



Efficient Modelisation for Complex Geometries of Tumor Growth via Thermo-Elastic Diffusion Partial Differential Equations and Artificial Neural Networks

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Abstract: *The availability of high quality image data urges the development of new conceptual techniques to realise cancer accurate prognostic and treatment. In this study we propose a boundary value problem to model tumor elasticity impacting various types of mechanical stresses on cancer cell properties, assuming isotropic and inhomogeneous condition. We show the solution of this multiscale model expressed by PDE is numerically approximated by means of an Artificial Neural Network Architecture based on generalised Fourier decomposition. The connective key step is the use of the Laplace Neural Operator, which contributes to an efficient algorithm convergence rate. While further research of this model may address critical points on machine learning optimality checks, this framework is a rational development for oncologic medical prognosis and therapy.*

Keywords: *boundary value problems; artificial neural network; Laplace neural operator; partial differential equations; radiotherapy.*

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1. Introduction

Mathematical oncology (Rockne & Jacob, 2019) is an interdisciplinary field that uses mathematical, computational, and biomedicine approaches to solve complex problems in cancer biology and treatment. As the future of medical care belongs to personalised medicine, these non-invasive multiparameter techniques are useful if developed with rigour and scientific depth. Our study develops these ideas, keeping track of new image technological progress.

For example, Hormuth et al. (2022) enumerate some categories of advanced multiparametric imaging: MRI, contrast-enhanced, and positron emission tomography. These techniques may estimate features of an individual patient's cancer, including cell density, blood volume fraction, blood flow, and hypoxia. These imaging data are expected to calibrate patient-specific mechanistic models of tumor growth and response to therapy. The future directions of medicine will incorporate multiparametric imaging data and mechanistic predictive modeling into clinical decision-making.

This paper investigates the rational path of mechanical predictive modeling.

The behaviour of cancer cell elasticity is modulated by biological, chemical, and physical changes, which in turn have the potential to alter cellular elasticity. This observation may constitute an encouraging prediction for the future discovery of cancer therapies. Mechanical features of cancer cells emerge as a distinct trait during the development and progression of solid tumors. This work creates a new mathematical framework to describe the dynamics of the cancer tumor geometry. The model is based on a 2D thermo elastic diffusion, Partial Differential Equation, whose solution is constrained by temperature and chemical potential equilibrium behaviour. If *a priori* this is a good tumor prognostic discriminant, in practice, addressing the numerical approximation of a boundary value problem is critical. There are various numerical ways to address this problem but their accuracy is not granted. For this reason, we propose a synergetic method using approximation theorems as a foundation to build multi-layer iterative parameters search.

Artificial Neural Network (ANN) (Berg, & Nyström, 2018) approaches play a major role in cancer research, through modeling and simulations of cancer cells and tissue mechanics and their applications. While ANN is not suitable for solving PDEs in low dimensions and simple geometries as long as classical mesh-based methods are performing well, for complex geometries and high-dimensional problems such as biomechanical cancer tumor study, they provide a solution. In this area most numerical PDE techniques become infeasible. The first step to feature an adapted ANN architecture is the pre-training of the network using the available boundary data and the second is to increase the number of hidden layers. In our case, we find a mapping between fundamental solutions at boundary points and interior points and we use the spectral decomposition's linear independence as layers. We chose a Fourier Network while the preamble is designed via a Laplace Neural Operator. The method may work efficiently giving small errors in a variety of domain shapes and the case of different boundary conditions and could be categorised in the class of neural networks methods which leads to good accuracy (Uteuliyeva et al., 2020; Wessels et al., 2022).

2. Problem Statement

Overall, the behaviour of cancer cell elasticity is modulated by biological, chemical, and physical changes, which in turn have the potential to alter cellular elasticity, and this may be an encouraging prediction for the future discovery of cancer therapies.

