Congrès SMAI 2021

June 21st-25th, 2021

The relaxation of the Cahn-Hilliard equation for the modelling of living tissues

and its numerical simulation

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June 20, 2021

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Introduction

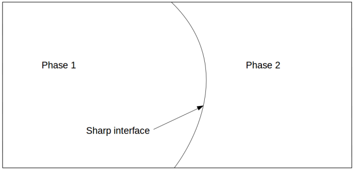
The Cahn-Hilliard equation

$$\partial_t n = \nabla \cdot (b(n)\nabla(-\gamma\Delta n + \psi'(n))) \quad \text{in} \quad \Omega \times (0, +\infty),$$

with Neumann boundary conditions

$$\frac{\partial n}{\partial \nu} = b(n)\frac{\partial(-\gamma\Delta n + \psi'(n))}{\partial \nu} = 0 \qquad \text{on} \quad \partial\Omega \times (0, +\infty).$$

- Introduced by Cahn and Hilliard (1958): models the spinodal decomposition.



The Cahn-Hilliard equation

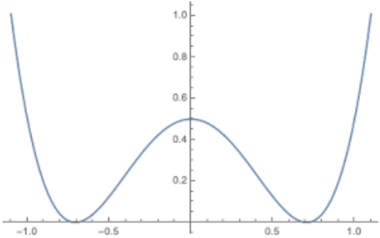
- Helmholtz free energy:

$$\mathcal{E}[n] = \int_\Omega \left[\frac{\gamma}{2}|\nabla n|^2 + \psi(n)\right].$$

- $n = \frac{n_1}{n_1+n_2}$: order parameter (relative volume fraction or density).
- $\frac{\gamma}{2}|\nabla n|^2$: represents surface tension and penalizes large gradients of n.

- $\gamma = \sqrt{\epsilon}$: width of the diffuse interface.
- $\psi(n)$: homogeneous free energy.
- Mass balance equation:

$$\partial_t n = \nabla \cdot \left(b(n)\nabla \frac{\delta \mathcal{E}}{\delta n}\right).$$



Modeling of living tissues

- Khain, Evgeniy and Sander, Leonard M., *A generalized Cahn-Hilliard equation for biological applications*, Physical Review E, 77,(2008).
    - Generalized Cahn-Hilliard equation + proliferation term.
    - Continuum limit of a discrete model: cells move, proliferate and interact via adhesion.

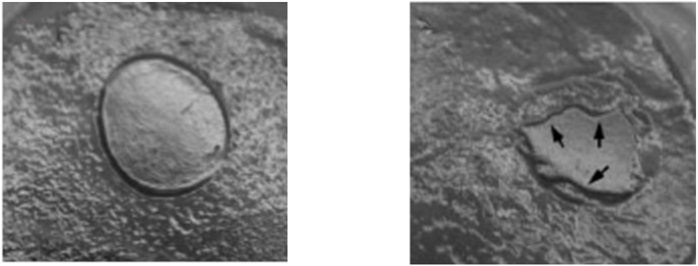


Figure 2: Taken from Ben Amar, M. and Wu, M. *Re-epithelialization: advancing epithelium frontier during wound healing*, Journal of The Royal Society Interface 11, 93, (2014).

Modeling of living tissues

- Agosti, Abramo and Cattaneo, Clara and Giverso, Chiara and Ambrosi, Davide and Ciarletta, Pasquale, *A computational framework for the personalized clinical treatment of glioblastoma multiforme*, 98, Z. Angew. Math. Mech., (2018).
    - Degenerate Cahn-Hilliard equation with single-well logarithmic potential.
    - Glioblastoma multiforme.
    - Proliferation and death of cells.
    - Effect of radiotherapy.

