

# Numerical implementation of a mathematical model describing prostate tumor growth: Radial basis function-generated finite difference (RBF-FD) scheme combined with a semi-implicit time discretization

Vahid Mohammadi<sup>a</sup>, Mehdi Dehghan<sup>a,\*</sup>, Stefano De Marchi<sup>b</sup>

<sup>a</sup>*Department of Applied Mathematics, Faculty of Mathematics and Computer Sciences, Amirkabir University of Technology, No. 424, Hafez Ave., 15914, Tehran, Iran*

<sup>b</sup>*Department of Mathematics "Tullio Levi-Civita", University of Padua, Italy*

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## Abstract

The aim of this work consists of finding a suitable numerical method for the solution of the mathematical model describing the prostate tumor growth, formulated as a system of time-dependent partial differential equations (PDEs), which plays a key role in the field of mathematical oncology. In the literature on the subject, there are a few numerical methods for solving the proposed mathematical model. The localized prostate cancer growth is known as a moving interface problem, which must be solved in a suitable stable way. The mathematical model considered in this paper, is a system of time-dependent nonlinear PDEs that describes the interaction between cancer cells, nutrients and prostate specific antigen (PSA). The first novelty here is to derive its non-dimensional form, which makes easier to implement different numerical techniques. The second novelty is the analysis of the numerical method describing the two-dimensional prostate tumor growth problem, based on radial basis function-generated finite difference (RBF-FD) scheme, in combination with a first-order time discretization. The numerical technique we use, does not need the use of any adaptivity techniques to capture the features in the interface. The discretization leads to solving a linear system of algebraic equations solved via the biconjugate gradient stabilized (BiCGSTAB) with zero-fill incomplete lower-upper (ILU) preconditioner. Comparing the results obtained in this investigation with those reported in the recent literature, the proposed approach confirms the ability of the developed numerical scheme. Besides, the effect of choosing constant parameters in the mathematical model is verified by many simulations on rectangular and circular domains.

*Keywords:* Time-dependent nonlinear partial differential equations, Radial basis function-generated finite difference scheme, Non-dimensionalization technique, Biconjugate gradient stabilized gradient, Mathematical oncology, Prostate tumor growth, A moving interface problem.

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\*Corresponding author

*Email addresses:* v.mohammadi@aut.ac.ir, v.mohammadi.aut@gmail.com (Vahid Mohammadi), mdehghan@aut.ac.ir, mdehghan.aut@gmail.com (Mehdi Dehghan), demarchi@math.unipd.it (Stefano De Marchi)

## 1. Introduction

Cancer is the result of abnormal proliferation of any of the different kinds of cells in the body. Accordingly, there are a hundred distinct types of cancer, which are different in responding to treatments and in behaviors [9]. Aging men may face to genitourinary diseases called *Prostate Cancer* (PCa) or the *Benign Prostatic Hyperplasia* (BPH) [43]. PCa is known as an adenocarcinoma (approximately 95 percentage), which means a type of cancer (originated in an epithelial tissue) that starts in the glands that lines the inside of one of the organs. Facts and figures given in [43] show that the second most common cancer and the fifth leading cause of death from cancer in men worldwide is PCa. Generally, the development process of PCa is as follows. At the first stage, it grows locally within the prostate. After that, the tumor tends to invade the surrounding tissues. Finally, it migrates to distant tissues by leaving some malignant cells from the original tumor and getting into the bloodstream (metastasis) [2, 3, 20, 28, 42].

As mentioned in [41], there are two main reasons for studying the prostate cancer in tissue-scale:

1. the prostate is a small organ;
2. the tumor growth can be estimated by measuring a PCa biomarker in blood, called *serum Prostate-Specific Antigen (PSA)*, and it may enable in vivo validation [41].

To predict clinical outcomes and design the optimal therapies on a patient, constructing and developing mathematical models with the simulations of diseases and their treatments, can be useful [41]. The tumor growth is followed by a complex biological mechanisms, which occurs at different scales, i.e., the molecular, cellular, and tissue scales [71]. In recent years, there are different types of mathematical models, which are able to describe the process of the tumor growth in tissue scale at two main stages: avascular and vascular (see among the many ones: [1, 3, 14, 15, 20, 28, 40, 48]). In some studies the role of nutrients is also considered in the mathematical model of the process of the tumor growth (for instance in [26, 27, 32, 37, 68, 69]). In fact, healthy and tumoral cells have a competition to gain nutrients, proliferate and control cell density in the harsh tumoral environment. To formulate a mathematical model describing PCa, in [41] the authors have derived a new phenomenological model based on a system of time-dependent nonlinear PDEs. Besides, they have assumed that the growth of PCa depends only on a nutrient, which is mainly composed of glucose [41]. More recently, in [43], a new mathematical model in tissue-scale has been derived, which shows the mechanical interaction of PCa and BPH. As a completion, the model describing PCa under the effect of therapies (i.e., chemotherapy and antiangiogenic therapy) has been presented in [8].

Since the exact solution of the model describing PCa is not available, numerical methods play an important role in simulating the process. **There exist few numerical methods to find the approximate solution of the mathematical model of PCa.** For example, the method based on hierarchically refined and coarsened splines is applied for space discretization and generalized- $\alpha$  method for time discretization in [42]. An isogeometric discretization based on the Galerkin method has been employed to discretize the space variables of the PCa model under the effect of therapies, while the generalized- $\alpha$  method is used to discretize the time variable (cf. [8]).

**So far, meshless methods were not applied to find the numerical solution for the mathematical model of PCa [41]. These methods distinguish them from mesh-dependent methods, such as finite element**

method (FEM) and finite volume method (FVM), for the following properties. Meshless methods do not need to generate the underlying mesh (or triangulation) for approximation [21, 49, 67]. With this, they can be easily implemented for finding the numerical solution of high-dimensional PDEs with arbitrary domain geometry. Overall, these techniques are categorized into strong form, weak form and local weak form, which are derived by choosing a suitable space of test functionals. Besides, the trial space would be constructed using an approximation based on scattered data. Method based on Radial Basis Functions (RBFs) and Moving Least Squares (MLS) approximation are two well-known meshless techniques [21, 49, 67]. The methods based on RBF approximation are known as **powerful numerical approaches for solving problems** in high-dimensional spaces [21, 67]. Recently, new techniques based on RBFs, namely rational RBFs partition of unity (RBFs-PU), RBFs-PU based on variably scaled kernels (VSKs) and RBFs combined with variably scaled discontinuous kernels (VSDKs) have been developed in [17, 18, 19]. Also, some applications of VSKs method for solving the time-dependent PDEs can be found in [12, 51]. See also [38, 44, 45, 50, 65].

In 1990, Ed Kansa [36] applied the traditional RBF method for finding a new numerical solution of an elliptical PDE. His technique, based on collocation, gave rise to a linear (nonlinear) system with a full ill-conditioned matrix [21, 67]. In 2000, Tolstykh introduced the initial idea of the RBF-FD scheme [64], approach also known as the Local RBF interpolation scheme (LRBFs) [53, 54]. Thanks to Schaback's paper [54], nowadays the technique is called a *generalized finite difference method*. Besides, a general and simple definition of the RBF-FD method is given in [70]. Unlike the finite difference methods (FDM), in LRBF method, multivariate polynomials are replaced by RBF, providing an easy method that works on different geometries with unstructured node layouts [24]. **To improve its accuracy and rate of convergence, it is possible to use more nodes in each stencil (called *support domain* or *local sub-domain* or *local domain of influence*) without reconstructing the approximation of derivatives based on any new ghost nodes [24].** On the other hand, applying this method for discretizing the differential operator of a PDE, gives rise to a sparse matrix, and this matrix has smaller condition number than the traditional global RBF method [24, 25]. Recently, authors of [59] have introduced a generalization form of the RBF-FD that is called the *overlapped RBF-FD scheme*. As explained in [59], this approach involves an overlap parameter, say  $\delta$ , which can recover the standard RBF-FD scheme by choosing  $\delta = 1$ . **In [5], the RBF interpolation augmented with polynomials (RBF+poly) has been presented as a constrained optimization problem, and has derived the convergence analysis for the local RBF augmented with polynomials (LRBF+poly). Also, the LRBF+poly method with polyharmonic splines (PHS) kernel has been rewritten as the best least squares approximation and quadratic minimization problem, deriving the convergence order of the method (see also Section 4) [6].** Interested readers can refer to [5, 6, 22, 23, 57, 59, 60] and references therein.

Over the past two decades, the RBF-FD technique has been successfully applied to solve numerically **practical mathematical models defined in high-dimensional spaces**. For example, it is applied to solve shallow water equations on the sphere [22], reaction-diffusion equations [57], reaction-diffusion equations on surfaces [58], Navier-Stokes equations [23], high-dimensional nonlinear Schrödinger equations [13], some PDEs on surfaces [61] and the damped Kuramoto-Sivashinsky (KS) equation [16].

The novelties of our approach are:

- the derivation of the non-dimensional form of the mathematical model introduced in [41], which allows an easier implementation of different numerical methods.
- The RBF-FD scheme is employed for discretizing the mathematical model [41] due to the space variables.

In comparison with known numerical methods, such those in [41, 42], the new technique has the following advantages.

- The implementation of the RBF-FD technique is simpler than the methods in [41, 42].
- Using the RBF-FD technique, we do not need any specific background mesh or triangulation and any adaptivity algorithms.
- The results are obtained on circular domains, and can be extended to other geometries in two-dimensions without any further new implementation.

We have then applied a semi-implicit backward differential formula of first-order (SBDF1) to discretize the time variable. This gives a new fully discrete scheme that is a linear system at any time step, in which the coefficient matrix is large and sparse. **To solve it efficiently**, we adopt known techniques, such those described in [15, 38, 48, 50]. In particular, we use the BiCGSTAB method with zero-fill ILU preconditioner. As a note, it is possible to use other time discretizations, such as explicit (conditionally stable) method, implicit-explicit and implicit schemes, for example see [60].

The outline of this manuscript is as follows. In Section 2, we briefly review the mathematical model, which will be solved numerically by a meshless technique in space and with the SBDF1 in time. In Section 3, the non-dimensional form of the model is derived. The details of the applied meshless technique are provided in Section 4. The fully discrete scheme is given in Section 6. In Section 7, some simulation results, based on parameters given in [42] and also parameters based on clinical data provided in [41], are presented. Finally, in Section 8 we present some concluding remark.

## 2. The mathematical model

In this section, **the mathematical model of the prostate tumor growth [41, 42] is briefly described. The interested reader may refer to [41, 42] to find out how the mathematical model is formulated, based on some required biological facts.**

The PCa growth depends on nutrients, hormones and proteins. In this model, only cancerous and non-cancerous cells are considered. For describing the dynamics of glucose, a generic nutrient  $\sigma$  is considered. Furthermore, the model studied here describes the value of PSA (produced by the healthy and tumoral cells) observed by a blood testing (see [41, 42] for more details). Due to these explanations, a differential equation, which describes the dynamics of the tissue PSA is formulated: its variable is denoted by  $p$ . **More specifically, all unknown space- and time-dependent variables of the mathematical model here considered, are defined as follows:**

- $\varphi(\mathbf{x}, t)$ : the concentration of the cell microstructure,

- $\sigma(\mathbf{x}, t)$ : the concentration of the nutrient,
- $p(\mathbf{x}, t)$ : the concentration of PSA,

where  $\mathbf{x} \in \Omega \subset \mathbb{R}^d$  (here is  $d = 2$ ),  $t \in [0, T]$  and  $T$  is the final time.

The model we are considering has been already studied in [41, 42], consists of a set of three PDEs. The first equation, showing the dynamic of the concentration of the cell microstructure, is

$$\frac{\partial \varphi}{\partial t} = \lambda \Delta \varphi - \frac{1}{\tau} F'(\varphi) + \chi \sigma - A \varphi, \quad (2.1)$$

where  $\varphi =: \varphi(\mathbf{x}, t)$  is a phase field variable or an order parameter aimed to identify one phase from the other of tumor evolution. It also shows transitions from the value 0 (the healthy host tissue) to 1 (tumor region) ( $t \in (0, T]$ ). Besides,  $\varphi = 0.5$  indicates the interface implicitly. This equation is derived based on the phase field method (cf. [8, 29]). For instance,  $F(\varphi) := 16\varphi^2(1 - \varphi)^2$  is a double-well potential.

In (2.1), the third term  $\chi \sigma$ , shows the growth due to nutrient. Indeed, the model assumes that tumor cells grow linearly in the presence of the nutrient at a rate  $\chi$ . The fourth term,  $-A \varphi$  represents apoptosis (programmed cell death). Following again [41, 42, 43], the tumor volume can be computed as

$$V_\varphi(t) := \int_{\Omega} \varphi \, d\mathbf{x}, \quad t \geq 0. \quad (2.2)$$

The second equation, shows the dynamic of the nutrient

$$\frac{\partial \sigma}{\partial t} = \epsilon \Delta \sigma + s - \delta \varphi - \gamma \sigma, \quad (2.3)$$

where  $\sigma =: \sigma(\mathbf{x}, t)$ ,  $s$  indicates a constant nutrient supply,  $\delta$  is the rate of consumption the nutrient by the tumor cells, and  $\gamma$  is the rate of natural decay. As a note, in (2.3), due to the results given in [7], here the effect of convection on the nutrient transport is negligible.

The last equation models the dynamic of PSA

$$\frac{\partial p}{\partial t} = \eta \Delta p + \alpha_h(1 - \varphi) + \alpha_c \varphi - \gamma_p p, \quad (2.4)$$

in which  $p =: p(\mathbf{x}, t)$ ,  $\alpha_h$  and  $\alpha_c$  represent the rates of production of PSA using healthy and tumoral tissues per unit volume, respectively. The parameter  $\gamma_p$  is the rate of natural decay PSA that is followed by the first order kinetics. To obtain the value of serum PSA, we use the formula

$$P_s(t) = \int_{\Omega} p \, d\mathbf{x}, \quad t \geq 0. \quad (2.5)$$

Initial and boundary conditions must be considered for three unknowns, i.e.,  $\varphi$ ,  $\sigma$  and  $p$ . In this paper, we use zero-valued Dirichlet boundary conditions for all variables.