Many methods in the theory of mathematical oncology require solving boundary value problems (BVPs). Much attention is paid to the construction of neural networks of solutions to admit efficient evaluation (Chumburidze & Lekveishvili, 2023) of tumor behaviour. In this article, we formulate and analyse a dynamical system of PDEs of thermo-diffusion models for the biomechanical structure of solid tumors.

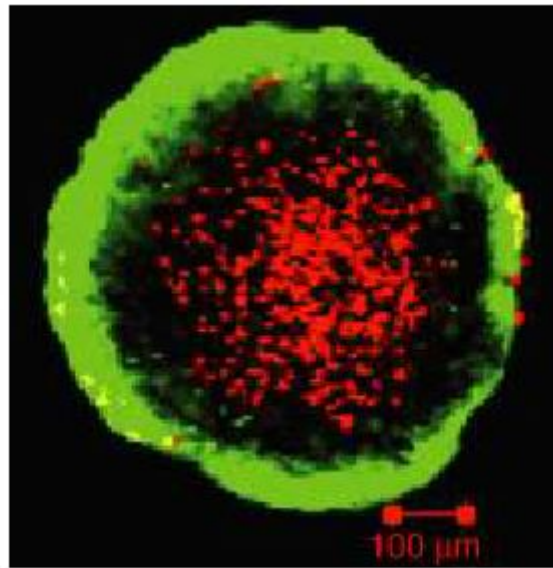


Figure 1. Solid Tumor with Boundary Fluorescent Activator as seen before a Radiotherapy Procedure

The boundary element methods, the method of fundamental solutions, can be used for both homogeneous and inhomogeneous elliptic PDEs. This approach became popular because of its simplicity and rapid convergence. This was verified only in a simple case, for a disk domain, and extended to other similar domains. At the same time, for a general domain $\mathbf{D}$, a convergence rate in Sobolev norms has still not been derived. In particular, we use neural networks with different structures for linear elliptic problems derived from the numerical solution of well-posed boundary value problems for Laplace's equation.

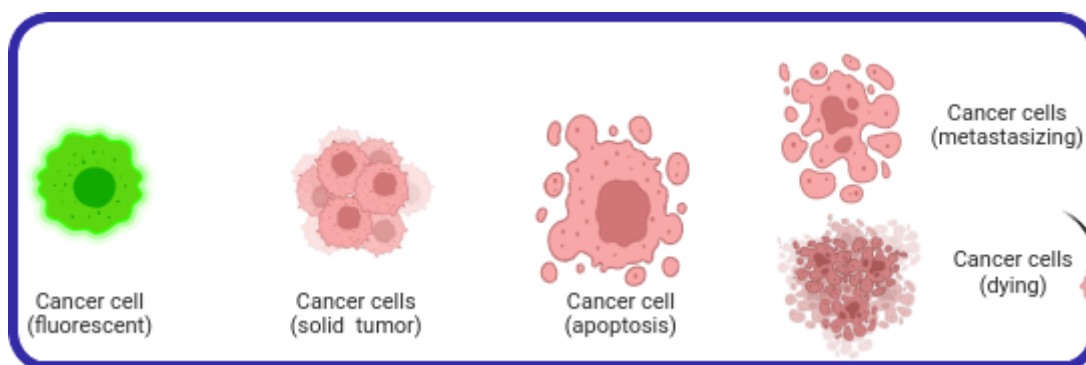


Figure 2. Dynamics of tumor geometry: the existence of a bifurcation point behaviour giving the treatment prognostic is a strong a priori argument of PDE modelling

Elastic deformation is one of the more studied biomechanical features of tumor cells, which plays an important role in tumorigenesis and development. Altered cell elasticity often brings many indications. In this paper the physical factors that may affect cell elasticity, such as temperature, and diffusion, are summarised in boundary-value problems (e.g., boundary integral methods), to simulate solid and vascular tumor growth. In particular, the tumor dynamics taught within the treatment of radiotherapies have been observed. Figure 1 depicts the image of an oncologic tumor where the border is activated by a fluorescent-inducing drug in order to delimit the tumor geometry. Figure 2 shows the dynamic progression of the tumor's geometrical shape. Note that the apoptosis mechanism is not enough to predict a remission prognostic. The hypothesis of a bifurcation point can be consensual with a Partial Differential Equation model. With these premises, we propose a

new model for the displacement components on the surfaces of cancer cells with temperature and chemical potential of tumor tissues and we build its numerical solution.