$$
\begin{aligned}
\frac{\partial \phi_c}{\partial t} - \mathrm{div}\left(\frac{\phi_c(1-\phi_c)^2}{M}\mathbf{T}\nabla\Sigma\right) &= \underbrace{\nu\phi_c[n-\delta]_+(1-\phi_c) - \nu_d\phi_c[\delta-n]_+}_{\text{proliferation and death}} - \underbrace{k_R(t)\phi_c - k_C(t)\phi_c}_{\text{radioterapy and chemoterapy}}, \\
\Sigma &= -\epsilon^2\Delta\phi_c + \psi'(\phi_c) - \chi_c n, \\
\frac{\partial n}{\partial t} - \mathrm{div}(\mathbf{D}\nabla n) &= \underbrace{S_n(1-n)(1-\phi_c) - \delta_n\phi_c n}_{\text{source and consumption}}, \\
\nabla\phi_c\cdot\boldsymbol{\nu} &= \nabla\mu\cdot\boldsymbol{\nu} = \nabla n\cdot\boldsymbol{\nu} = 0 \quad \text{on } \partial\Omega \quad + \text{ IC.}
\end{aligned}
$$

Degenerate Cahn-Hilliard model

- Coupled second-order system of equations:

$$\begin{cases} \partial_t n &= \nabla \cdot \left(b(n) \nabla w \right), \\ w &= -\gamma \Delta n + \psi'(n), \end{cases}$$

$$\frac{\partial n}{\partial \nu} = b(n) \frac{\partial w}{\partial \nu} = 0.$$

- $b(n) = n(1-n)^2$.
- ψ: single-well logarithmic potential.
- $\psi = \psi_+ + \psi_-$: convex-concave decomposition.

Singular single-well potential

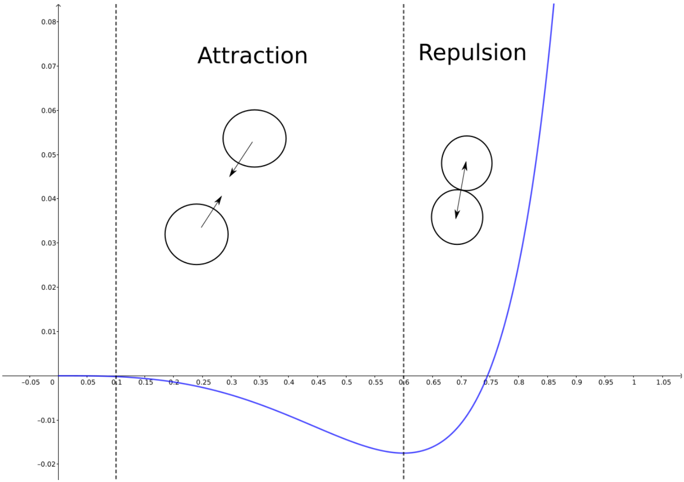


Figure 3: Single-well potential of Lennard-Jones type.

Relaxation of the degenerate Cahn-Hilliard model

RDCH model

- Relaxed-degenerate Cahn-Hilliard model

$$\begin{cases} \partial_t n_\sigma = \nabla \cdot \big(b(n_\sigma)\nabla\left(\varphi_\sigma + \psi'_+(n_\sigma)\right)\big) & \text{in } \Omega\times(0,+\infty), \\ -\sigma\Delta\varphi_\sigma + \varphi_\sigma = -\gamma\Delta n_\sigma + \psi'_-\left(n_\sigma - \dfrac{\sigma}{\gamma}\varphi_\sigma\right) & \text{in } \Omega\times(0,+\infty). \end{cases}$$

- Zero-flux boundary conditions

$$\frac{\partial(\gamma n_\sigma - \sigma\varphi_\sigma)}{\partial\nu} = b(n_\sigma)\frac{\partial\big(\varphi_\sigma + \psi'_+(n_\sigma)\big)}{\partial\nu} = 0 \qquad \text{on } \partial\Omega\times(0,+\infty).$$

- Parabolic-elliptic system of two second-order coupled equations.
- σ = relaxation parameter.
- Perthame, Benoît and Poulain, Alexandre, *Relaxation of the Cahn–Hilliard equation with singular single-well potential and degenerate mobility*, European Journal of Applied Mathematics, (2020).