### 3. The non-dimensional form

In [42], equations (2.1)-(2.4) are solved numerically via a method consisting of a hierarchically refined and coarsened splines, without considering any non-dimensional approach. Here instead, we present the non-dimensional form of equations (2.1)-(2.4). To do so, we define the new dimensionless variables

$$\tilde{\sigma} = \frac{\sigma}{\sigma^*}, \quad \tilde{p} = \frac{p}{p^*}, \quad \tilde{t} = \frac{t}{t^*}, \quad \tilde{\mathbf{x}} = \frac{\mathbf{x}}{\mathbf{x}^*}, \quad (3.1)$$

with  $\sigma^* = g/L$  and  $p^* = g/L^2$  are the units of variables  $\sigma$  and  $p$ , respectively, where  $g$  and  $L$  represent *gram* and *litre*, respectively. With these positions, the phase field variable  $\varphi$  belongs to  $[0, 1]$  (cf. [8, §2.2.1]), the unit of time  $t^*$  corresponds to one year, and the characteristic length scale  $\mathbf{x}^* := 0.1cm$  (cf. [28, 20]). Following [28], the value  $\mathbf{x}^*$  corresponds to the maximum invasion distance at the early stage of tumor. Its value, as firstly studied in [3], should be reasonably taken in the range  $[0.1, 1]$  centimeters.

Also, all constant parameters introduced in (2.1)-(2.4) should be written with their units such that the left-hand side and right-hand side of each equation have the same unit. Then, these constant parameters are divided by their units, which give dimensionless parameters (cf. [3, 20, 28]).

Hence, replacing (3.1) into (2.1)-(2.4) we get the non-dimensional form of the model,

$$\begin{aligned} \frac{\partial \varphi}{\partial \tilde{t}} &= \tilde{\lambda} \Delta \varphi - \frac{1}{\tilde{\tau}} F'(\varphi) + \tilde{\chi} \tilde{\sigma} - \tilde{A} \varphi, \\ \frac{\partial \tilde{\sigma}}{\partial \tilde{t}} &= \tilde{\epsilon} \Delta \tilde{\sigma} + \tilde{s} - \tilde{\delta} \varphi - \tilde{\gamma} \tilde{\sigma}, \\ \frac{\partial \tilde{p}}{\partial \tilde{t}} &= \tilde{\eta} \Delta \tilde{p} + \tilde{\alpha}_h (1 - \varphi) + \tilde{\alpha}_c \varphi - \tilde{\gamma}_p \tilde{p}, \end{aligned} \quad (3.2)$$

in which the quantities indicated with the tilde are now dimensionless. We do not use this notation for  $\varphi$  because it is already dimensionless. Hence, (3.2) is a type of reaction-diffusion system or a quasi-linear parabolic system.

**Remark.** There are different reaction-diffusion systems in the literature such as Turing-type models, namely Gierer-Meinhardt [30], Gray-Scott [31], Lengyel-Epstein [39], Brusselator [34, 47], Selkov [55] and Schnakenberg [56]. But, the studied mathematical model here is different from those models due to the nonlinear term  $F'$ .

The boundary conditions for the unknowns  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  are taken as follows:

$$\varphi(\mathbf{x}, t) = 0, \quad \tilde{\sigma}(\mathbf{x}, t) = 0, \quad \tilde{p}(\mathbf{x}, t) = 0, \quad \mathbf{x} \in \Omega, \quad t \geq 0. \quad (3.3)$$

As an example, in Table 1 we report the list of parameters used in [42], with the corresponding units and their non-dimensional counterparts.

In the next section, we introduce the numerical method which will be applied to approximate the unknowns  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  in (3.2), together with the boundary conditions (3.3) for the space variables.

Parameter	Value	Unit	Dimensionless parameter	Value
$\lambda$	$1.6 \times 10^5$	$\mu\text{m}^2/\text{year}$	$\tilde{\lambda}$	0.16
$\tau$	0.01	years	$\tilde{\tau}$	0.01
$\chi$	600	$L/(\text{g}\cdot\text{year})$	$\tilde{\chi}$	600
$A$	600	1/year	$\tilde{A}$	600
$\epsilon$	$5 \times 10^6$	$\mu\text{m}^2/\text{year}$	$\tilde{\epsilon}$	5
$s$	2.7	$\text{g}/(\text{L}\cdot\text{day})$	$\tilde{s}$	$9.8550 \times 10^2$
$\delta$	2.75	$\text{g}/(\text{L}\cdot\text{day})$	$\tilde{\delta}$	$1.0038 \times 10^3$
$\gamma$	1000	1/year	$\tilde{\gamma}$	1000
$\eta$	$1.6 \times 10^5$	$\mu\text{m}^2/\text{year}$	$\tilde{\eta}$	0.16
$\alpha_h$	6.25	$(\text{ng}/\text{mL})/(\text{cm}^3\cdot\text{year})$	$\tilde{\alpha}_h$	0.00625
$\alpha_c$	$15\alpha_h$	$(\text{ng}/\text{mL})/(\text{cm}^3\cdot\text{year})$	$\tilde{\alpha}_c$	$15\tilde{\alpha}_h$
$\gamma_p$	100	1/year	$\tilde{\gamma}_p$	100

Table 1: Example of the used constant parameters in the proposed mathematical model [42] **with their non-dimensionalized counterparts.**

#### 4. The RBF-FD technique

This section is devoted to briefly present the RBF-FD scheme that we are then applying as our discretization method. This technique is known also as a *generalized FD scheme* [54]. Unlike to the standard FD scheme this method is based on Radial Basis Functions (RBF) approximation of the differential operators involved.

Just to recall, RBF approximation of functions is a linear combination of functions  $\{\phi(\|\cdot - \mathbf{x}_j\|_2), j = 1, \dots, N\}$ , where  $\mathbf{x}_j$  are (scattered) points, called centers, belonging to some domain  $\Omega \subset \mathbb{R}^d$ . The radial function  $\phi : [0, \infty) \rightarrow \mathbb{R}$  can be considered *positive definite* or *conditionally positive definite* (cf. e.g. [21, 67])

**Definition 4.1.** [21, 67] *A continuous radial function  $\phi$  is conditionally positive definite of order  $m$  on  $\mathbb{R}^d$  if*

$$\sum_{i=1}^N \sum_{j=1}^N c_i c_j \phi(\|\mathbf{x}_i - \mathbf{x}_j\|_2) > 0,$$

for any  $N$  pairwise distinct points  $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N \in \mathbb{R}^d$  and any non zero vector  $\mathbf{c} = [c_1, c_2, \dots, c_N]^T \in \mathbb{R}^N$  satisfying the following condition

$$\sum_{j=1}^N c_j p(\mathbf{x}_j) = 0, \quad \text{for all } p \in \mathbb{P}_{m-1}^d,$$

where  $\mathbb{P}_{m-1}^d$  is the space of  $d$ -variable polynomials of degree at most  $m - 1$ . Also,  $\phi$  is called *positive definite* if it is conditionally positive definite of order  $m = 0$ .

Examples of radial functions  $\phi$  are provided in Table 2. The parameter  $\varepsilon$  is called *shape parameter* that affects the accuracy and stability of the RBF approximation, i.e., the so called *trade-off principle* that can be described as follows (cf. i.e. [21, 67]).

For a fixed shape parameter  $\varepsilon$ , increasing the number of nodes the error decreases, improving the accuracy, but on the other hand the interpolation matrix becomes more ill-conditioned. The trade-off principle suggests to find a suitable  $\varepsilon$ , say  $\varepsilon^*$  that balances the error versus the ill-conditioning of the approximation matrix. Below, in the Section 7, we briefly show this issue with some numerical results.

RBF	$\phi(r)$	Parameters	Order $m$
Gaussian (GA)	$\exp(-\varepsilon^2 r^2)$	$\varepsilon > 0$	0
Inverse multiquadric(IMQ)	$(1 + \varepsilon^2 r^2)^{-\beta}$	$\beta > d/2, \varepsilon > 0$	0
Multiquadric (MQ)	$(1 + \varepsilon^2 r^2)^\beta$	$\beta > 0, \beta \notin \mathbb{N}, \varepsilon > 0$	$\lceil \beta \rceil$
Wendland's functions	$\phi_{d,k}(\varepsilon r)$	$k \in \mathbb{N}_0, d \in \mathbb{N}, \varepsilon > 0$	0
Polyharmonic spline (PHS)	$r^\beta$	$0 < \beta \notin 2\mathbb{N}$	$\lceil \beta/2 \rceil$

Table 2: Some examples of RBF with  $r := \|\mathbf{x}\|_2$ ,  $\mathbf{x} \in \mathbb{R}^d$  [21, 67].

According to the third row of Table 2, choosing  $0 < \beta < 1$  gives an RBF which is conditionally positive definite of order one [21, 67], but due to [67, Theorem 8.5] or [21, Theorem 9.7], there is no need to add the constant term to the interpolation problem, and thus the matrix  $A_{\phi,X} := [\phi(\|\mathbf{x}_i - \mathbf{x}_j\|_2)]$  is invertible. To find out more details about RBF approximation and its error analysis, we refer to [21, 67] and all references related to this subject. For the definition and construction of the Wendland's functions  $\phi_{d,k}(\varepsilon r)$  in the last row of Table 2, refer to [67, Chapter 9].

We now present the **details** of the RBF-FD technique. To do so, suppose that  $N$  scattered points (nodes)  $X = \{\mathbf{x}_1, \dots, \mathbf{x}_N\} \subset \Omega \subset \mathbb{R}^d$  are chosen. **The idea is finding an RBF approximation of  $\Delta u(\mathbf{x})$  at the point  $\mathbf{x}_1$ , with  $u : \Omega \rightarrow \mathbb{R}$  the unknown function, solution of a differential problem. We then suppose that  $n \ll N$  nodes, i.e.,  $P_1 = \{\mathbf{x}_j\}_{j=1}^n$  are in a neighborhood of our point, i.e.,  $\mathbf{x}_1 \in X$ . At the first, we define the family of indices**

$$I(\mathbf{x}_1) = \{j \in \{1, 2, \dots, N\} \mid \|\mathbf{x}_j - \mathbf{x}_1\|_2 \leq \delta\}, \quad (4.1)$$

where  $\delta$  is the radius of influence. Thus,  $|I(\mathbf{x}_1)| = n$  (see Figure 1 which shows a domain of influence of an interior point), and  $\Delta u(\mathbf{x}_1)$  can be approximated by (cf. e.g. [4, 16, 22, 23, 24, 25, 70])

$$\Delta u(\mathbf{x}_1) \approx \sum_{j=1}^n w_{1j}^L u_j. \quad (4.2)$$

To determine the coefficients  $w_{1j}^L$ , at a sample node  $\mathbf{x}_1$  in (4.2), we assume that the approximate



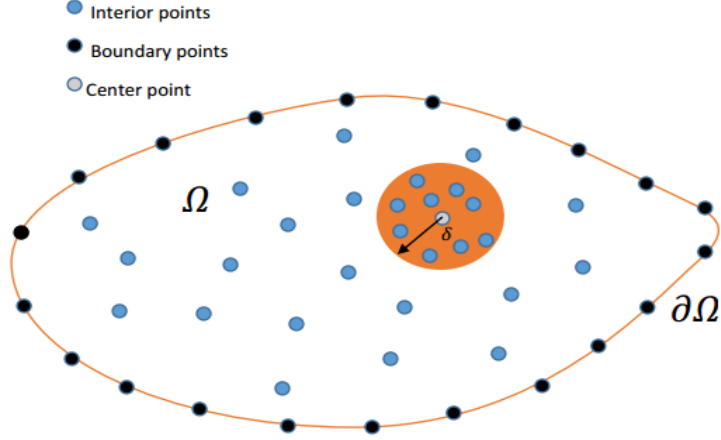


Figure 1: In orange a small circle representing the local **domain of influence** of a point inside  $\Omega$  with  $\partial\Omega$  its boundary (this picture is taken from [16]).

solution  $u$  can be written as

$$u(\mathbf{x}) \approx I_\phi u(\mathbf{x}) := \sum_{k \in I(\mathbf{x})} \alpha_k \phi(\|\mathbf{x} - \mathbf{x}_k\|_2), \quad \mathbf{x} \in \Omega, \quad (4.3)$$

where  $\phi$  is any of the RBF from Table 2. Because of (4.3),  $\Delta u(\mathbf{x}_1)$  can be approximated by

$$\Delta u(\mathbf{x}_1) \approx \Delta I_\phi u(\mathbf{x}_1) = \sum_{k=1}^n \alpha_k \Delta \phi(\|\mathbf{x}_1 - \mathbf{x}_k\|_2). \quad (4.4)$$

Thanks to (4.2) and (4.4), we can write

$$\sum_{k=1}^n \alpha_k \Delta \phi(\|\mathbf{x}_1 - \mathbf{x}_k\|_2) = \sum_{j=1}^n w_{1j}^L u_j = \sum_{j=1}^n w_{1j}^L \left( \sum_{k=1}^n \alpha_k \phi(\|\mathbf{x}_j - \mathbf{x}_k\|_2) \right). \quad (4.5)$$

Therefore, by using (4.5), the coefficients  $w_{1j}$  are obtained solving the linear system

$$A_{\phi, P_1} \mathbf{w}^L = \mathbf{b}, \quad (4.6)$$

where

$$A_{\phi, P_1} = [\phi(\|\mathbf{x}_i - \mathbf{x}_j\|_2)]_{1 \leq i, j \leq n}, \quad \mathbf{w}^L = [w_{1j}^L]_{1 \leq j \leq n}^T, \quad \mathbf{b} = [\Delta \phi(\|\mathbf{x}_1 - \mathbf{x}_j\|_2)]_{1 \leq j \leq n}^T.$$

Then we repeat the procedure for the other nodes,  $\mathbf{x}_2, \dots, \mathbf{x}_N$ .