The dynamical system of BVPs for 2-D thermo elastic diffusion materials of solid tumors (Chumburidze, & Lekveishvili, 2017) for isotropic inhomogeneous elastic materials of cancer cells has the form:

$$\begin{aligned} (\lambda + 2\mu)u(\partial x, \partial t) - \gamma_1 \nabla T - \gamma_2 \nabla P - \rho \frac{\partial^2}{\partial t^2} \Delta u &= 0 \\ \varkappa_1 T(x, t) - a_{12} \frac{\partial}{\partial t} T - a_{12} \frac{\partial}{\partial t} P - \gamma_1 \frac{\partial}{\partial t} \Delta u &= 0 \\ \varkappa_2 P(x, t) - a_{12} \frac{\partial}{\partial t} P - a_{12} \frac{\partial}{\partial t} T - \gamma_2 \frac{\partial}{\partial t} \Delta u &= 0 \end{aligned} \quad (1)$$

where $x = (x_i)_{i=1,2}$ are points of the 2D geometry tumor space and the displacement vector of the cancer cells, depending on time is given by the two-dimensional vector u . The variation in temperature is given by T . Another factor that impacts the equilibrium is the chemical potential, which variation is a function denoted by P . Also the model depends on some constants:

1. $\rho > 0$, tumor density
2. $\mu > 0, (\lambda + 2\mu) > 0$ elasticity tumor parameters
3. $a_1, a_2, a_{12} > 0$ bio-chemical parameters of tumor
4. $\gamma_1, \gamma_2 > 0$ temperature related
5. $\varkappa_1, \varkappa_2 \in \mathbb{R}^*$ equilibria adjustment parameters.

Our approach is to find an approximation $U(x, t)$ of the solution for the well-defined Boundary value problem represented by the system (1), where temperature and chemical potential are considered in the boundary constraints, via Navier-Stokes equations. The idea is to use a linear combination of fundamental solutions on boundary points.

This strategy implied two choices:

- A. The type of Linear Operator separating the input space of solutions.
- B. The type of fundamental system of solutions in boundary points.

In this paper, we show that the combination of the Laplace Neural Operator (Cao, Goswami, & Karniadakis, 2023), and the Fourier System of fundamental solutions gives a good approximation for the displacement of cancer tumoral cells.

Figure 3 depicts the structural role of the Laplace neural operator (LNO), which leverages the Laplace transform to decompose the input space.

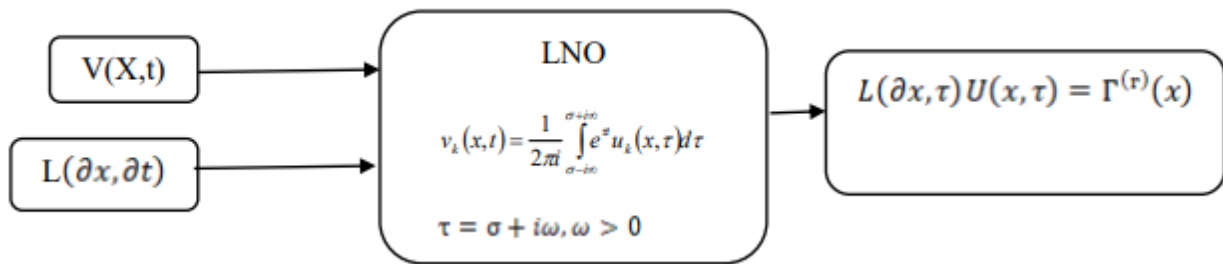


Figure 3. The general structure of LNO

Particularly, in our context, $L(\partial x, \tau)$ - the Laplace neural operator is defined in the matrix operator as follows:

