UFSM

CIÊNCIA e NATURA

ISSN 2179-460X

OPEN ACCESS

Ci. e Nat., Santa Maria, v. 46, n. esp. 1, e87268, 2024 • https://doi.org/10.5902/2179460X87268
Submitted: 03/26/2024 • Approved: 06/25/2024 • Published: 04/11/2024

Special edition ERMAC e ENMC

Allen-Cahn Equation for Modeling Temporal Evolution of Non-Conserved Field Variables in Cancer Cell Migration

Equação de Allen-Cahn para Modelagem da Evolução Temporal de Variáveis de Campo Não Conservativas na Migração de Células Cancerígenas

João Gabriel Piraine Bandeira [I], **Gustavo Braz Kurz** [II], **Daniela Buske** [II], **Régis Sperotto de Quadros** [II]

[I]Control and Automation Engineering, Federal University of Pelotas, RS, Brazil
[II]Postgraduate Program in Mathematical Modeling, Federal University of Pelotas, RS, Brazil

ABSTRACT

This work explores the temporal evolution of non-conserved field variables through the application of the Allen-Cahn equation. The equation forms the basis for various phase-field models used in cell migration studies, particularly in the context of tumor cells and cancer metastasis. The model portrays cells as 2D soft bodies, integrating mechanical and biological aspects to simulate cell movement. The investigation delves into the mathematical representation of cell migration, vital in understanding cancer development and metastasis. The model employs an order parameter to characterize each cell, representing their presence within a cell cluster. By minimizing a specific free energy functional, the equilibrium shape of the soft cell bodies is determined, incorporating parameters that influence elasticity and energetic costs. Additionally, the interaction between cells is incorporated, contributing to a comprehensive portrayal of cell migration. The study yields insights into the complex dynamics of cell migration, enhancing our comprehension of biological processes and potentially informing cancer research strategies.

Keywords: Cell migration; Phase-field models; Allen-Cahn equation; Cancer metastasis; Mathematical modeling

RESUMO

Este trabalho explora a evolução temporal de variáveis de campo não conservativas através da aplicação da equação de Allen-Cahn. A equação forma a base para diversos modelos de campo de fase usados em estudos de migração celular, especialmente no contexto de células tumorais e metástase do câncer. O modelo retrata as células como corpos macios 2D, integrando aspectos mecânicos e biológicos para simular o movimento celular. A investigação aprofunda-se na representação

matemática da migração celular, fundamental para entender o desenvolvimento do câncer e a metástase. O modelo emprega um parâmetro de ordem para caracterizar cada célula, representando sua presença dentro de um aglomerado celular. Ao minimizar uma função específica de energia livre, determina-se a forma de equilíbrio dos corpos celulares macios, incorporando parâmetros que influenciam a elasticidade e os custos energéticos. Além disso, a interação entre as células é incorporada, contribuindo para uma representação abrangente da migração celular. O estudo oferece insights sobre a dinâmica complexa da migração celular, aprimorando a compreensão dos processos biológicos e potencialmente informando estratégias de pesquisa do câncer.

Palavras-chave: Migração celular; Modelos de campo de fase; Equação de Allen-Cahn; Metástase do câncer; Modelagem matemática

1 INTRODUCTION

Cancer, a disease with profound global implications, ranks among the leading causes of death in many countries. The scarcity of adequate medical resources contributes significantly to the loss of lives. The risk of developing cancer increases with age, particularly affecting individuals aged 55 or older. Throughout life, the likelihood of developing or succumbing to cancer is approximately 1 in 2 for men and 1 in 3 for women. As a result, research into cancer treatment has garnered extensive attention from various disciplines (Farayola et al., 2020). The higher mortality rate associated with this disease can be understood by examining the characteristics of cancer cells. To enhance treatment outcomes, mathematical models have been employed to analyze the impact of radiotherapy on cancer cells and study their movement within the body (Biner, 2017; Farayola et al., 2020; Kolev et al., 2013).