Outline of the analysis

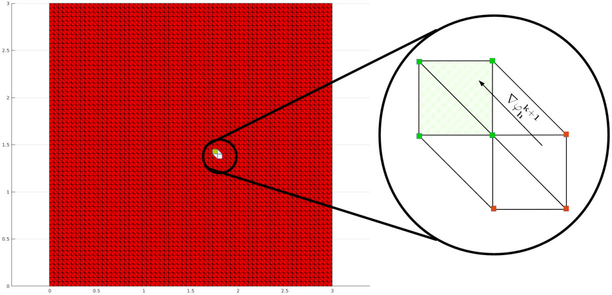
1. Regularized problem.
    - Non-degenerate mobility + non-singular potential.
2. Existence of solutions for the regularized problem.
3. Existence of global weak solutions for the RDCH model.

$$n_\sigma \in L^2(0,T;H^1(\Omega)), \quad \partial_t n_\sigma \in L^2\big(0,T;(H^1(\Omega))'\big).$$
$$\varphi_\sigma \in L^2(0,T;H^1(\Omega)),$$
$$n_\sigma - \frac{\sigma}{\gamma}\varphi_\sigma \in L^2(0,T;H^2(\Omega)), \quad \partial_t\left(n_\sigma - \frac{\sigma}{\gamma}\varphi_\sigma\right) \in L^2\big(0,T;(H^1(\Omega))'\big).$$
$$0 \le n_\sigma < 1, \qquad \text{a.e. in } \Omega_T.$$

4. Convergence to the solutions of the DCH model as $\sigma \to 0$.
5. Convergence of the solutions to steady-states as $t \to +\infty$.
    - Inequalities from energy and entropy estimates.
    - Compactness of important quantities.
    - Limit $\epsilon \to 0$ and/or $\sigma \to 0$.

Numerical simulation

- Goals:
  - Use simple $P-1$ finite elements.
  - Can be solved using standard sofwares for parabolic and elliptic equations.
  - Avoid Newton iterations and the variational inequality.
  - Preserve **energy decay**, **non-negativity of the solution** and **mass conservation**.



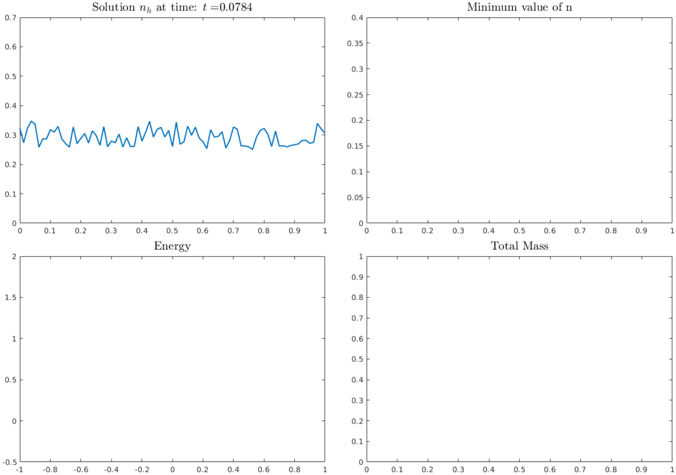
Existence and non-negativity of the discrete solution

Bubba, Federica and Poulain, Alexandre, *A non-negativity preserving finite element scheme for the relaxed Cahn-Hilliard equation with single-well potential and degenerate mobility*, Submitted.

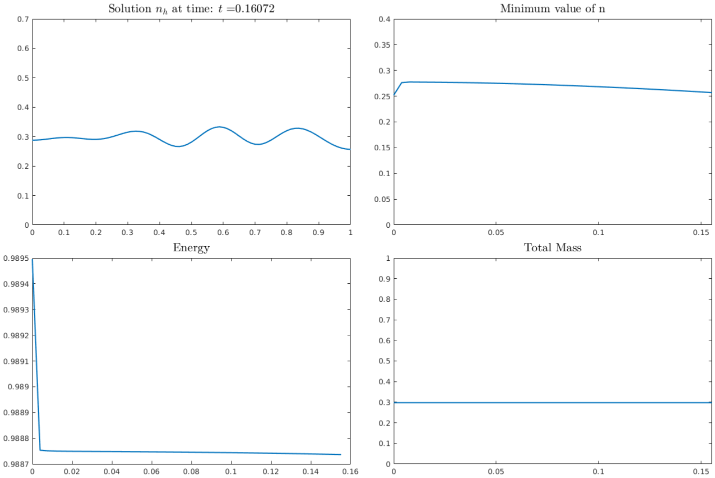
1. Regularized problem.
    - Smooth potential $\psi_{\epsilon,+}$.
2. Existence of solutions for the regularized problem using Brouwer's fixed-point theorem.
3. Non-negativity is proved using the upwind method.
4. Passing to the limit of the regularization parameter, we proved the existence of discrete non-negative solutions.
5. Convergence analysis for $d = 1, 2, 3$ is achieved using discrete a priori estimates.