$$L(\partial x, \tau) = \begin{bmatrix} |L^{(1)} - q_r \tau^2|_{2 \times 2} & |-\gamma_{1\tau} G^T(\partial x)|_{2 \times 1} & |-\gamma_{2\tau} G^T(\partial x)|_{2 \times 1} \\ |-\gamma_{1\tau} \tau G(\partial x)|_{1 \times 2} & \Delta - \frac{\tau a_{1\tau}}{\aleph_1} & -\frac{\tau a_{12}}{\aleph_1} \\ |-\gamma_{2\tau} \tau G(\partial x)|_{1 \times 2} & -\frac{\tau a_{12}}{\aleph_2} \Delta & -\frac{\tau a_{2\tau}}{\aleph_2} \end{bmatrix}$$

where

$\gamma_{\tau k} = \gamma_k(1 + \tau_1 \tau)$, $a_{\tau k} = a_k(1 + \tau_0 \tau)$, $k = 1, 2$, $\tau_1 > \tau_0 > 0$ are constants of temperature and difusión relaxation in tumor tissues. This model has the inconvenience of adding new relaxation parameters to be fitted from iterative machine learning procedures.

As a numerical study, our problem at hand becomes:

Problem $P^+(it)$. It is required to find in the D^+ regular vector - U , a solution with the following conditions:

$$\forall x \in D^+ \quad L(\partial x, \tau)U(x, \tau) = 0 \quad (3)$$

$$\forall z \in l \quad [U(z, \tau)]^+ = F^{(1)}(z) \quad (4)$$

3. Artificial Neural Networks Approximation

At this stage, we use a heuristic approach to solve our problem. Because many parameters need to be estimated, the robustness of the solution is a problem itself, which deserves another study based on large data sets.

Here we describe the theoretical framework for the machine learning approach. Having used the Laplace Neural Operator, the problem to solve becomes $P^+(it)$, a linear elliptic problem. The existence of a solution is a standard result. Following the theory of boundary integral equations, it can expressed by a form given as

$$U(x, \tau) = \int_l P(\partial_y, n) \Phi(y - x, \tau) \varphi(y) d_y l \quad (5)$$

where $P_{(q)}(\partial_y, n)$ is a neural operator of stress (Wessels et al., 2022) $\Phi(y-x)$ matrix of fundamental solutions described in (Chumburidze, Lekveishvili, & Bitsadze, 2018) by means of $H_0^{(1)}(\sigma_K |x|)$ Hankel Function of the First Kind (the zero order).

Let us consider a countable set the vectors $\{\Phi^{(j)}(y - x^k)\}_{k=1}^\infty$, indexed on a countable set of outer points. The machine learning algorithm is based on iterations taking into account larger sets of points from one step to another, such that the accuracy is increased.

A main observation is the fact that (5) could be approximated with an appropriate sum of fundamental solutions by modifying the learning data of neural networks approximating fundamental solutions at interior points by a linear combination of fundamental solutions on boundary points. Briefly, we are looking for an approximation expressed as,

$$U(X) \approx \sum_{j=1}^m F_j^{(1)} \Phi^{(j)}(y - x^k) \quad (6)$$

defining the ANN Architecture. The convergence expressed in the above formula is verified in particular by the generalised Fourier series. Therefore it is justifiable to the use Fourier neural networks approach to solve this problem. Take n boundary points $y^k \in \partial D$ and m arbitrary points $x^k \in D$, which will be called the outer points, see Figure 3. We will approximate the solution of $P^+(i\tau)$ as a linear combination of the functions $\{\Phi^{(j)}(y - x^k)\}_{k=1}^{\infty}$.

More exactly, the following theorem holds.

Theorem 1.