Cell migration is an indispensable and crucial process for development, differentiation, and the body's ability to respond to diseases. Over the years, it has undergone meticulous experimental investigation and has been the subject of modeling by researchers from various fields, including mathematicians, engineers, and physicists (Flaherty et al., 2007; Mousavi et al., 2014; Nieto and Urrutia, 2016; Taylor et al., 2011). Initial models were rudimentary due to limited knowledge. However, as cellular biology advanced and quantitative data became available, more sophisticated models were developed, incorporating principles from areas such as materials science, mechanical engineering, and condensed matter physics. These mathematical models not only deepen our understanding of cellular processes but also enable researchers to compare competing hypotheses and make accurate predictions that can be

empirically tested through experiments (Carlsson and Sept, 2008).

Cell motility, a crucial biological process in the functioning of our bodies, poses a complex challenge for researchers. Mathematical models have become essential tools for gaining profound insights into this intricate biological phenomenon. By employing computational models, scientists can effectively explore various scenarios, surpassing the limitations of traditional in vitro investigations (Flaherty et al., 2007). However, to advance in this research area, a solid understanding of the fundamentals of cell motility is essential for developing accurate and meaningful mathematical models.

Cell migration holds immense importance in various physiological, biological, and pathological processes, such as tissue morphogenesis, cell differentiation, cancer development, and wound healing. The behavior of cell migration is influenced by complex biochemical, biophysical, and mechanical factors. To enhance our understanding of this phenomenon, researchers have proposed a three-dimensional model that takes into account how cells perceive their environment and exert forces to move. This model shows promising agreement with experimental and numerical data, providing valuable insights into cell locomotion across diverse scenarios (Flaherty et al., 2007; Mousavi et al., 2014).

Cell migration, especially in the context of tumor cells, has been extensively studied using mathematical models, given its crucial role in cancer development and metastasis. These models incorporate various biological mechanisms and mechanical factors to simulate cell movement. While some models adopt a purely mechanical approach, similar to molecular dynamics, others utilize lattice-based methods for dense tissues. Understanding the behavior of individual cells at low density is essential for comprehending how tissues collectively behave at higher densities. Through the implementation of efficient algorithms, researchers have made significant advancements in exploring cell movement and interactions, thereby gaining a deeper understanding of cellular behavior in diverse environments (Nieto and Urrutia, 2016; Taylor et al., 2011).

2 METHODOLOGY

In this model, each cell is represented by an order parameter φ within the phase field, taking the value of 1 inside the cell and 0 outside of it. Treating the cells as soft 2D

bodies, their equilibrium shape is determined by minimizing the following free energy (Biner, 2017):

$$F_0 = \sum_n \left[\gamma_n \int_V \left[(\nabla \varphi_n)^2 + \frac{30}{\lambda^2} \varphi_n^2 \left(1 - \varphi_n\right)^2 \right] dV + \frac{\mu_n}{\pi R^2} \left(\pi R^2 - \int_V \left(\varphi_n^2\right) dV \right)^2 \right], \tag{1}$$

where R is the radius, λ represents the width of the cell boundary, μ_n is considered a parameter that determines the energy cost associated with changes in cell area while maintaining its volume approximately constant, and γ_n is a parameter that controls cell elasticity.

The first term corresponds to the conventional Allen-Cahn equation, which is non-conservative and includes gradient energy and a double well potential for the order parameter. This partial differential equation describes how the order parameter evolves over time and models phase separation in physical systems. In this case, the non-conservative nature of the Allen-Cahn equation means that the total quantity of the order parameter is not conserved over time.

Furthermore, the Allen-Cahn equation is modified to incorporate gradient energy terms that account for spatial variations of the order parameter and its gradient. These gradient energy terms capture the influence of interfaces and boundaries between phases in the system.

The double well potential is a mathematical function that describes the shape of the potential associated with the order parameter. It has two symmetric wells, indicating the existence of two distinct phases in the system. The design of the double well potential aims to favor phase separation and facilitate the formation of domain structures.