Numerical results

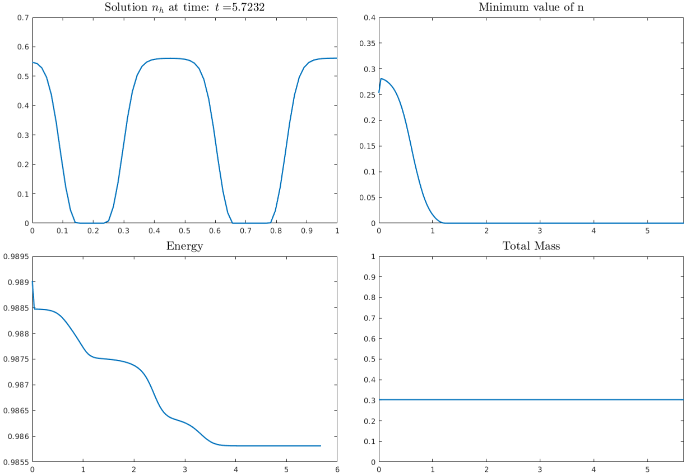
1D numerical simulation



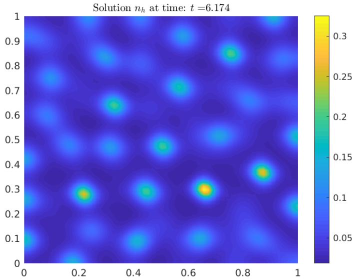
1D numerical simulation

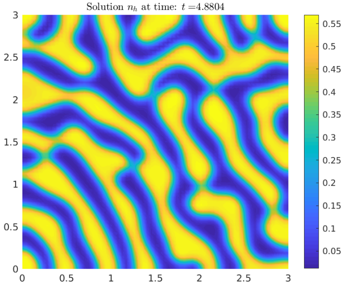


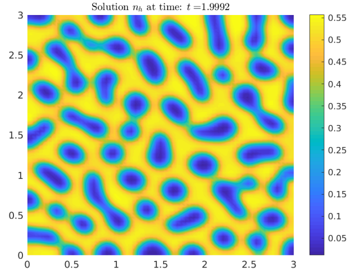
1D numerical simulation



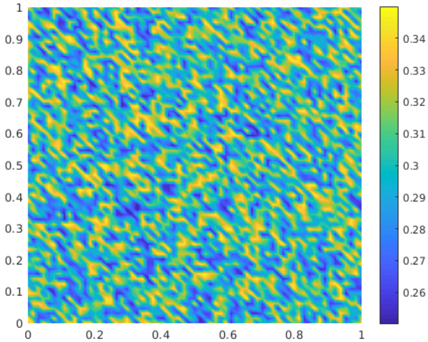
2D numerical simulations

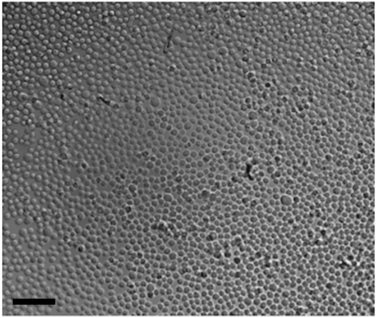






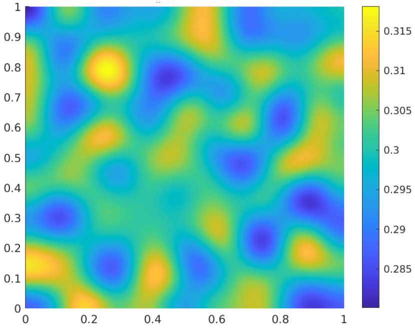
2D numerical simulations

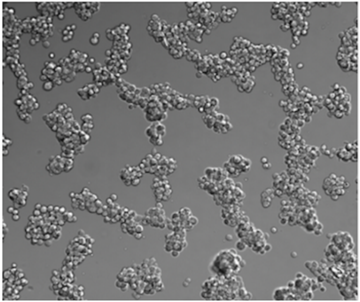




Right figure: Aggregation of glioma cells (T=0) from rat during time reproduced from L. Adenis et al. (2020), (CC BY-NC 3.0).