Finally, a **sparse differentiation matrix**, say  $W_X^L$ , with size  $N \times N$  can be constructed, by re-arranging the computed weights for each node.

Concerning the convergence analysis of the RBF-FD method, R. Schaback in [54] presented a new proof for the nodal meshless methods. Later on, D. Mirzaei [46] employed the same idea to prove the error analysis of the Generalized Moving Least Squares (GMLS) approximation for solving a PDE problem on the sphere. O. Davydov in [10, 11] introduced error bounds for kernel-based numerical differentiation using the idea of *growth functions*, while V. Shankar [59] used Davydov's approach to prove local estimate of the augmented RBF-FD method. Recently, in [35] the authors have applied Schaback's theory with Davydov's extension to obtain the error bound of the weak-form for the RBF-FD method on each local stencil. In addition, V. Bayona [6] presented an error analysis based on local polynomial reproduction property as MLS approximation with *PHS* kernel applied in *LRBF+poly* method, with high degree polynomials. In the paper he showed that the order of convergence of the RBF-FD method is  $\mathcal{O}(h^{l+1})$  for the interpolation problem, where  $h$  is the average internodal distance within the stencil and  $l$  represents the degree of the polynomial in a  $d$ -dimensional space. Besides, he claimed that the size of stencil has insignificant effect on the accuracy of this method in computing the derivatives of a given function. For more details on this subject, the interested reader is referred to the above references.

## 5. The semi-discrete problem

For this step we use the Method of Lines (MOL). That is, first we derive the semi-discrete problem, by employing the RBF-FD technique for discretizing the spatial variables (3.2) with the boundary conditions (3.3), then, we apply a semi-implicit time-stepping scheme to solve the resulting system of ordinary differential equations (ODEs).

To this aim, let us consider a set of scattered nodes

$$X = \{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N\} = \{\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_{N_I}\} \cup \{\mathbf{x}_{N_I+1}, \mathbf{x}_{N_I+2}, \dots, \mathbf{x}_{N_I+N_B}\}$$

as trial points distributed in  $\Omega \subset \mathbb{R}^2$ , where  $N := N_I + N_B$ ,  $N_I$  and  $N_B$  stand the number of interior and boundary nodes, respectively. The approximate solutions  $\varphi(\mathbf{x}, t)$ ,  $\tilde{\sigma}(\mathbf{x}, t)$  and  $\tilde{p}(\mathbf{x}, t)$  at any  $\mathbf{x} \in \Omega$  and  $t \geq 0$ , can then be written by using trial functions  $w_j(\mathbf{x})$ ,  $j \in I(\mathbf{x})$  as follows

$$\begin{aligned} \varphi(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} w_j(\mathbf{x}) \varphi_j(t), \\ \tilde{\sigma}(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} w_j(\mathbf{x}) \tilde{\sigma}_j(t), \\ \tilde{p}(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} w_j(\mathbf{x}) \tilde{p}_j(t). \end{aligned} \tag{5.1}$$

By using (5.1), we have

$$\begin{aligned}
\Delta\varphi(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} \Delta w_j(\mathbf{x}) \varphi_j(t), \\
\Delta\tilde{\sigma}(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} \Delta w_j(\mathbf{x}) \tilde{\sigma}_j(t), \\
\Delta\tilde{p}(\mathbf{x}, t) &\approx \sum_{j \in I(\mathbf{x})} \Delta w_j(\mathbf{x}) \tilde{p}_j(t),
\end{aligned} \tag{5.2}$$

where  $\Delta w_j(\mathbf{x}) := w_j^L(\mathbf{x})$ .

Replacing (5.1) and (5.2) into (3.2) at the interior points (test points)  $\mathbf{x}_i$ ,  $i = 1, \dots, N_I$  gives

$$\begin{aligned}
\sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \frac{d\varphi_j(t)}{dt} &= \tilde{\lambda} \sum_{j \in I(\mathbf{x}_i)} w_j^L(\mathbf{x}_i) \varphi_j(t) - \frac{1}{\tilde{\tau}} F' \left( \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \varphi_j(t) \right) + \tilde{\chi} \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \tilde{\sigma}_j(t) \\
&\quad - \tilde{A} \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \varphi_j(t), \\
\sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \frac{d\tilde{\sigma}_j(t)}{dt} &= \tilde{\epsilon} \sum_{j \in I(\mathbf{x}_i)} w_j^L(\mathbf{x}_i) \tilde{\sigma}_j(t) + \tilde{s} - \tilde{\delta} \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \varphi_j(t) - \tilde{\gamma} \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \tilde{\sigma}_j(t), \\
\sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \frac{d\tilde{p}_j(t)}{dt} &= \tilde{\eta} \sum_{j \in I(\mathbf{x}_i)} w_j^L(\mathbf{x}_i) \tilde{p}_j(t) + \tilde{\alpha}_h \left( 1 - \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \varphi_j(t) \right) + \tilde{\alpha}_c \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \varphi_j(t) \\
&\quad - \tilde{\gamma}_p \sum_{j \in I(\mathbf{x}_i)} w_j(\mathbf{x}_i) \tilde{p}_j(t),
\end{aligned} \tag{5.3}$$

where the weights  $w_j(\mathbf{x}_i)$  and  $w_j^L(\mathbf{x}_i)$  are computed by the RBF-FD scheme. In vectorial form (5.3) can be compactly re-written

$$\begin{aligned}
\frac{d\boldsymbol{\varphi}_I}{dt} &= \tilde{\lambda} \mathbf{W}_{X_I}^L \boldsymbol{\varphi}_X - \frac{1}{\tilde{\tau}} F'(\boldsymbol{\varphi}_I) + \tilde{\chi} \tilde{\boldsymbol{\sigma}}_I - \tilde{A} \boldsymbol{\varphi}_I, \\
\frac{d\tilde{\boldsymbol{\sigma}}_I}{dt} &= \tilde{\epsilon} \mathbf{W}_{X_I}^L \tilde{\boldsymbol{\sigma}}_X + \tilde{s} - \tilde{\delta} \boldsymbol{\varphi}_I - \tilde{\gamma} \tilde{\boldsymbol{\sigma}}_I, \\
\frac{d\tilde{\boldsymbol{p}}_I}{dt} &= \tilde{\eta} \mathbf{W}_{X_I}^L \tilde{\boldsymbol{p}}_X + \tilde{\alpha}_h (1 - \boldsymbol{\varphi}_I) + \tilde{\alpha}_c \boldsymbol{\varphi}_I - \tilde{\gamma}_p \tilde{\boldsymbol{p}}_I,
\end{aligned} \tag{5.4}$$

in which

$$\boldsymbol{\varphi}_I = [\varphi_j(t)]_{1 \leq j \leq N_I}, \quad \tilde{\boldsymbol{\sigma}}_I = [\tilde{\sigma}_j(t)]_{1 \leq j \leq N_I}, \quad \tilde{\boldsymbol{p}}_I = [\tilde{p}_j(t)]_{1 \leq j \leq N_I},$$

and

$$\mathbf{W}_{X_I}^L = [w_j^L(\mathbf{x}_i)]_{1 \leq i \leq N_I, 1 \leq j \leq N},$$

which is a sparse differentiation matrix thanks to the RBF-FD scheme. The vectors  $\boldsymbol{\varphi}_X$ ,  $\tilde{\boldsymbol{\sigma}}_X$  and  $\tilde{\boldsymbol{p}}_X$  can be partitioned in  $\boldsymbol{\varphi}_X = [\boldsymbol{\varphi}_I \ \boldsymbol{\varphi}_B]^T$ ,  $\tilde{\boldsymbol{\sigma}}_X = [\tilde{\boldsymbol{\sigma}}_I \ \tilde{\boldsymbol{\sigma}}_B]^T$  and  $\tilde{\boldsymbol{p}}_X = [\tilde{\boldsymbol{p}}_I \ \tilde{\boldsymbol{p}}_B]^T$ , where again the indices  $I$  and  $B$  show the approximation value of each unknown variable at interior and boundary points, respectively.

Using the fact that the boundary conditions are of Dirichlet type, we can impose them directly in equations (5.4). In fact,  $\boldsymbol{\varphi}_B = 0$ ,  $\tilde{\boldsymbol{\sigma}}_B = 0$  and  $\tilde{\boldsymbol{p}}_B = 0$ . Considering this, we can rewrite (5.4) as follows

$$\begin{aligned}\frac{d\boldsymbol{\varphi}_I}{dt} &= \tilde{\lambda}W_{X_I}^{L,I}\boldsymbol{\varphi}_I - \frac{1}{\tilde{\tau}}F'(\boldsymbol{\varphi}_I) + \tilde{\chi}\tilde{\boldsymbol{\sigma}}_I - \tilde{A}\boldsymbol{\varphi}_I, \\ \frac{d\tilde{\boldsymbol{\sigma}}_I}{dt} &= \tilde{\epsilon}W_{X_I}^{L,I}\tilde{\boldsymbol{\sigma}}_I + \tilde{\mathbf{s}} - \tilde{\delta}\boldsymbol{\varphi}_I - \tilde{\gamma}\tilde{\boldsymbol{\sigma}}_I, \\ \frac{d\tilde{\boldsymbol{p}}_I}{dt} &= \tilde{\eta}W_{X_I}^{L,I}\tilde{\boldsymbol{p}}_I + \tilde{\alpha}_h(1 - \boldsymbol{\varphi}_I) + \tilde{\alpha}_c\boldsymbol{\varphi}_I - \tilde{\gamma}_p\tilde{\boldsymbol{p}}_I,\end{aligned}\tag{5.5}$$

with  $W_{X_I}^{L,I} = [w_j^L(\mathbf{x}_i)]_{1 \leq i, j \leq N_I}$ .

Finally, (5.5) with the proper initial conditions can be written in matrix form as below

$$\begin{aligned}\frac{d\mathbf{u}_I}{dt} &= B\mathbf{u}_I + F(X_I, t, \mathbf{u}_I), \\ \mathbf{u}_I(0) &= G(X_I, 0),\end{aligned}\tag{5.6}$$

in which  $\mathbf{u}_I = [\boldsymbol{\varphi}_I, \tilde{\boldsymbol{\sigma}}_I, \tilde{\boldsymbol{p}}_I]_{3N_I \times 1}^T$ ,  $B$  is a sparse matrix with size  $3N_I \times 3N_I$  due to (5.6).  $F$  is the nonlinear term vector with size  $3N_I \times 1$  (cf. (5.5)), and  $G$  represents the value of the unknown variables at time  $t = 0$  and at interior points  $X_I$ . By solving (5.6) at every time step, we can also obtain the approximate value of each variable at the boundary nodes.

## 6. The fully discretized scheme

We discuss how to solve (5.6) with respect to  $t$ . We recall that different approaches can deal with the time discretization of MOL. Just to mention the most commonly used, there are explicit integrators, as the fourth-order Runge-Kutta (RK4) or implicit time integrators, such as the backward differential formulas (BDFs) or SBDFs (cf. e.g. [22, 23, 25, 47, 60]).

As it is well-known, a necessary condition for stability of the MOL is that all eigenvalues of the differentiation matrix  $B$  in (5.6), lie in the stability region. In [59], an implicit condition for showing all the eigenvalues of the differentiation matrix (here is called  $W_X^L$ ) obtained via the augmented (overlapped) RBF-FD method, which lie in the left half complex plane, has been derived. However, until now, there is no theoretical proof on how to derive an explicit condition for this, but we can numerically verify it, by computing all the eigenvalues, for instance by using the MATLAB function `eigs` (which allows a stable computation of all the eigenvalues at once). As an illustrative example, Figure 2 displays the eigenvalues of  $B$  for  $n = 13$  with  $\varepsilon = 15, 20$  and  $N_I = 3969, 16129$  and  $25281$  uniform points (see Section 7). The results show that all eigenvalues of  $B$  belong to the left half complex plane (i.e., they have negative real parts) even for a low number  $N$  of points. Besides, the imaginary part is in magnitude much smaller than the real part. We also should mention that the choice of  $n$  and  $\varepsilon$  can affect the results. The user should

therefore choose these parameters carefully so that the numerical solution be “*acceptable*”, that is not too far from what one expect. In the next section, we show how these two parameters can affect the results and can properly be chosen.

Due to this, in this work, we consider a *SBDF1 algorithm* for discretizing (5.6) in time, so that  $B\mathbf{u}_I$  and  $F(X_I, t, \mathbf{u}_I)$  are considered as the implicit and the explicit terms, respectively.

We now assume that the time interval  $[0, T]$  is divided uniformly into  $[t_{k-1}, t_k]$ ,  $k = 1, \dots, M$  (i.e.,  $M$  sub-intervals), where  $t_0 = 0$ ,  $t_k = k\Delta t$  for  $k = 1, \dots, M$  and  $\Delta t = T/M$ , is the time step.

Applying the SBDF1 method to the MOL (5.6) gives

$$(I - \Delta t B)\mathbf{U}_I^{n+1} = \mathbf{U}_I^n + \Delta t F(X_I, t^n, \mathbf{U}_I^n), \quad n = 0, 1, \dots, M - 1, \quad (6.1)$$

where  $I$  is the identity matrix of order  $3N_I$ ,  $\mathbf{U}_I^{n+1}$  is the vector of approximation values of the unknowns at  $t = t_{k+1} := (k + 1)\Delta t$  and at the  $X_I$  points. By computing the approximation value of each variable at  $X_I$ , by using (6.1), the approximation of  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  can be obtained at  $X_B$ , at any time step. Using these values, the approximated solution of  $\varphi$ ,  $\sigma$  and  $p$  will be computed at an arbitrary node  $\mathbf{x} \in \Omega$  thanks to (5.1).