The free energy F_0 represents individual cells, while the total energy, taking interactions between them into account, is given by

$$F = F_o + F_{int}, \tag{2}$$

where the internal force F_{int} is defined, by Biner (2017), as

$$F_{\text{int}} = \frac{30\kappa}{\lambda^2} \int_V \left(\sum_{n,m \neq n} \varphi_n^2 \varphi_m^2 \right) dV, \tag{3}$$

and the constant κ is the coefficient of gradient energy. Furthermore, the temporal evolution of each cell is described as follows (Biner, 2017):

$$\frac{\partial \varphi_n}{\partial t} + v_n \cdot \nabla \varphi_n = -\frac{1}{2}\frac{\delta F}{\delta \varphi_n} \, , \tag{4}$$

where v_n is the time-dependent velocity of the cell, divided into two components: $v_n = v_{n,I} + v_{n,A}$. The component $v_{n,A}$ represents the active part of the velocity, i.e., the self-propulsion of the cell. In the model, it is considered to have a constant magnitude. On the other hand, the velocity $v_{n,I}$ is determined by the forces arising from the interaction with other cells and is defined in Biner (2017) as

$$v_{n,I} = \frac{60\kappa}{\xi \lambda^2} \int_V \left(\varphi_n \left(\nabla \varphi_n \right) \sum_{m \neq n} \varphi_m^2 \right) \, , \tag{5}$$

where ξ represents the friction between the cells and the surrounding liquid environment. Finally, by solving the functional derivative $\delta F / \delta \varphi_n$, we obtain the equation describing the temporal evolution of the cells:

$$\begin{aligned} \frac{\partial \varphi_n}{\partial t} =& \gamma_n \nabla^2 \varphi_n - \frac{30}{\lambda^2} \left[\gamma_n \varphi_n \left(1 - \varphi_n\right) \left(1 - 2\varphi_n\right) + 2\kappa \sum_{m \neq n} \varphi_n \varphi_m^2 \right] \\ & - \frac{2\mu}{\pi R^2} \varphi_n \left[\int_V \left(\varphi_n^2 \right) dV - \pi R^2 \right] - v_n \cdot \nabla \varphi_n \, . \end{aligned} \tag{6}$$

The Laplace operator and the directional derivatives described in equations 5 and 6 are approximated utilizing a finite difference algorithm, employing a five-point stencil within a two-dimensional spatial domain. The temporal integration is executed through a straightforward explicit Euler time-stepping scheme.

For the simulation, three distinct grids were selected. Grid 1 is $N_x N_y = 100 \times 100$, comprising 40 cells with a radius of 8. Grid 2 was configured as $N_x N_y = 150 \times 150$, featuring 50 cells with a radius of 11, while grid 3 consists of $N_x N_y = 200 \times 200$ dimensions, each containing 60 cells with a radius of 13. All of them include 5 cancerous cells. The parameters are defined according to Biner (2017) as $\lambda = 7$, $\kappa = 60$, $\mu = 40$, and $\xi = 1500$. The only difference between normal and cancerous cells is the parameter γ_n. For normal cells, $\gamma_n = 5$, whereas for cancerous cells, $\gamma_n = 2.5$, rendering them softer. The temporal step is $\Delta t = 0.005$, consistent across all grids.