The countable set of the vectors $\{\Phi^{(j)}(y - x^k)\}_{k=1}^{\infty}$, $j = 1, 2, 3, 4$, $y \in S$, $R_{e\tau} > 0$ is linearly independent and complete in the space $L_2(S)$.

For a fixed parameter, $U(x) = U(x, \tau)$ is the direct solution of the problem $P^+(i\tau)$.

The proof is a standard application of a Hilbert space countable base existence.

Using Theorem 1 and the method of potential and integral equations from (Chumburidze, Lekveishvili & Bitsadze, 2018) we can explicitly show the accuracy of our ANN approximation.

Theorem 2.

If $R_{e\tau} > 0$ then for any $\varepsilon > 0$ can be found the natural number N_0 such, that when $N > N_0$, in any domain $\overline{D'} \subset D^+$, uniformly holds the inequality such that

$$|U(x) - U^N(x)| < \varepsilon, x \in \overline{D'} \quad (7)$$

where

$$U^N(x) = \sum_{k=1}^N \sum_{j=1}^k F_j^{(1)} a_k^j \Phi^{e_j} \left(y - x^{\left[\frac{j+3}{4} \right]} \right) dy \quad (8)$$

$$e_j = k - 4 \left[\frac{j-1}{4} \right] \quad (9)$$

Therefore

$$U_N(X) = \sum_{k=1}^N \sum_{j=1}^k F_k^{(1)} a_k^j \Phi^{(j)}(y - x^k) \quad (10)$$

where

$$F_k^{(1)} = \int_l F^{(1)}(y) \varphi^k(y) dl \quad (11)$$

is defined from boundary conditions.

a_k^j are coefficients of the orthonormalisation. According to the above

$$F^{(1)}(z) \in C^{0,\alpha}(S), \alpha > 0$$

Therefore we have:

$$F^{(1)}(y) \approx \sum_{k=1}^N F_k^{(1)} \varphi^k(y), y \in l \quad (4) \quad (12)$$

The ANN algorithm will iterate such that the parameters $F_j^{(1)}$, $j = 1 \dots k$, corresponding to the linear mapping in (3) delivers a minimal error in (4).

According to above assumptions, we have:

$$\varphi^k(y) = \sum_{j=1}^k a_k^j \Phi^{(j)}(y - x^k) \quad y \in l \quad (13)$$

The layers defining the Artificial Neural Network are presented in Figure 4.