**Remark 6.1.** *The fully discretized scheme (6.1) is a linear system of algebraic equations that has to be solved at each time step. For this issue, we have applied the BiCGSTAB method with zero-fill ILU as preconditioner [62]. We notice that many authors successfully applied this approach to solve the linear system of algebraic equations arising from the discretization of time-dependent PDEs via meshless techniques in space and explicit, implicit, semi-implicit approaches in time (cf. e.g. [15, 48, 38, 50]).*

## 7. Results

We present some simulation of the non-dimensional model (3.2) to show the prostate tumor growth in two-dimensional domains: in a rectangle and in a circle. For the results presented here, two sets of nodes are considered: *uniform* and *quasi-uniform*. Both sets, can easily be generated by MATLAB functions. The uniform ones by the function `meshgrid` available in the standard MATLAB distribution, while the quasi-uniform nodes by the package `distmesh` (see [52]), which is widely used in solving PDEs problem. The package is freely available at the website: <https://popersson.github.io/distmesh/>.

Using the definition (4.1), to find  $n$  nearest points (the size of local domain of influence) around each point of  $X$  we use another MATLAB function: `knnsearch`. With this, we can construct the differentiation matrix  $W_{X_I}^{L,I}$  by using, for instance, multiquadrics (MQ) radial basis function with  $\beta = 1/2$  (see the third row of Table 2)

$$\phi(r) = \sqrt{1 + \varepsilon^2 r^2}, \quad (7.1)$$

with  $r := \|\mathbf{x} - \mathbf{y}\|_2$ ,  $\mathbf{x}, \mathbf{y} \in \Omega$ . All figures presented in this section are drawn with the fixed shape parameter  $\varepsilon = 15$ . We recall that for finding a proper or optimal shape parameter  $\varepsilon^*$ , interested readers can refer, for instance, to [21, 53], but here, we will not discuss this issue.

The sparsity pattern of the matrix  $W_X^L$  is drawn in Figure 3 for a fixed value of  $N = 25921$  uniform points and  $n = 13, 17, 21$  and  $31$ . Besides, the approximate percentage of non-zero ( $nz$ ) elements of the

matrix  $W_X^L$  are reported in Table 3 for the chosen values of  $n$  and  $N$ .

$n$	$N = 6561$	$N = 25921$	$N = 103041$
13	20%	5%	1.3%
17	26%	6.6%	1.6%
21	32%	8.1%	2%
31	47%	12%	3%

Table 3: The approximate percentage of non-zero ( $nz$ ) elements of the matrix  $W_X^L$  for different values of  $n$  and  $N$ .

The time step is chosen as  $\Delta t = 1e - 4$  due to the time discretization proposed here. In order to apply the BiCGSTAB method for solving the linear system (6.1) at each time step, the tolerance and the maximum number of iterations are fixed as  $\mathbf{tol} = 1e - 6$  and  $\mathbf{maxit} = 100$ , respectively.

**Remark:** *the results presented here are obtained with iterations  $\leq 2$  for all chosen  $N$ . The numerical experiments have been done in MATLAB 2017a using standard double precision, on a PC Core i7 – 2670QM with 8 GB of RAM.*

### 7.1. Results on rectangular and circular domains

Here we provide some numerical simulations to show the prostate tumor growth in the two-dimensional space. Due to the non-dimensionalization technique given in Section 3, we have some freedom in the choice of the domains. We have then taken the rectangular domain  $\Omega = [0, 2]^2$  and the circular domain  $\Omega = \{(x, y) \in \Omega : (x - 1)^2 + (y - 1)^2 \leq 1\}$ . For these simulations, the constant parameters given in Table 1 are used in non-dimensional form. Following [42], the initial condition function  $\varphi$ , is taken to be

$$\varphi(x, y, 0) = \begin{cases} 1, & \frac{(x-1)^2}{(0.1)^2} + \frac{(y-1)^2}{(0.15)^2} \leq 1, \\ 0, & o.w. \end{cases} \quad (7.2)$$

while the initial conditions for  $\tilde{\sigma}$  and  $\tilde{p}$  are set to be zero.

We note that the exact solution of the problem is not known, so to measure the accuracy of the method we use the following strategy:

- as exact solution we consider the approximate solution at  $N = 410881$  uniform points,  $n = 60$ ,  $\varepsilon = 35$  and constant time step, i.e.,  $\Delta t = 1e - 4$ ;
- the maximum relative error,  $e_\infty$  is computed for different values of  $N$ , where

$$e_\infty := \frac{\|u_{ex} - u_{app}\|_\infty}{\|u_{ex}\|_\infty}, \quad (7.3)$$

in which  $u_{ex}$  and  $u_{app}$  denote the exact and approximation solutions, respectively, which are computed on  $26400 = 220 \times 120$  evenly spaced point grid of  $[0, 2]^2$  and  $\|\cdot\|_\infty$  represents the usual maximum norm.

In Table 4, we report the maximum relative errors for  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  together with the CPU time at  $t = 1e-2$  via different values of  $N$ , for  $n = 13$  and  $\varepsilon = 26$ .

$N$	$e_{\infty, \varphi}$	$e_{\infty, \tilde{\sigma}}$	$e_{\infty, \tilde{p}}$	CPU time(s)
6561	$1.91e + 0$	$5.59e - 1$	$9.12e - 1$	9.041
25921	$2.00e - 1$	$3.56e - 2$	$1.26e - 1$	18.860
103041	$1.86e - 2$	$4.72e - 3$	$1.19e - 2$	97.085

Table 4: The errors  $e_{\infty, *}$ ,  $'*'$  =  $\varphi, \tilde{\sigma}, \tilde{p}$ , the CPU time at  $t = 1e - 2$ ,  $n = 13$   $\varepsilon = 26$ , for different  $N$ .

To show the effect of the choice of the shape parameter on the accuracy and the rate of convergence of the RBF-FD scheme, we have fixed  $n = 13$  and used  $\varepsilon = 15, 20$  and  $25$ . The maximum relative errors are computed for  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  in Figure 4. From this figure, we can see that by increasing the value of shape parameter, the accuracy of the RBF-FD method is improving giving almost the same rate of convergence. Furthermore, the condition number of the matrix  $W_X^L$  is computed for different values of  $\varepsilon$  and values are displayed in Table 5. According to the results of Table 5, it is clear that on different  $N$  when the value of

$N$	$\varepsilon = 10$	$\varepsilon = 15$	$\varepsilon = 20$	$\varepsilon = 25$
6561	$3.03e + 7$	$3.41e + 5$	$2.06e + 5$	$1.10e + 5$
25921	$4.25e + 9$	$5.61e + 7$	$1.23e + 8$	$2.62e + 6$
103041	$1.72e + 11$	$2.57e + 10$	$2.92e + 10$	$8.96e + 8$

Table 5: The condition number of the matrix  $W_X^L$  with different values of  $\varepsilon$  and  $N$ , fixed  $n = 13$ .

shape parameter increases the condition number of  $W_X^L$  decreases, as expected by the trade-off principle.

In addition, we have fixed the shape parameter  $\varepsilon = 25$ , and we have computed the maximum relative errors for  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  via  $n = 17, 21$  and  $25$ . The results are reported in Figure 5. This figure also shows that when the number of points in each stencil has been increased the accuracy of the method is slowly improving. Of course, it certainly depends on the choice the shape parameter.

In Figure 6, the initial condition and the numerical solution of the tumor phase field  $\varphi$  are provided at different time steps  $t = 0.2, 0.4$  and  $0.6$  by using  $N = 16641$  uniform nodes. The same results are given in Figure 7 with  $N = 66049$  uniform nodes. The results agree with those reported in [41, 42]. To see the steady-state solution of our dimensionless model with the parameters given in Table 1, we wrote a MATLAB program, supplied in GitHub (available at the link <https://github.com/VM-2020-MATH/MATLAB-codes-for-the-Prostate-Tumor-Growth.git>, the program `Main_PCa_RBF_FD.m`) that has been run until  $\|\Phi^{n+1} - \Phi^n\|_{\infty} < 10^{-6}$ ,  $\|\tilde{\sigma}^{n+1} - \tilde{\sigma}^n\|_{\infty} < 10^{-6}$  and  $\|\tilde{p}^{n+1} - \tilde{p}^n\|_{\infty} < 10^{-6}$ . The steady-state solutions of  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  are presented in Figure 8.

To show the capability of our numerical meshless method, we did the same simulations with  $N = 17799$  quasi-uniform nodes generated by `distmesh` with the boundary nodes distributed uniformly and fixed shape parameter  $\varepsilon = 10$ . The results are shown in Figure 9.

On the circular domain, we used the same initial conditions as for the rectangular case. Figure 10

shows the approximate solution of  $\varphi$  at different time steps using  $N = 11027$  uniform nodes (generated by `distmesh`) in which the boundary nodes are distributed uniformly. In Figure 11, the results are those obtained using  $N = 22999$  uniform nodes, with uniformly distributed boundary nodes.

In Figure 12, we report the simulation results of the prostate tumor growth on circular domain with  $N = 21077$  quasi-uniform nodes with the boundary nodes distributed uniformly. The numerical solution of tumor phase field  $\varphi$ , is plotted at different time steps  $t = 0.2, 0.4$  and  $0.6$ .

## 7.2. Results based on parameters seen in clinical practice and experiments

Here we present some simulations, which are obtained using the parameters observed experimentally in [41]. The diffusion coefficient of the phase field,  $\lambda$  and nutrient diffusivity  $\epsilon$ , were measured and their values are  $5 \times 10^{-11} \text{ cm}^2/\text{s}$  and  $2 \times 10^{-9} \text{ cm}^2/\text{s}$ , respectively. To show the effect of choosing different values of the nutrient supply  $s$ , the numerical results have been obtained taking the values  $2.60 \text{ g}/(\text{L.day})$ ,  $2.70 \text{ g}/(\text{L.day})$  and  $2.80 \text{ g}/(\text{L.day})$ , as indicated in [41]. Other parameters are fixed as in Table 1. The number of nodes, uniformly distributed in the rectangular domain, is  $N = 25921$ . The numerical solutions of the prostate tumor growth, the nutrient and PSA are drawn at different time levels with  $s = 2.60 \text{ g}/(\text{L.day})$  in Figure 13,  $s = 2.70 \text{ g}/(\text{L.day})$  in Figure 14 and  $s = 2.80 \text{ g}/(\text{L.day})$  in Figure 15. As can be observed the *fingered morphology grows with thinner and less branches* when  $s = 2.60 \text{ g}/(\text{L.day})$  (i.e., nutrient supply is reduced). By increasing the value of the nutrient supply to  $s = 2.80 \text{ g}/(\text{L.day})$ , wider branches have been produced in the fingered morphology of the prostate tumor growth. It also can be observed that when the value of  $s$  is low, the growth of tumor is slow, but by increasing this value up to  $2.80$  makes the tumor grows at a faster rate (see also supplementary movies).

In addition, the results obtained here and those reported in [41], show that the tumor initially grows spherically. If the tumor keeps developing on with this morphology, it consumes more nutrients and thus the nutrient concentration will be decreased, which makes hypoxia, starvation, and necrosis. Finally, the tumor reaches a volume such that it changes to the displayed fingered morphology. As pointed out in [41], the nutrient concentration within the tumor is not important at all, see Figure 15.

Figure 16 shows the values of tumor volume (formula (2.2) in  $\mu\text{m}^3$  and serum PSA, (formula (2.5)) in  $\text{ng}/\text{ml}$ , at different time levels. Furthermore, the steady-state solutions of  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  are given in Figure 17 for  $s = 2.80 \text{ g}/(\text{L.day})$  (see the details given in Subsection 7.1).

To show the simulation results that can support the experimental results in [33], we used  $s = (2.75 + c) \text{ g}/(\text{L.day})$  as nutrient supply, where  $c$  is a mild heterogeneity (due to vasculature) such that  $s$  changes between  $2.55 \text{ g}/(\text{L.day})$  (far from the blood vessels) and  $2.95 \text{ g}/(\text{L.day})$  (near the blood vessels). This choice is a more realistic distribution in the nutrient supply for a tissue domain, as pointed out in [41]. We then used the following initial conditions for the nutrient and PSA [8].

$$\tilde{\sigma}(x, y, 0) = c_{\tilde{\sigma}}^0 + c_{\tilde{\sigma}}^1 \phi(x, y, 0), \quad (7.4)$$

$$\tilde{p}(x, y, 0) = c_{\tilde{p}}^0 + c_{\tilde{p}}^1 \phi(x, y, 0), \quad (7.5)$$

where  $c_{\tilde{\sigma}}^0 = 1$ ,  $c_{\tilde{\sigma}}^1 = -0.8$ ,  $c_{\tilde{p}}^0 = 6.2500 \times 10^{-8}$ ,  $c_{\tilde{p}}^1 = 7.9750 \times 10^{-7}$  are chosen in non-dimensional form. Figure 18 illustrates the numerical solutions of the prostate tumor growth, the nutrient and PSA using



$N = 25961$  uniform nodes. The fingered tumor growth pattern, which was observed in vitro 3D Matrigel culture of RWPE-1 cells [33], can be seen in this simulation, as well.

## 8. Conclusion and the future work

The non-dimensional form of the mathematical model for the prostate tumor growth has been derived. It makes easy to apply different numerical methods for solving this model which arise in oncology. In this paper, a meshless technique, namely RBF-FD method in space and a semi-implicit approach based on SBDF1 formulas in time, have been successfully applied to solve it numerically on rectangular and circular regions, with uniform and quasi-uniform node distributions. We have shown that the method is numerically accurate and stable. Some numerical simulations have been done on clinical data borrowed from the literature, with results in agreement with those reported in the literature. The main advantages of the proposed numerical scheme are:

- Its implementation is simpler than the mesh-dependent methods. In fact, the differentiation matrix (which is a sparse matrix) is constructed at the scattered nodes without using a background mesh or triangulation (as given in Section 4).
- When different types of distribution nodes are used to construct the differentiation matrix in the rectangular and circular domains no new implementation is needed.