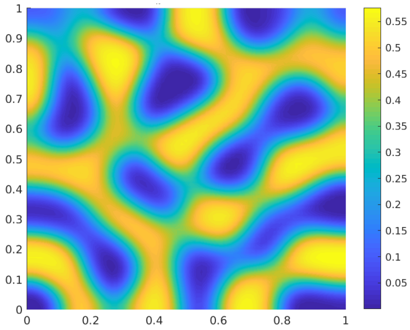
2D numerical simulations

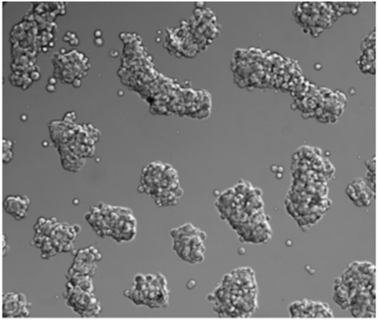




Right figure: Aggregation of glioma cells (T=6h) from rat during time reproduced from L. Adenis et al. (2020), (CC BY-NC 3.0).

2D numerical simulations





Right figure: Aggregation of glioma cells (T=12h) from rat during time reproduced from L. Adenis et al. (2020), (CC BY-NC 3.0).

Conclusion and further works

Conclusion and further directions

- Summary:
  - **Relaxation of the Cahn-Hilliard equation** with degenerate mobility and single-well logarithmic potential.
  - **Existence of global weak solutions** and **convergence to the initial problem**.
  - $P-1$ **finite element numerical scheme**: preserves the energy and the physical bound of the solution.
- Further directions
  - **Multiphase Cahn-Hilliard model** with degenerate mobility and singular degenerate potential.
  - Model including cancer and immune cells: **immunotherapy**.
  - Incompressible limit in general living tissue models with surface tension.

Heterogeneity of tumors

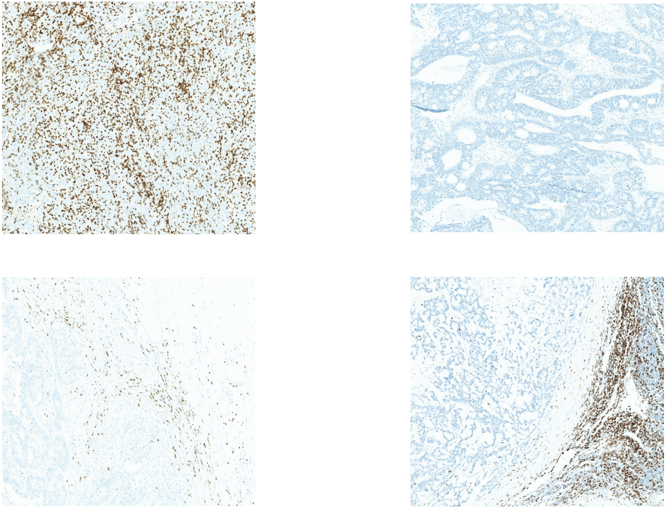


Figure 4: Taken from J. Galon and D. Bruni, *Approaches to treat immune hot, altered and cold tumours with combination immunotherapies*, Nature Reviews | Drug Discovery (2019).

Thank you

Questions?

Energy estimates

- Regularization:

$$b_1 < B_\epsilon(n) < B_1, \quad \forall n \in \mathbb{R} \text{ and } B_\epsilon \in C(\mathbb{R}, \mathbb{R}^+),$$

$$\psi_{+,\epsilon}(n) \in C^2(\mathbb{R}, \mathbb{R}) \quad \psi_{+,\epsilon}(n) \geq -D_1, \quad \psi_- \in C_b^2(\mathbb{R}), \quad \forall n \in \mathbb{R}.$$