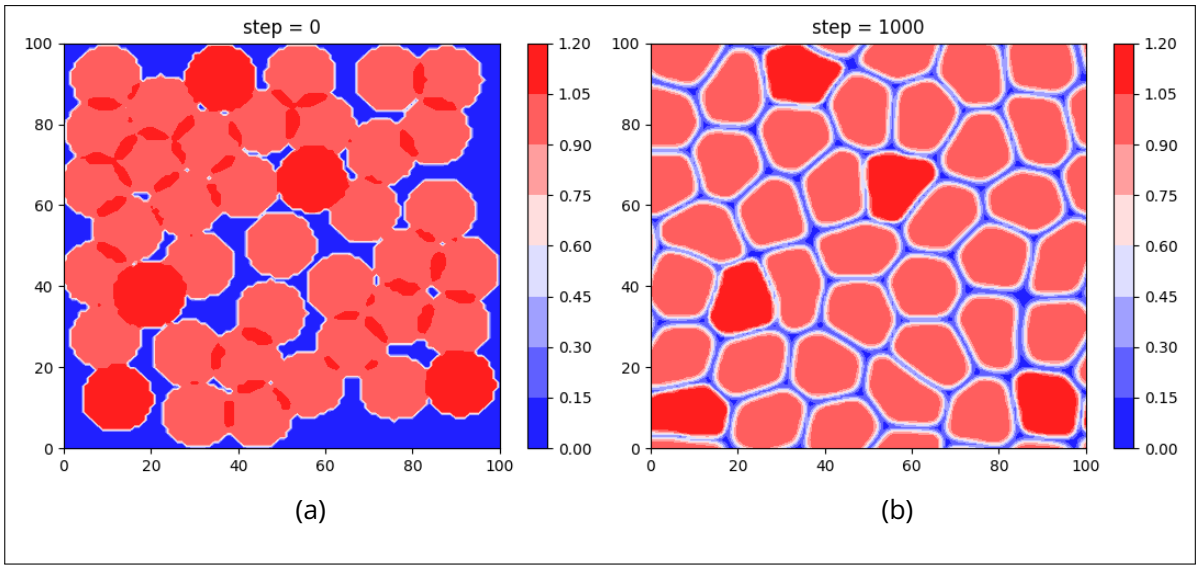
In this study, the focus will be exclusively on the simulation carried out using grid 1, due to the similarity of results among the three grids. The effectiveness of the simulation remains unchanged in the face of variations in the three mesh sizes, allowing for a comprehensive observation of the system's behavior. However, significant differences in computational time arose among the grids. Specifically, the time required to execute 15000 time steps in grid 1, grid 2, and grid 3 was, respectively, four days, two weeks, and one month and four days.

Having defined the equations and conditions, algorithms were developed in the Python programming language for simulating the problem and graphically visualizing the multicellular system, as depicted in the upcoming section.

3 RESULTS AND DISCUSSION

The results obtained from the simulation are illustrated in the figures 1 to 4, where we can observe in greater detail the effects of the adopted configurations. Among the present cells, five of them stand out due to their dark red shade; these are cells identified as the cancerous or alternatively, soft cells. The elasticity parameter γ_n sets their respective elasticities apart, with cancerous cells being inherently softer compared to normal cells.

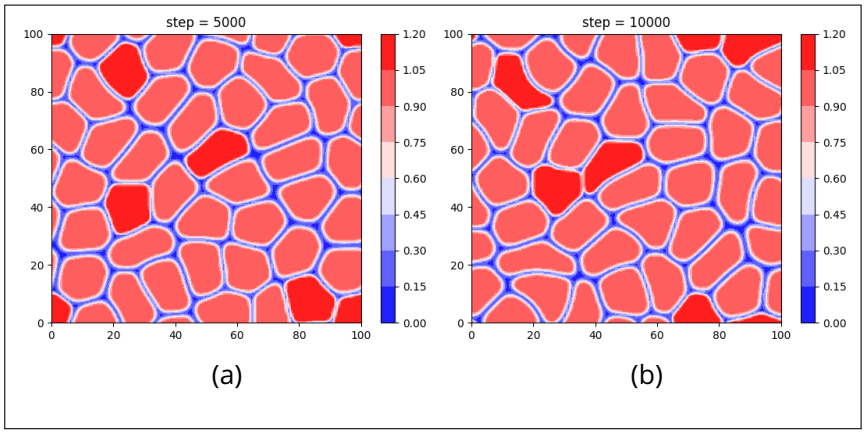
Figure 1 – Dynamic evolution of cells over time



Caption: The (a) figure shows the simulation at time $t = 0$ and (b) shows the simulation at time $t = 1000$