To the best of our knowledge, in this work the following new strategies have been successfully applied.

- The non-dimensional form of the prostate tumor growth mathematical model has been derived, which makes an easier implementation if combined with other numerical techniques.
- The meshlessness nature of our approach allows us to easily implemented it on rectangular or circular regions simply by the use of two different node distributions, uniform, and quasi-uniform.
- All simulations done can also be obtained by increasing the number of nodes in each local domain of influence, by changing  $n$ . Of course, the computational cost will be increased but not significantly.
- Unlike the methods of [41, 42], it is not necessary to use any adaptivity algorithms for solving this mathematical model.
- As we have mentioned in this paper, it is possible to apply different algorithms for finding a proper shape parameter.
- Although this method can be implemented in higher dimensions, the computational cost will be increased dramatically. On the other side, we had no access to fast and powerful computers, so that we were not able to get, for instance, three-dimensional results. We can access to clusters, or we can do parallel computing in the future.

## Supplementary movies

The process of tumor phase field, nutrient and the prostate specific antigen in two-dimensional tissue are provided for  $N = 25961$  uniform nodes, with supply nutrient  $s = 2.80 \text{ g}/(L.day)$  in three separate movies, downloadable at the link

<https://github.com/VM-2020-MATH/Simulation-Prostate-Tumor-Growth-RBF-FD-Scheme>.

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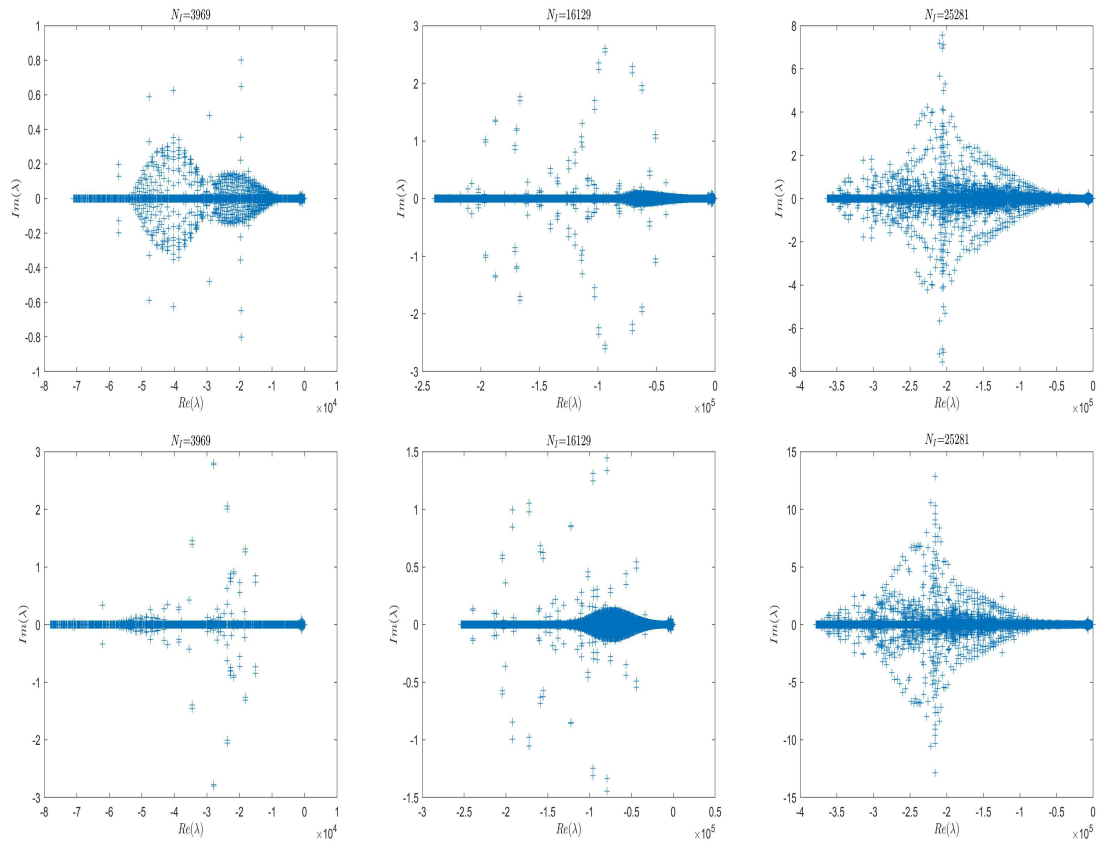


Figure 2: The eigenvalues of  $B$  with  $n = 13$  and uniform points  $N_I = 3969, 16129$  and  $25281$ . First row: for  $\varepsilon = 15$ . Second row  $\varepsilon = 20$ .



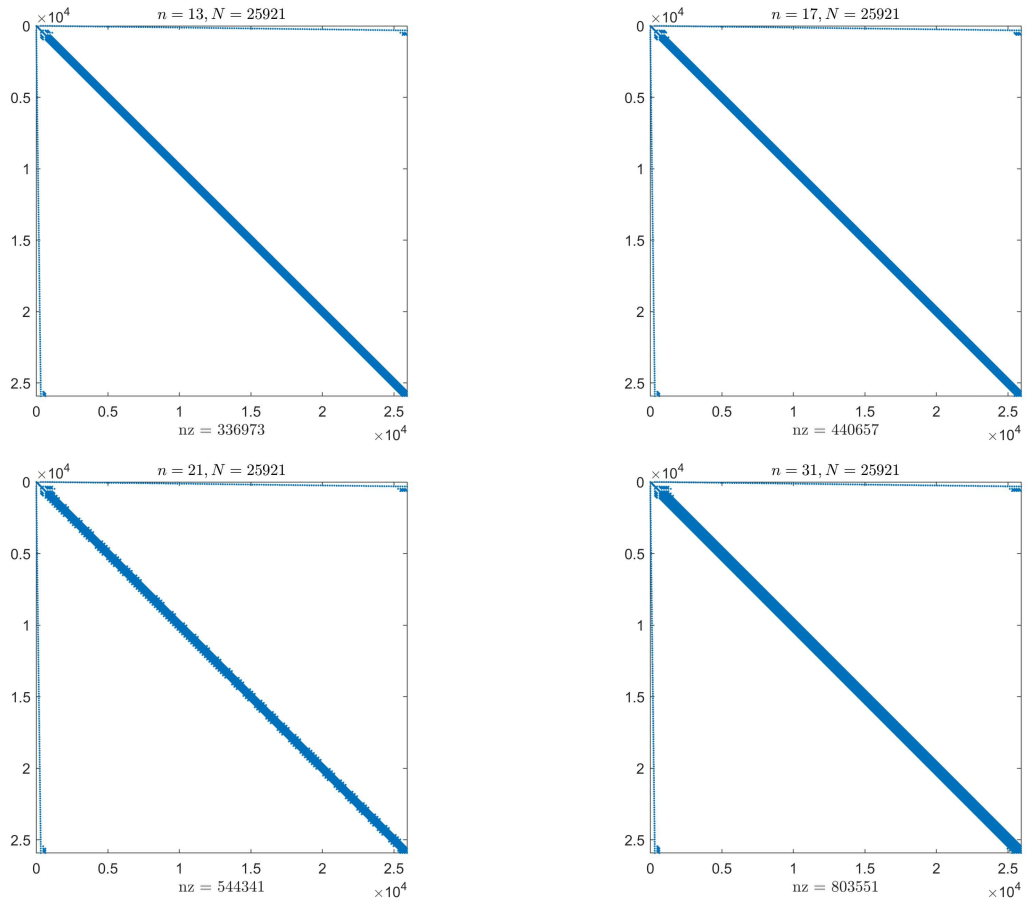


Figure 3: The sparsity pattern of the matrix  $W_X^L$  for  $N = 25921$  uniform points,  $n = 13, 17, 21$  and  $31$ .

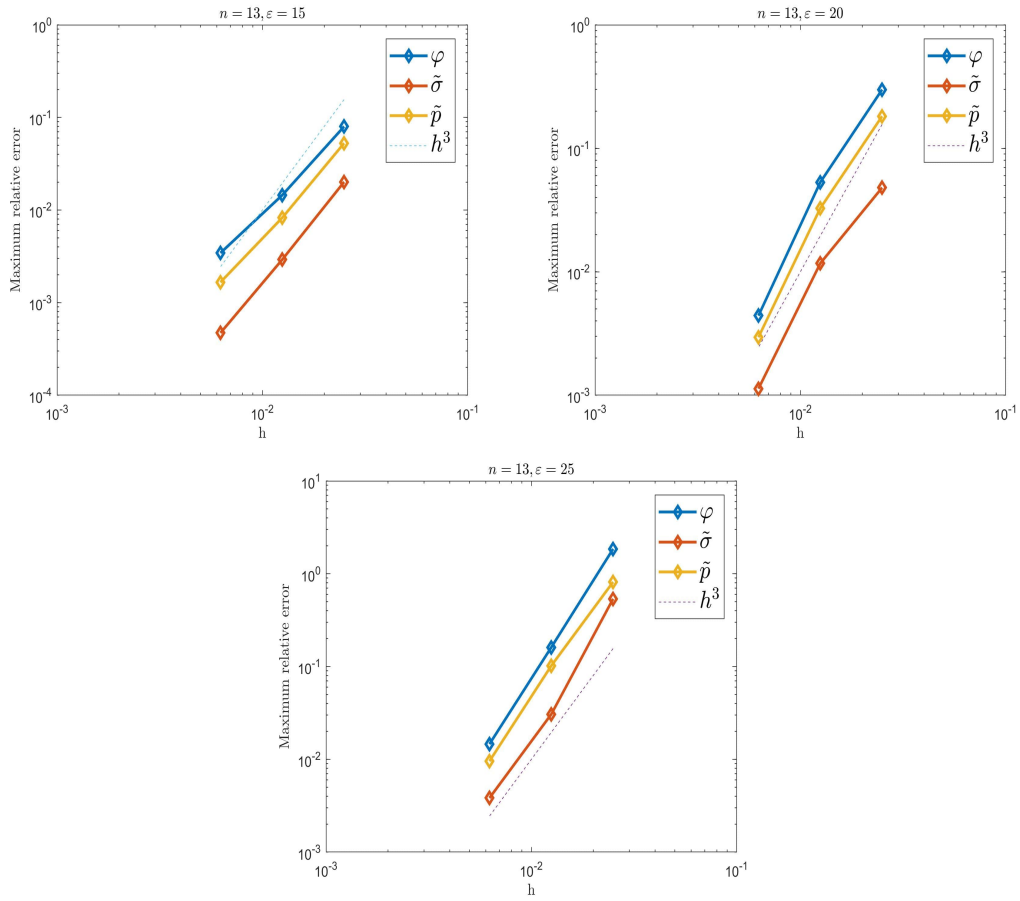


Figure 4: The maximum relative errors for  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  via  $n = 13$  and different values of  $\epsilon$ . Top left,  $\epsilon = 15$ ; top right,  $\epsilon = 20$  and bottom,  $\epsilon = 25$ .

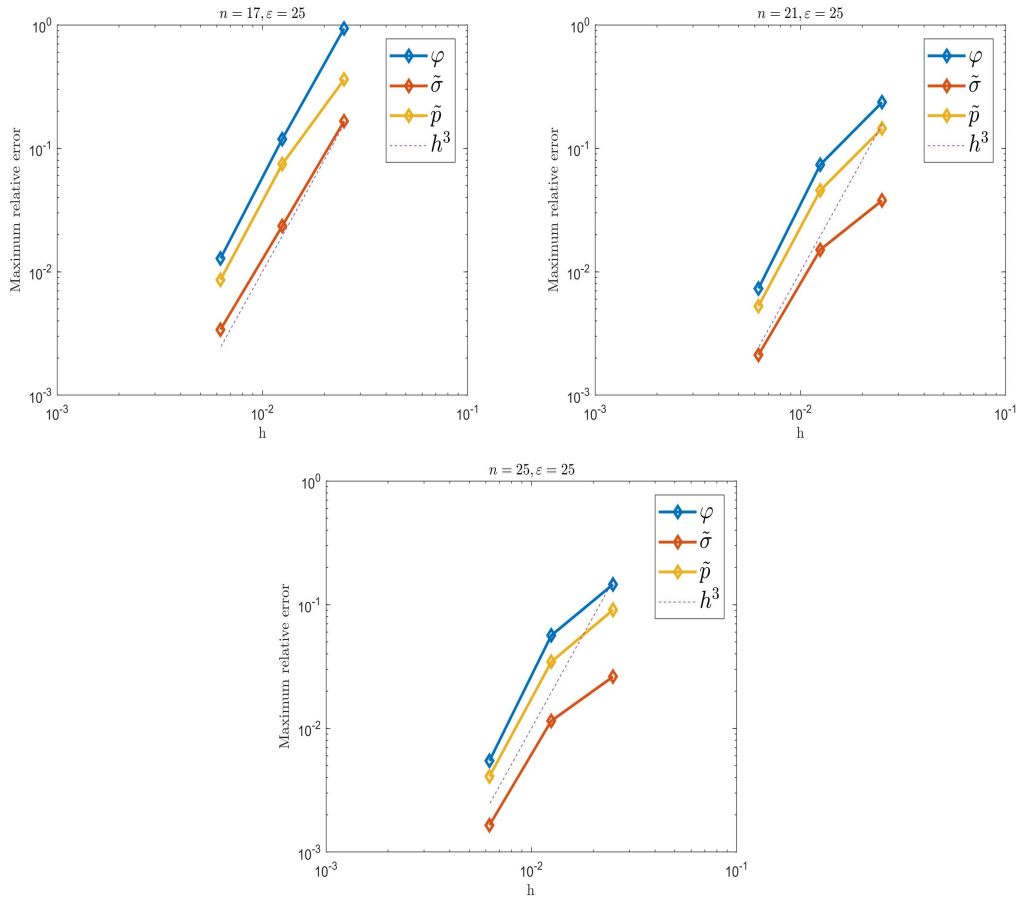


Figure 5: The maximum relative errors for  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  via  $\epsilon = 25$  and different values of  $n$ . Top left,  $n = 17$ ; right top,  $n = 21$  and bottom,  $n = 25$ .