Definition (Energy)

$$\frac{d}{dt}\mathcal{E}_{\sigma,\epsilon}[n_{\sigma,\epsilon}(t)] = -\int_\Omega B_\epsilon(n_{\sigma,\epsilon})\left|\nabla(\varphi_{\sigma,\epsilon} + \psi'_{+,\epsilon}(n_{\sigma,\epsilon}))\right|^2 \leq 0.$$

$$\mathcal{E}_{\sigma,\epsilon}[n_{\sigma,\epsilon}(T)] + \int_0^T \int_\Omega B_\epsilon(n_{\sigma,\epsilon})\left|\nabla(\varphi_{\sigma,\epsilon} + \psi'_{+,\epsilon}(n_{\sigma,\epsilon}))\right|^2 = \mathcal{E}_{\sigma,\epsilon}[n^0].$$

with

$$\mathcal{E}_{\sigma,\epsilon}[n_{\sigma,\epsilon}] = \int_\Omega \Big[\psi_{+,\epsilon}(n_{\sigma,\epsilon}) + \frac{\gamma}{2}|\nabla(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma}\varphi_{\sigma,\epsilon})|^2 + \frac{\sigma}{2\gamma}|\varphi_{\sigma,\epsilon}|^2 + \psi_-(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma}\varphi_{\sigma,\epsilon})\Big],$$

Entropy estimate

Definition (Entropy)

$$\phi_\epsilon : [0,\infty) \mapsto [0,\infty)$$

$$\phi_\epsilon''(n) = \frac{1}{B_\epsilon(n)}, \qquad \phi_\epsilon(0) = \phi_\epsilon'(0) = 0,$$

$$\Phi_\epsilon[n] = \int_\Omega \phi_\epsilon\big(n(x)\big)\,dx.$$

$$\frac{d\Phi_\epsilon[n_{\sigma,\epsilon}(t)]}{dt} = -\int_\Omega \gamma\left|\Delta\left(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma}\varphi_{\sigma,\epsilon}\right)\right|^2 + \frac{\sigma}{\gamma}|\nabla\varphi_{\sigma,\epsilon}|^2$$
$$+ \psi_-''(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma}\varphi_{\sigma,\epsilon})\left|\nabla(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma}\varphi_{\sigma,\epsilon})\right|^2 + \psi_{+,\epsilon}''(n_{\sigma,\epsilon})|\nabla n_{\sigma,\epsilon}|^2.$$

Lemma (Compactness of time derivative)

$$||\partial_t n_{\sigma,\epsilon}||_{L^2(0,T;(H^1(\Omega))')} \leq C,$$

$$||\partial_t \left(n_{\sigma,\epsilon} - \frac{\sigma}{\gamma} \varphi_{\sigma,\epsilon} \right) ||_{L^2(0,T;(H^1(\Omega))')} \leq C.$$

- In the limit $\sigma \to 0$, the solutions satisfy:

For all $\chi \in L^2(0, T; H^2(\Omega)) \cap L^\infty(\Omega_T)$ with $\nabla \chi \cdot \nu = 0$ on $\partial\Omega \times (0, T)$,

$$\begin{cases} \int_0^T < \chi, \partial_t n > & = \int_{\Omega_T} J \cdot \nabla \chi, \\ \int_{\Omega_T} J \cdot \nabla \chi & = - \int_{\Omega_T} \gamma \Delta n \left[b'(n) \nabla n \cdot \nabla \chi + b(n) \Delta \chi \right] + (b\psi'')(n) \nabla n \cdot \nabla \chi. \end{cases}$$

- This is the Degenerate Cahn-Hilliard model.

1D parameters

- $\Omega = [0, 1]$.
- $\mathcal{T}^h$: uniform mesh, 1D bar elements.
- $h = 0.01$, $\Delta t = 2\gamma$.
- Total number of elements: 100.
- $\gamma = (0.014)^2$.
- $\sigma = 1e^{-5}$.
- $n^\star = 0.6$.
- $n_h^0 = 0.3$.

2D numerical simulations

- $\Omega = [0,3] \times [0,3]$.
- $\mathcal{T}^h$: uniform mesh, triangular elements.
- $h = 0.03$, $\Delta t = 2\gamma$.
- Total number of elements: 20000.
- $\gamma = (0.014)^2$.
- $\sigma = 1e^{-5}$.
- $n^\star = 0.6$.
- $n_h^0 = [0.05, 0.3, 0.36]$.