log r - \log (1 - m) + V$$
$$\xi = \partial_b E(r, b) = \log b - \log (1 - m) - V$$

convex conjugate Entropy fulfills

$$\partial_\eta E^*(\eta, \xi) = r$$
$$\partial_\xi E^*(\eta, \xi) = b$$
Linear Stability

linearization in entropy variables $\eta = \eta_\infty + \epsilon u$ and $\xi = \xi_\infty + \epsilon v$

small perturbations $u$ and $v$

First Order Linearization

$$\partial_\eta r \partial_t u + \partial_\xi r \partial_t v = \nabla \cdot (r_\infty (1 - \rho_\infty) \nabla u)$$

$$\partial_\eta b \partial_t u + \partial_\xi b \partial_t v = \nabla \cdot (Db_\infty (1 - \rho_\infty) \nabla v)$$

$$\nabla E^*(\eta, \xi) := \begin{pmatrix} r \\ b \end{pmatrix} \quad H_{E^*} := \begin{pmatrix} \partial_\eta r & \partial_\xi r \\ \partial_\eta b & \partial_\xi b \end{pmatrix}$$
Linear Stability

\[ H_{E^*} \left( \begin{array}{c} \partial_t u \\ \partial_t v \end{array} \right) = \nabla \cdot \left( M : \left( \begin{array}{c} \nabla u \\ \nabla v \end{array} \right) \right) \]

with

\[ M := \left( \begin{array}{cc} r_\infty (1 - \rho_\infty) & 0 \\ 0 & Db_\infty (1 - \rho_\infty) \end{array} \right) \]
Linear Stability

\[ H_{E^*} := \begin{pmatrix} \frac{e^{\xi+V}(1+e^{-V})}{(1+e^{\xi+V}+e^{-V})^2} & \frac{-e^{\xi+V}e^{-V}}{(1+e^{\xi+V}+e^{-V})^2} \\ \frac{-e^{\xi+V}e^{-V}}{(1+e^{\xi+V}+e^{-V})^2} & \frac{e^{-V}(1+e^{\xi+V})}{(1+e^{\xi+V}+e^{-V})^2} \end{pmatrix} = \begin{pmatrix} a & b \\ b & c \end{pmatrix} \]

\( H_{E^*} \) positive definit: \( a \geq |b| \), and \( c \geq |b| \)

\[ M := \begin{pmatrix} r_\infty(1 - \rho_\infty) & 0 \\ 0 & Db_\infty(1 - \rho_\infty) \end{pmatrix} \]

\( M \) positiv semidefinit

\( \Rightarrow \) System is linear stable
Existence and Uniqueness near Equilibrium

Consider

\[ \partial_t r = \nabla \cdot ((1 - m) \nabla r + r \nabla m) \]  
\[ \partial_t b = \nabla \cdot (D((1 - m) \nabla b + b \nabla m)) \]

with initial data \( r_0, b_0 \in H^2 \) Assume

\[ \| r_0 - r_\infty \|_{H^2} \leq \epsilon, \| b_0 - b_\infty \|_{H^2} \leq \epsilon. \]

Then, there exists a unique solution to (1), (2) in

\[ B_R = \{(r, b) : \| r - r_\infty \|_X \leq R, \| b - b_\infty \|_X \leq R \} \]

with \( X := L^\infty((0, T); H^2) \cap L^2((0, T); H^3) \cap H^1((0, T); H^1) \),
where the constant \( R \) depends on \( \epsilon \) only.
Sketch of Proof

The proof is based on Banach’s fixed point theorem:

1. Step: construction of fixed point operator

\[
\frac{\partial}{\partial t} (r - r_\infty) - (1 - b_\infty) \Delta r - r_\infty \Delta b = \\
(b_\infty - b) \Delta (r - r_\infty) - (r_\infty - r) \Delta (b - b_\infty) \\
:= F_1(r, b)
\]

\[
\frac{\partial}{\partial t} (b - b_\infty) - (1 - r_\infty) \Delta b - b_\infty \Delta r = \\
(r_\infty - r) \Delta (b - b_\infty) - (b_\infty - b) \Delta (r - r_\infty) \\
:= F_2(r, b)
\]

2. Step: splitting of fixed point operator in heat operator and in a part that is of order $\epsilon^2$ in $L^2$
Sketch of Proof

3. Step: define Operator $S$ which maps $r - r_\infty$, $b - b_\infty$ on linear combinations $w_{1,2} = (r - r_\infty) + \alpha_{1,2}(b - b_\infty)$. $w_{1,2}$ fulfills heat equation

$$\partial_t w_{1,2} - k_{1,2} \Delta w_{1,2} = F_1 + \alpha_{1,2} F_2 =: F$$

4. Step: apply well-known results for heat operator:
   $w_1, w_2 \in X$ and $\|w_{1,2}\|_X \leq R_{1,2}(\epsilon)$

5. Step: reiterating we finally obtain $R \leq C(R^2 + \epsilon)$ and hence

$$B_R = \{(r, b) : \|r - r_\infty\|_X \leq R, \|b - b_\infty\|_X \leq R\}$$
Sketch of Proof

6. Step: the operator $G = S' \circ L \circ S \circ F$ is selfmapping ($L$ ”solution operator” of the heat equation)

7. Step: we estimate $\|F_1(r_1, b_1) - F_1(r_2, b_2)\|_{L^2}$ and $\|F_2(r_1, b_1) - F_2(r_2, b_2)\|_{L^2}$ to show contractiveness of $G$

Banach’s fixed point theorem:
⇒ we have existence and uniqueness of solutions $(r, b)$ in $B_R$
Global Existence

There exists a weak solution for

\[ \partial_t r = \nabla \cdot ((1 - m) \nabla r + r \nabla m) \]
\[ \partial_t b = \nabla \cdot ((1 - m) \nabla b + b \nabla m) \]

in \((L^2((0, T); L^2)) \cap H^1((0, T); H^{-1}))^2\), such that

\[ \rho, \sqrt{1 - \rho r}, \sqrt{1 - \rho b} \in L^2((0, T); H^1), \]

and furthermore

\[ 0 \leq r, \quad 0 \leq b, \quad b + r \leq 1 \quad \text{almost everywhere}. \]
Sketch of Proof

The proof consists mainly of these steps:

1. regularization of problem
2. Galerkin approximation
3. existence for approximated system
4. passing to the limit $n \to \infty$
5. passing to the limit $\epsilon \to 0$
Open Questions

- agreement with experimental data?
- uniqueness?
- longtime behaviour for the general case?
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