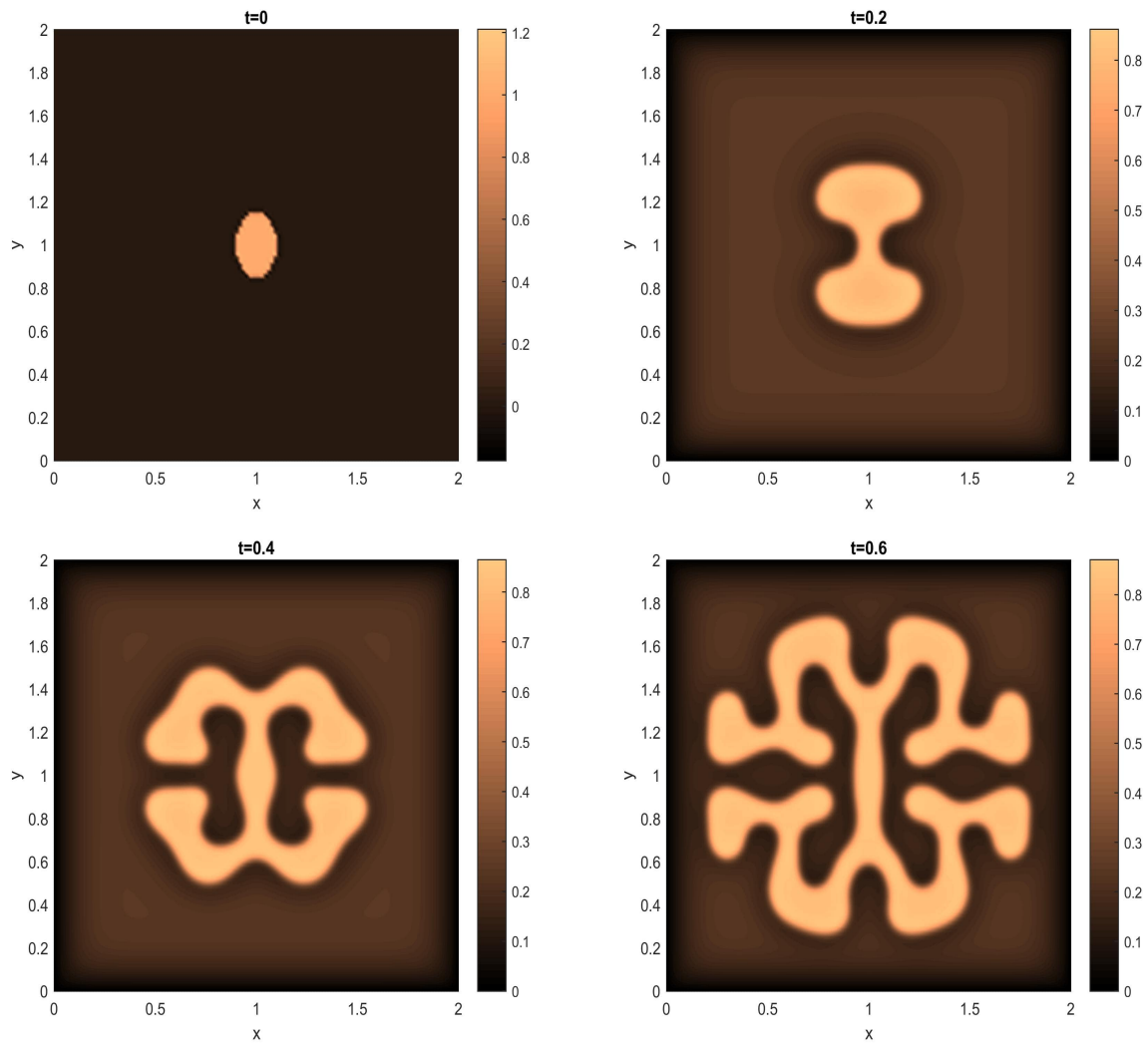


Figure 6: The initial condition and numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 16641$  uniform nodes.

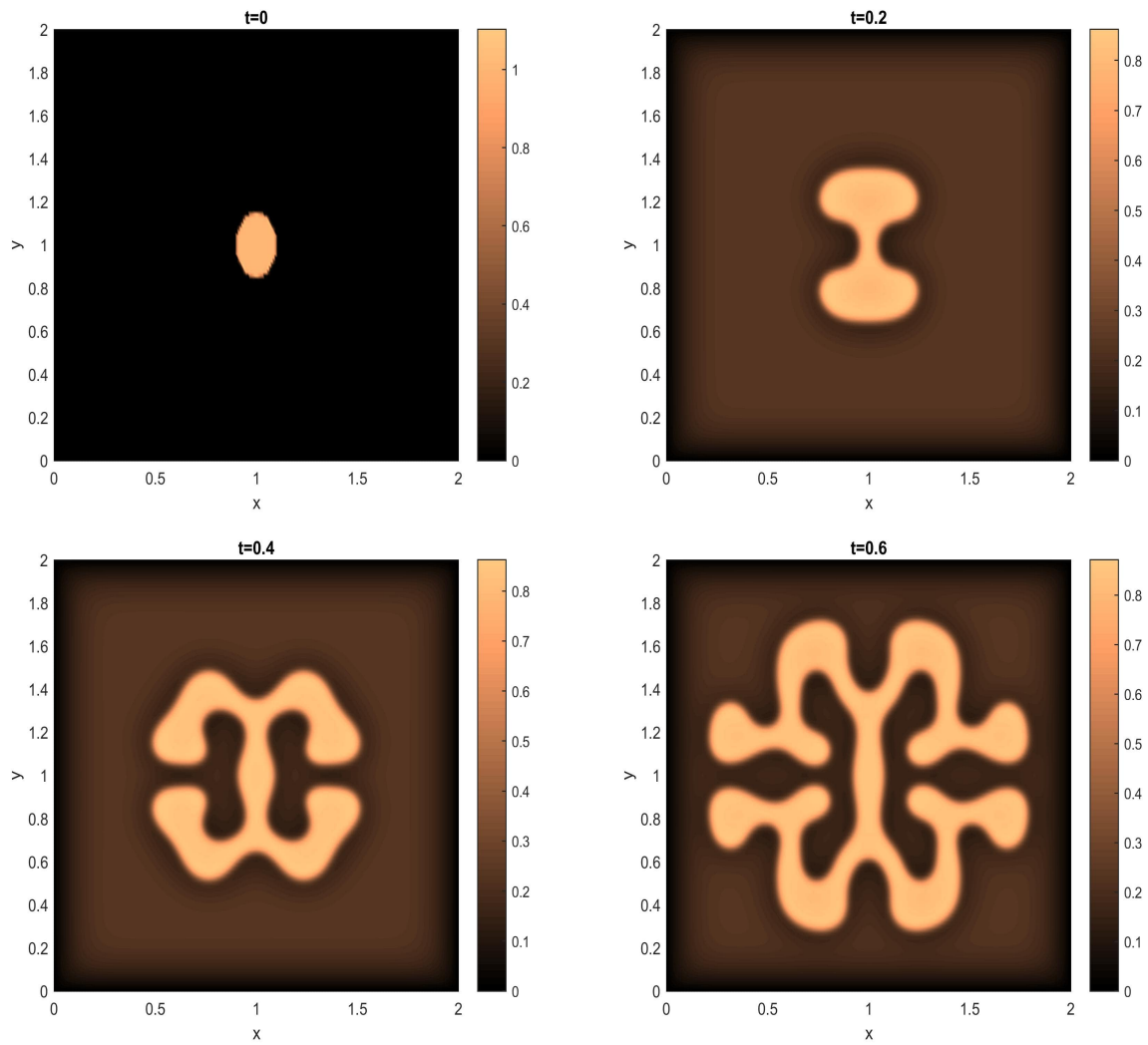


Figure 7: The initial condition and numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 66049$  uniform nodes.

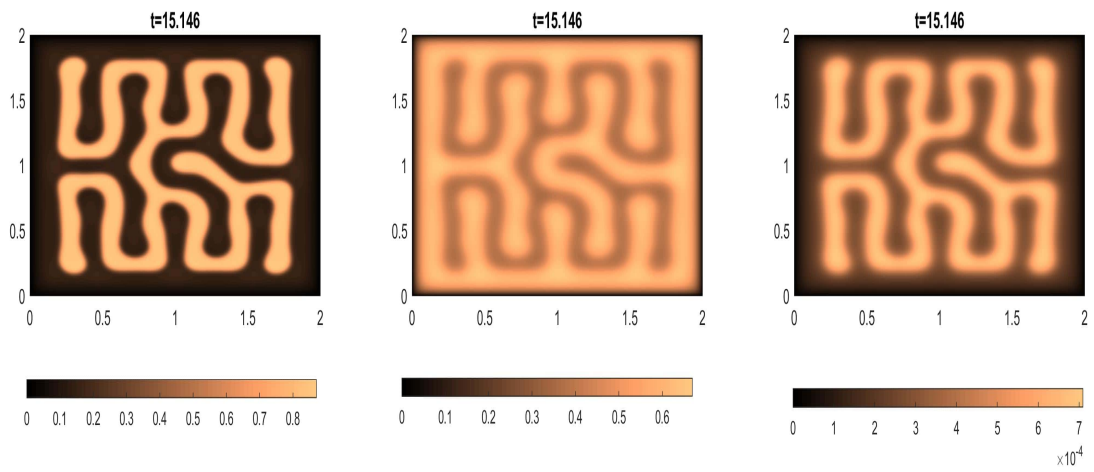


Figure 8: The steady-state solutions of  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  using  $N = 25921$  uniform points.

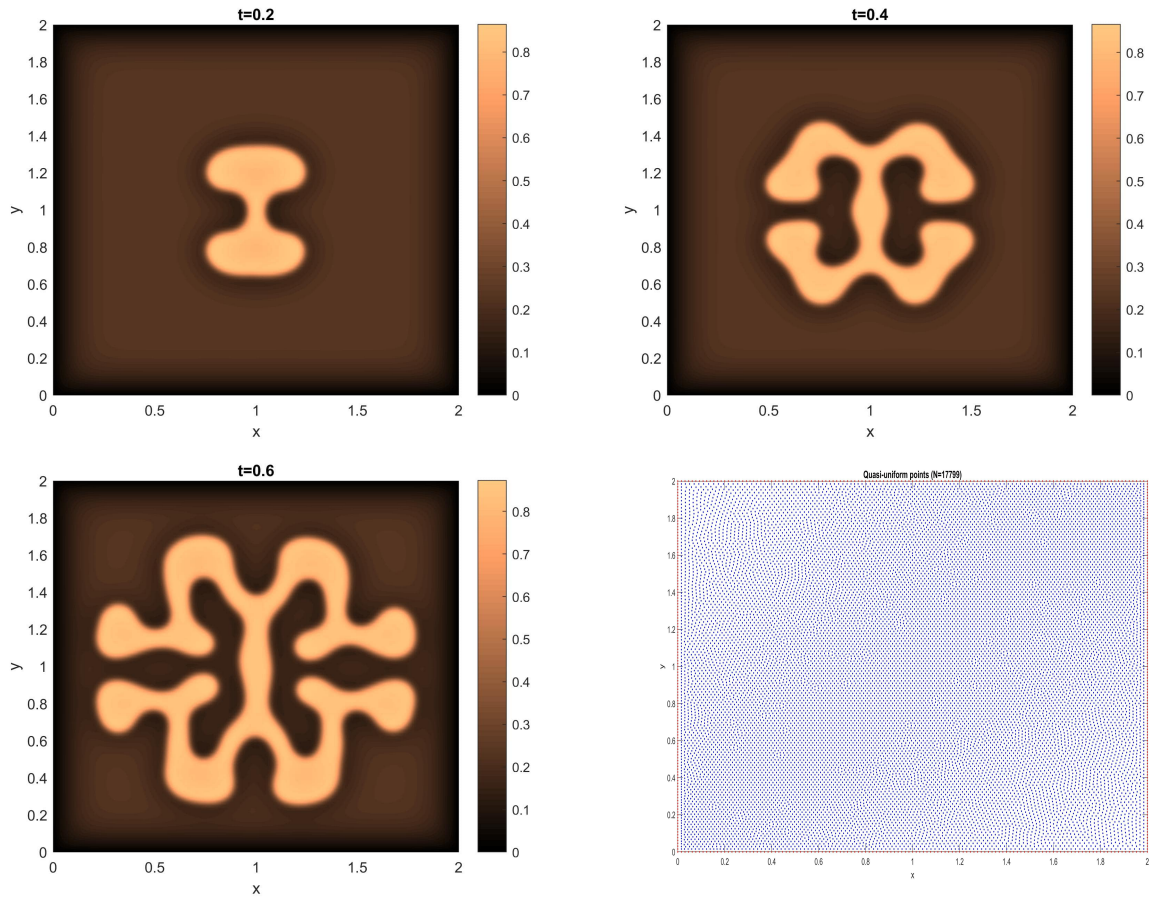


Figure 9: The numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 17799$  quasi-uniform nodes.