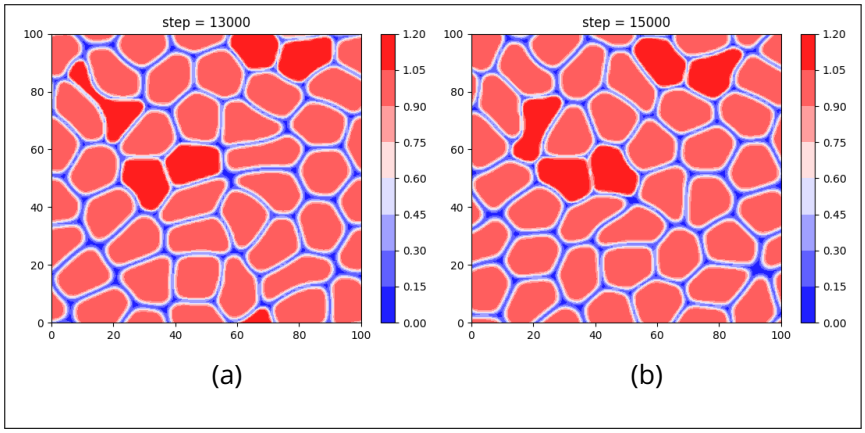
The distinction in elastic behavior between these two cell types is particularly evident in Fig. 3, corresponding to a stage of the simulation at time $t = 13000\,\Delta t$. At this specific point, the notable deformation suffered by the cancerous cell located in the upper-left corner draws attention. This cell is visibly stretched and twisted between two common cells, indicating the significant impact of the elasticity difference. Furthermore, this can also be observed in Fig. 4c, in the cancerous cell near the lower-left corner. This observation suggests the critical influence that mechanical properties exert on the overall system behavior, emphasizing the importance of considering such parameters in future studies and approaches.

Figure 2 – Dynamic evolution of cells over time



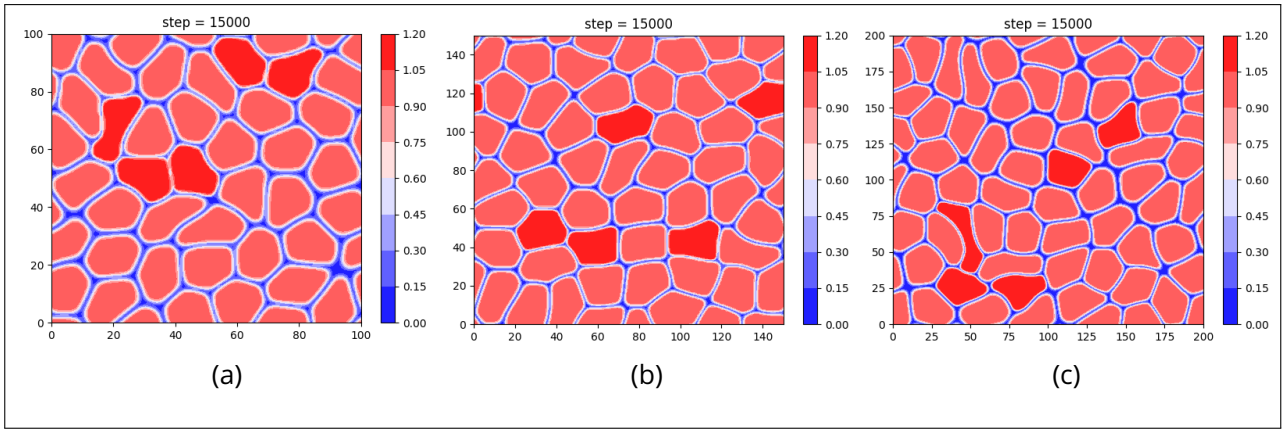
Caption: The (a) figure shows the simulation at time $t = 5000$ and (b) shows the simulation at time $t = 10000$

Figure 3 – Dynamic evolution of cells over time



Caption: The (a) figure shows the simulation at time $t = 13000$ and (b) shows the simulation at time $t = 15000$

Figure 4 – Comparison among the different simulated grids at time $t = 15000\,\Delta t$



Caption: The (a) figure represents grid 1, (b) represents grid 2 and (c) represents grid 3

4 CONCLUSIONS

In conclusion, this research delved into the temporal evolution of non-conserved field variables using the Allen-Cahn equation, with a focus on cell migration modeling. The study employed a mathematical representation to simulate cell movement, emphasizing its relevance in understanding cancer development and metastasis. The model considered both mechanical and biological aspects, offering insights into the complex dynamics of cell migration. Notably, the simulation results highlighted the significant impact of mechanical properties, such as cell elasticity, on cell behavior within a multicellular system.