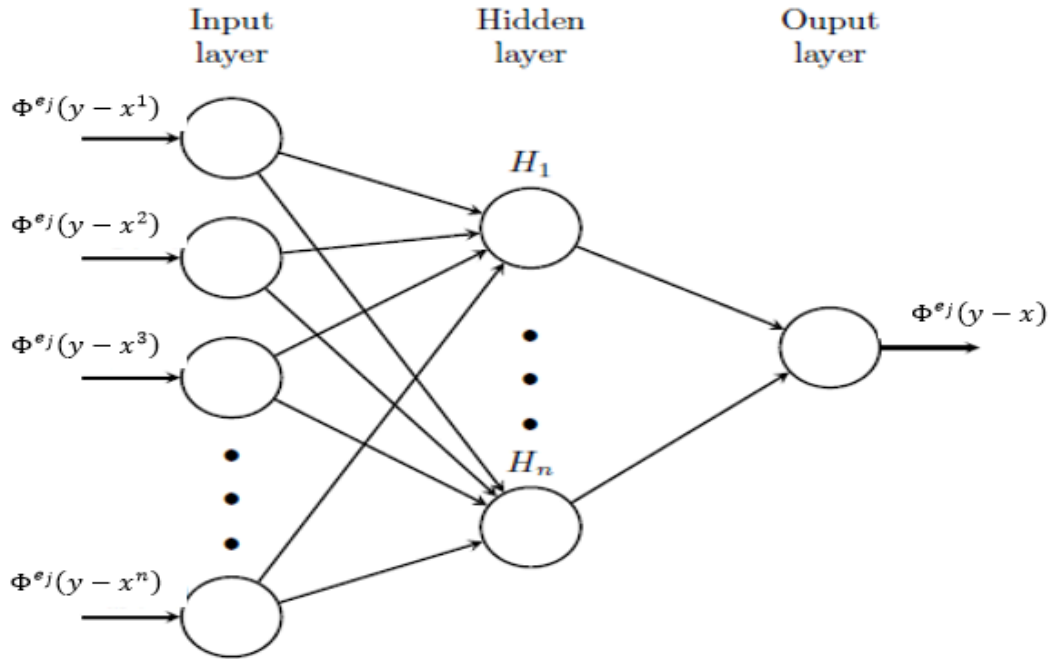


Figure 4. Artificial Neural Network Structure

To validate our approach, we considered a simplified system model solved by a standard numerical procedure and the implementation of the ANN algorithm. The results are mapped in Figures 5 and 6. The comparison shows almost identical findings, preserving the utility of developing further research based on our study.

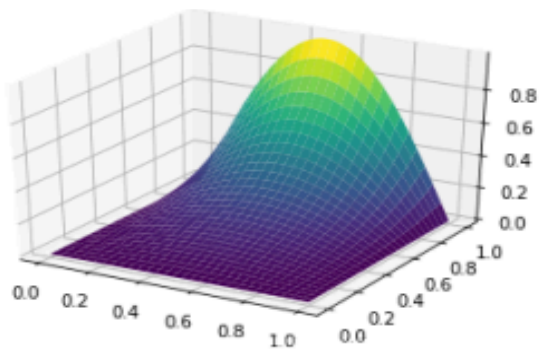


Figure 5. Discretised Analytical solution.

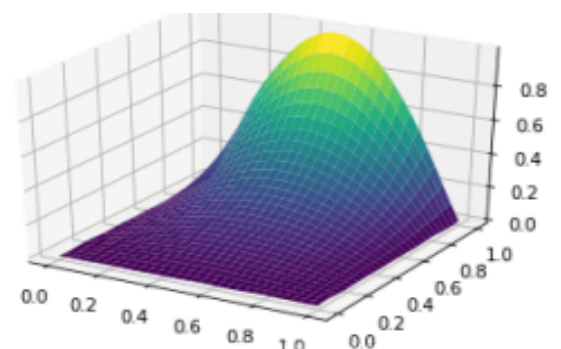


Figure 6. Numerical Solution from ANN approach.

The algorithmic problem has to be addressed separately in further studies, such that typical Machine Learning procedural problems could be addressed. Among these, we enumerate here the critical ones:

- compute the optimal number of the boundary and outer points
- there is an optimal distance of the outer points from the boundary

- which distribution of the boundary and outer points performs better
- how rapidly the algorithm converges assuming we determined all optimal parameters.

4. Conclusion

This work has three significant outputs:

- a. We develop a multiparameter mechano-biochemistry model using Partial Differential Equations to describe the evolution of an oncogene tumor geometry in time and nano-space. This is done by the exploration of the elastic-diffusive properties of the cancer cells.
- b. Because of the parametric complexity of the model in its generality, the numerical investigation of the solution is mandatory. We propose here a mathematical validated approach based on the Laplace Neural Operator and Artificial Neural Networks based on Fourier approximation. The implementation is very close to the analytical solution for test cases.
- c. The synergy between the mathematical model and its numerical implementation via the machine learning approach is an example of less studied methods for artificial intelligence applications in recent years despite their capital importance. Here, we propose solutions for real problems from the perspective of the ‘concept first’ as opposed to the ‘data sets first’.

Therefore the study opens a street of investigation to the possibility of predicting tumor behaviour within radiotherapy of cancers regarding temperature and diffusion conditions, as an application of basic Boundary value problems for isotropic inhomogeneous cancer cells. Nonetheless, a more exhaustive study may add important observations about the optimality of parameter choice.

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