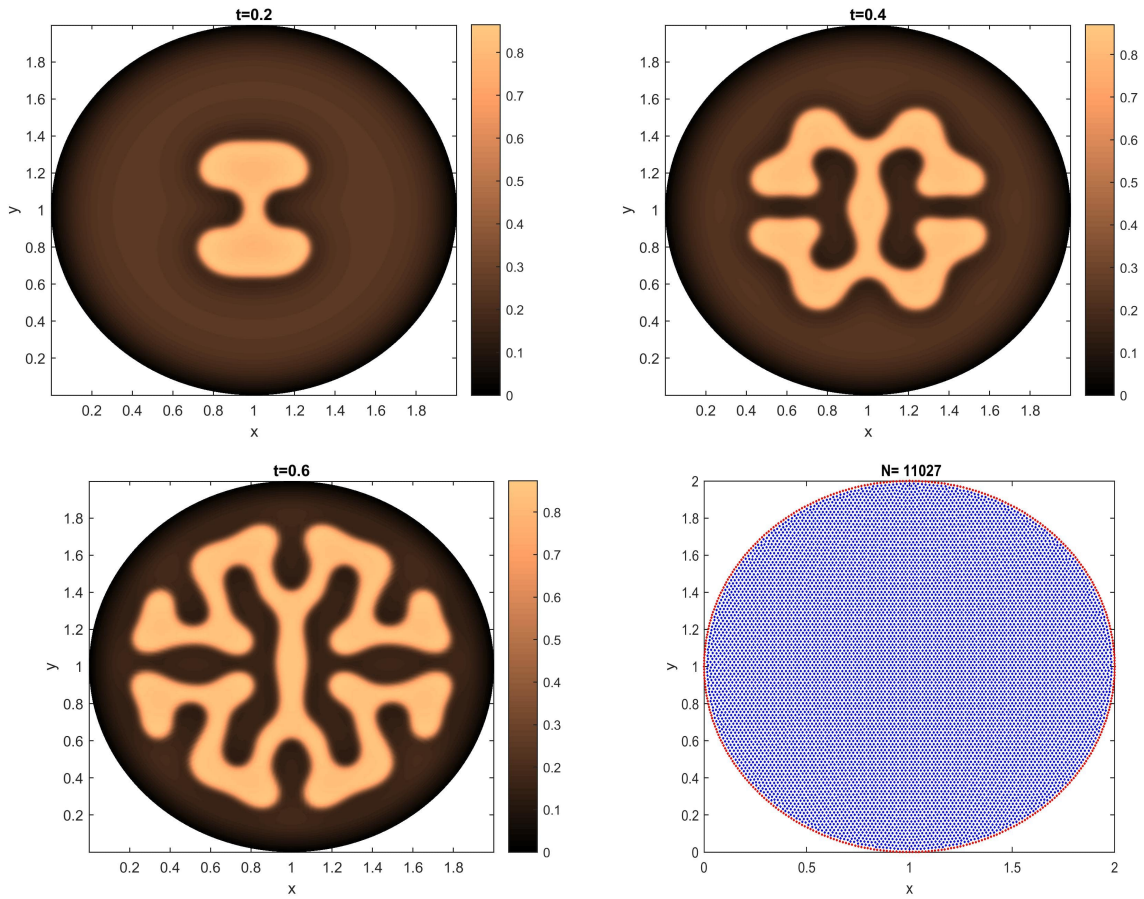


Figure 10: The numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 11027$  uniform nodes restricted to the unit disk centered in  $(1, 1)$ .



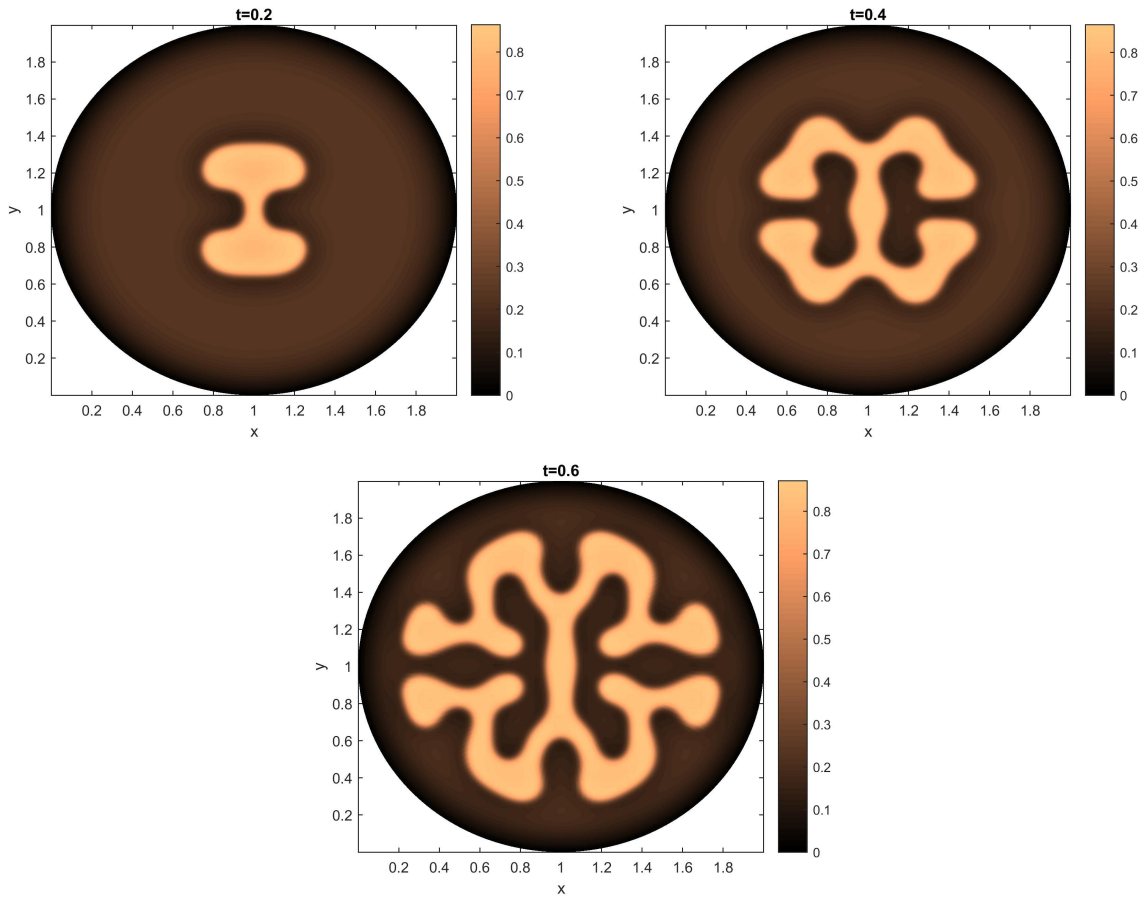


Figure 11: The numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 22999$  uniform nodes.

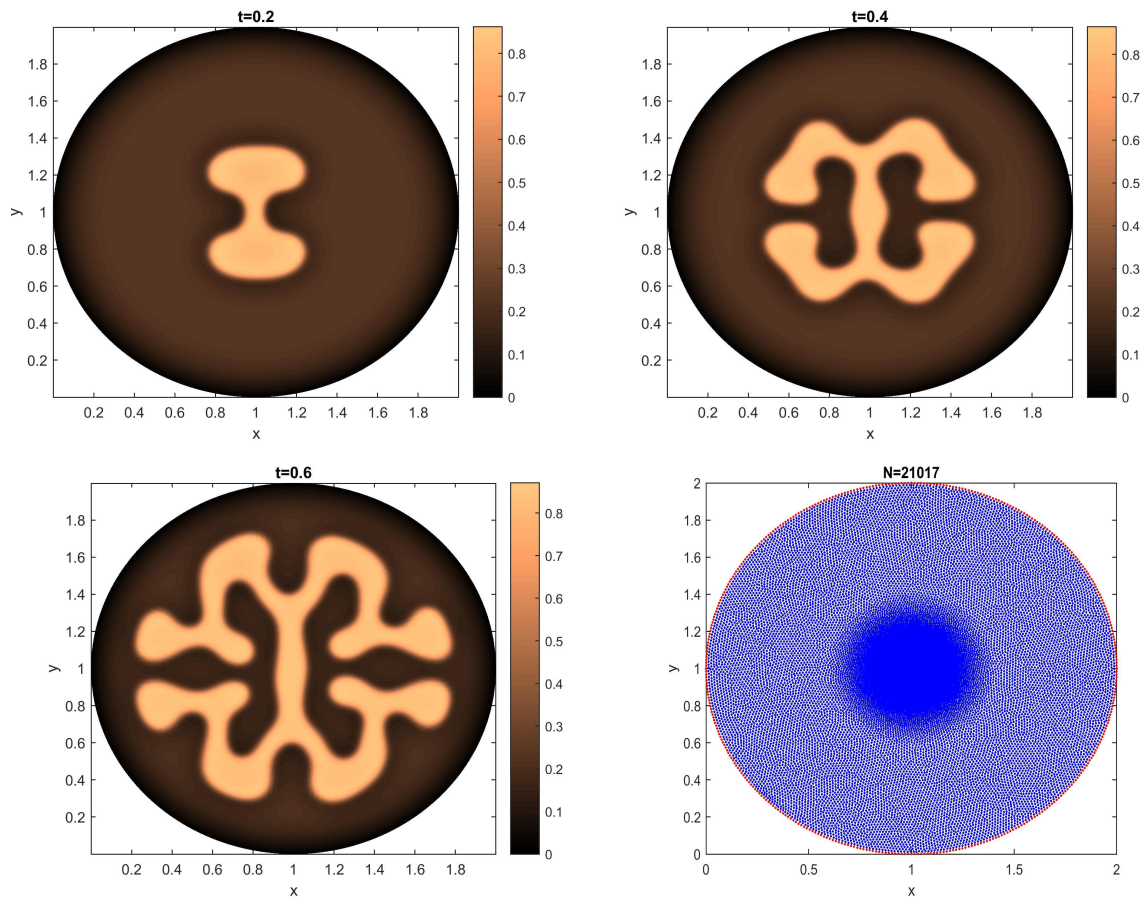


Figure 12: The numerical solution of tumor phase field  $\varphi$  at different time levels using  $N = 21077$  quasi-uniform nodes with a different central density.

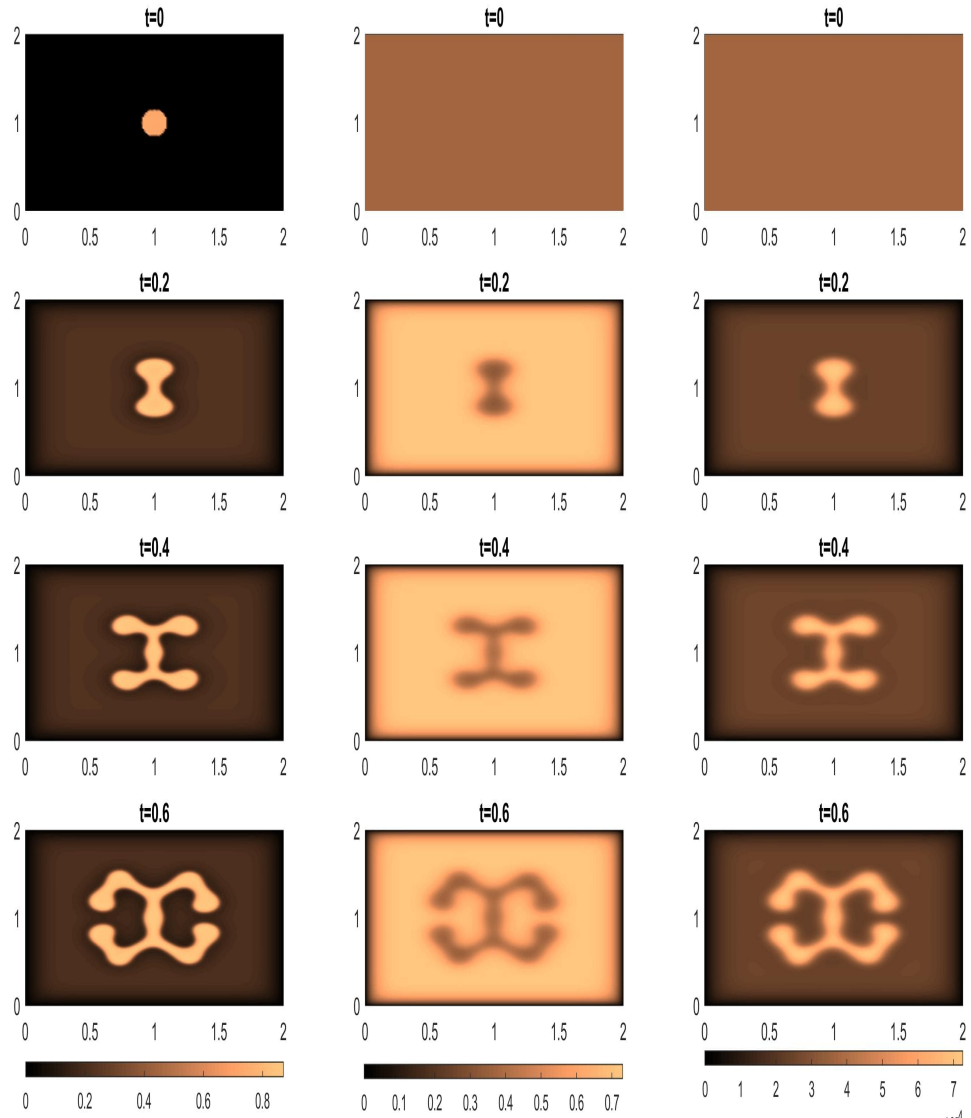


Figure 13: The numerical solution of tumor phase field  $\varphi$ , nutrient  $\tilde{\sigma}$  and PSA  $\tilde{p}$  at different time levels using  $N = 25921$  uniform nodes and  $s = 2.60 \text{ g}/(L.day)$ .