This work serves as an initial step in cell migration research, and future studies can build upon these principles and equations. Further investigations may involve refining the model by incorporating additional parameters and refining its accuracy. The continual advancement of mathematical modeling in cell migration holds the potential to enhance our comprehension of biological processes, offering insights that may shape strategies in cancer research and drive progress within the field.

ACKNOWLEDGEMENTS

The authors would like to thank GDISPEN, the Pollutant Dispersion & Nuclear Engineering Group at UFPel, for their contributions, as well as the support from the National Council for Scientific and Technological Development (CNPq) for research funding.

References

Biner, B. (2017). *Programming Phase-Field Modeling*. Springer International Publishing.

Carlsson, A. E. and Sept, D. (2008). Mathematical modeling of cell migration. In *Biophysical Tools for Biologists, Volume One: In Vitro Techniques*, volume 84 of *Methods in Cell Biology*, pages 911–937. Academic Press.

Farayola, M. F., Shafie, S., Mohd Siam, F., and Khan, I. (2020). Numerical simulation of normal and cancer cells' populations with fractional derivative under radiotherapy. *Computer Methods and Programs in Biomedicine*, 187:105202.

Flaherty, B., McGarry, J. P., and McHugh, P. E. (2007). Mathematical models of cell motility. *Cell Biochemistry and Biophysics*, 49(1):14–28.

Kolev, M., Nawrocki, S., and Zubik-Kowal, B. (2013). Numerical simulations for tumor and cellular immune system interactions in lung cancer treatment. *Communications in Nonlinear Science and Numerical Simulation*, 18(6):1473–1480.

Mousavi, S. J., Doweidar, M. H., and Doblaré, M. (2014). Computational modelling and analysis of mechanical conditions on cell locomotion and cell–cell interaction. *Computer Methods in Biomechanics and Biomedical Engineering*, 17(6):678–693. PMID: 22871181.

Nieto, J. and Urrutia, L. (2016). A multiscale model of cell mobility: From a kinetic to a hydrodynamic description. *Journal of Mathematical Analysis and Applications*, 433(2):1055–1071.

Taylor, W., Katsimitsoulia, Z., and Poliakov, A. (2011). Simulation of cell movement and interaction. *Journal of Bioinformatics and Computational Biology*, 09(01):91–110.

Author contributions

1 – João Gabriel Piraine Bandeira (Corresponding Author)
Student of the Control and Automation Engineering course at the Federal University of Pelotas.
https://orcid.org/0000-0001-9839-8923 • joaogabrielpbandeira@gmail.com
Contribution: Conceptualization, Literature Review, Methodology, Data Analysis, Writing – original draft, Writing – review & editing

2 – Gustavo Braz Kurz
Graduated in Mathematics, master's degree holder and currently a PhD student in the PPGMap at UFRGS.
https://orcid.org/0000-0002-8774-2394 • gustavobk@gmail.com
Contribution: Writing – review & editing

3 – Daniela Buske
Graduated in Mathematics, master's and PhD in Mechanical Engineering, and a post-doctorate in Nuclear Engineering. Professor at the Department of Mathematics and Statistics at UFPel and participates in the PPGMMat and PPGCAmb, the research and projects developed are in the area of Geosciences and Applied Mathematics.
https://orcid.org/0000-0002-4573-9787 • danielabuske@gmail.com
Contribution: Supervision, Writing – review & editing

4 – Régis Sperotto de Quadros
Graduated in Mathematics, master's and PhD in Applied Mathematics, and post-doctorate in Nuclear Energy. He is a professor in the Department of Mathematics and Statistics and participates in the PPGMMat. The work developed is in Mathematics with an emphasis on Numerical Analysis and Optimization.
https://orcid.org/0000-0002-9720-8013 • quadros99@gmail.com
Contribution: Conceptualization, Supervision, Data Analysis, Writing – review & editing

How to cite this article

Bandeira, J. G. P., Buske, D., Quadros, R. S., & Kurz, G. B.(2024), Allen-Cahn Equation for Modeling Temporal Evolution of Non-Conserved Field Variables in Cancer Cell Migration. Ciência e Natura, Santa Maria, v. 46, esp. 1, e87268, 2024. https://doi.org/10.5902/2179460X87268