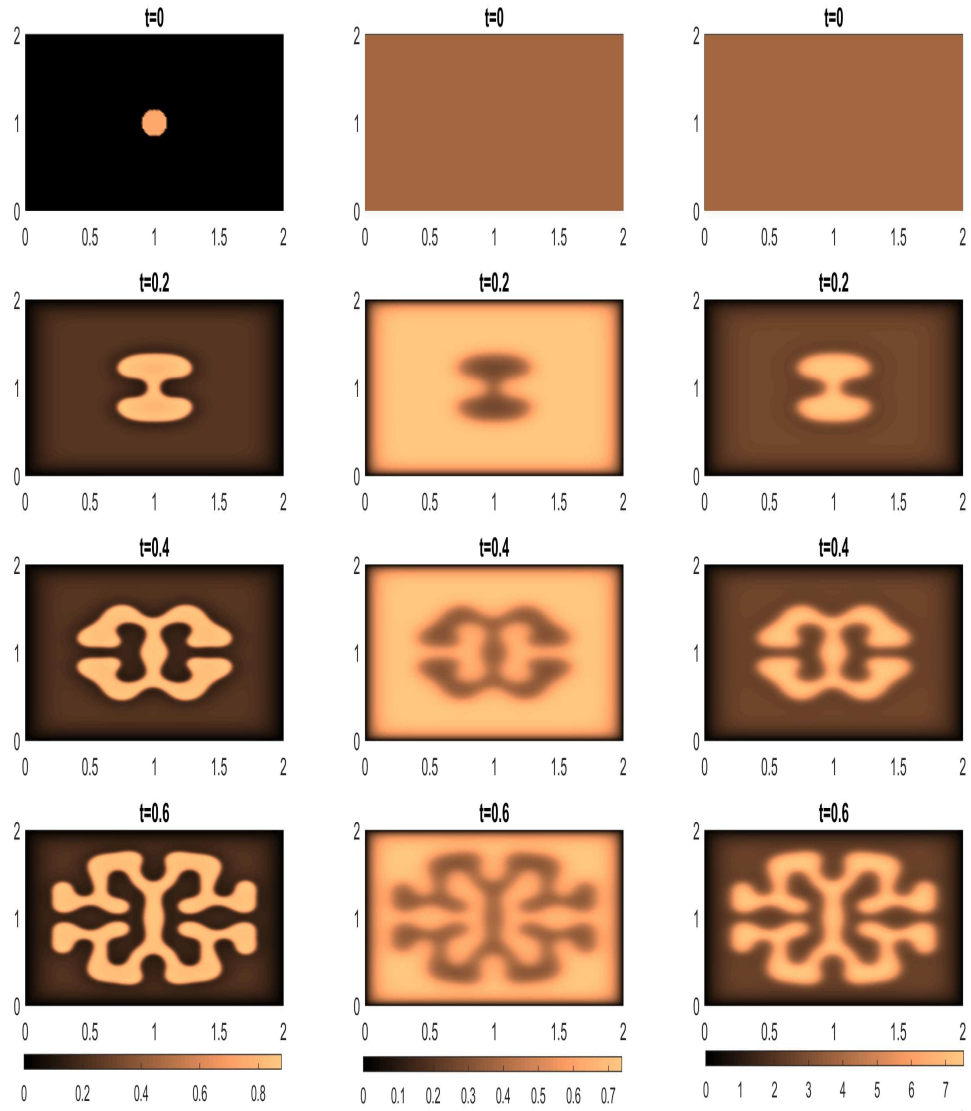


Figure 14: The numerical solution of tumor phase field  $\varphi$ , nutrient  $\tilde{\sigma}$  and PSA  $\tilde{p}$  at different time levels using  $N = 25921$  uniform nodes and  $s = 2.70 \text{ g}/(L.day)$ .

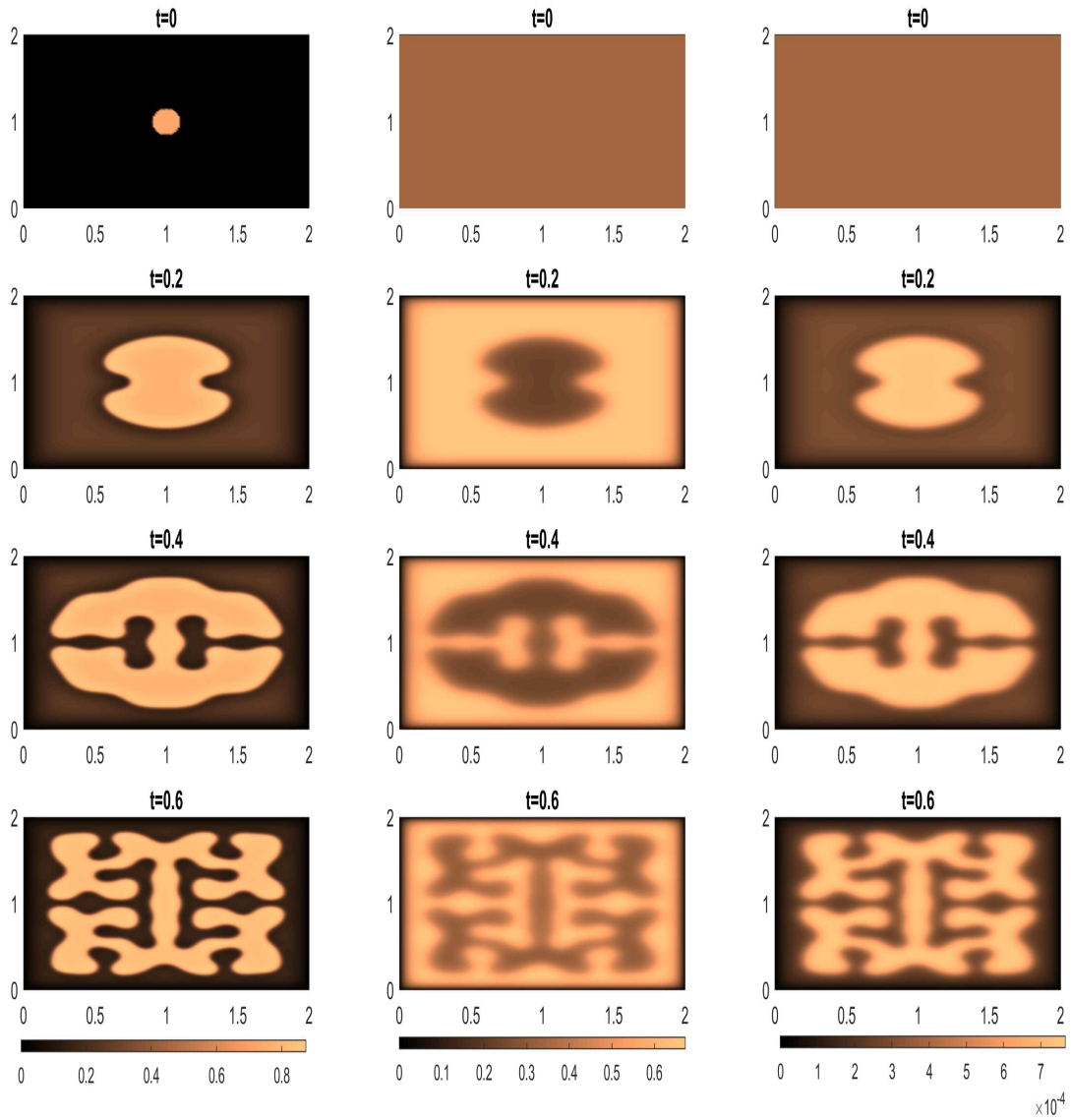


Figure 15: The numerical solution of tumor phase field  $\varphi$ , nutrient  $\tilde{\sigma}$  and PSA  $\tilde{p}$  at different time levels using  $N = 25921$  uniform nodes and  $s = 2.80$  g/(L.day).

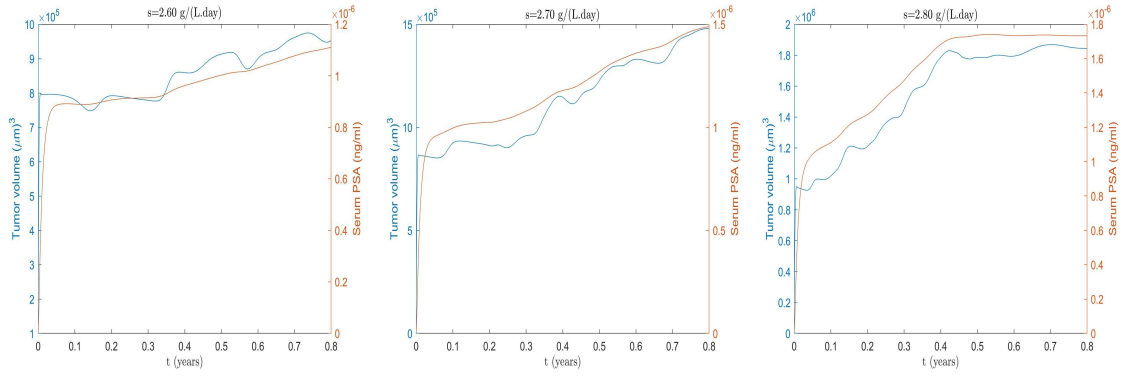


Figure 16: Tumor volume and serum PSA for different values of  $s$  at different time levels.

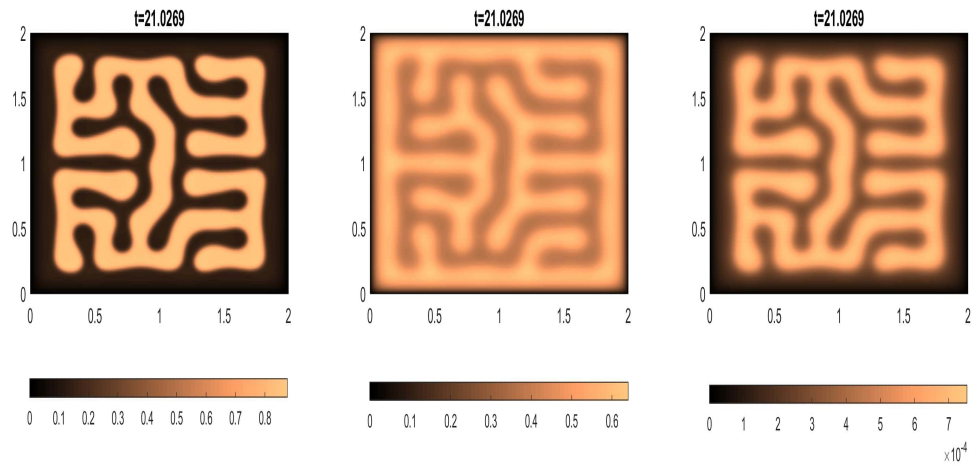


Figure 17: The steady-state solutions of  $\varphi$ ,  $\tilde{\sigma}$  and  $\tilde{p}$  via  $N = 25921$  uniform points.

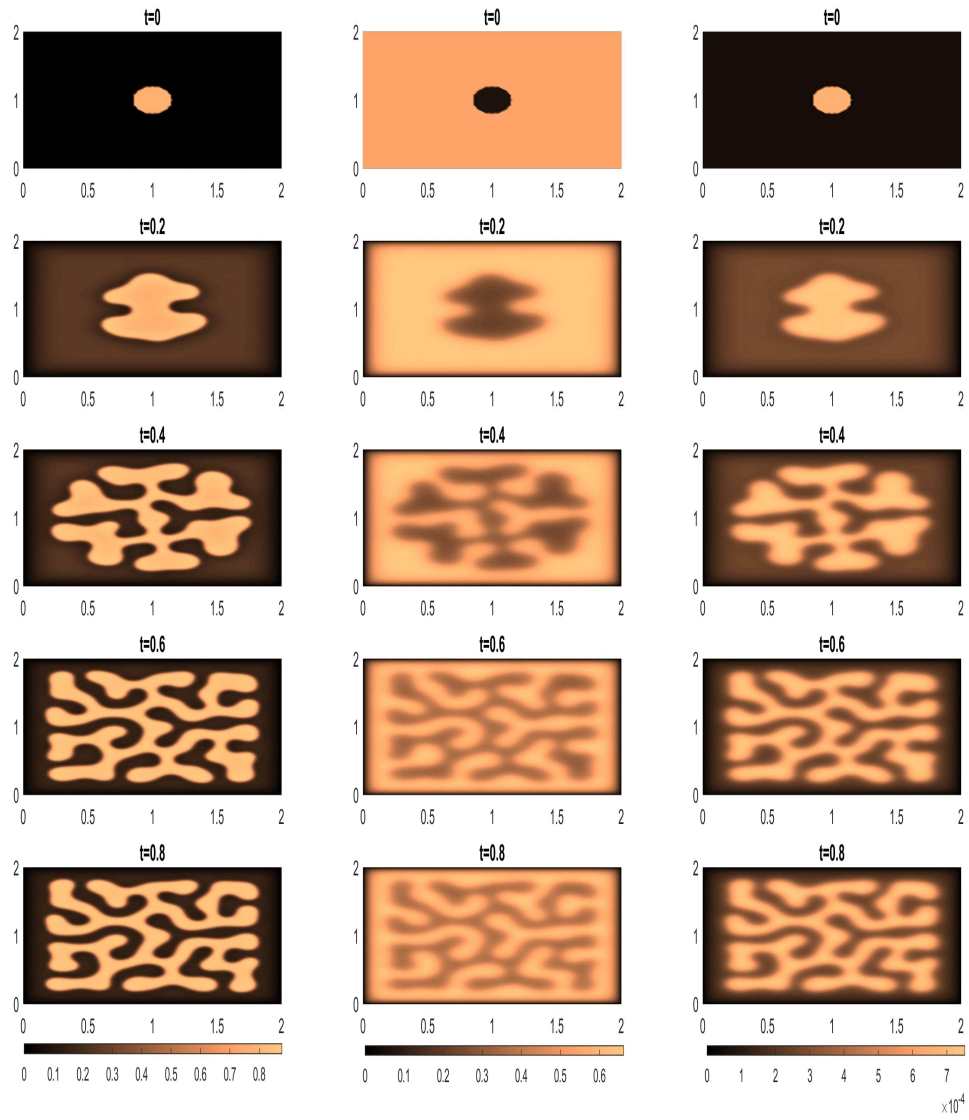


Figure 18: The numerical solution of tumor phase field  $\varphi$ , nutrient  $\tilde{\sigma}$  and PSA  $\tilde{p}$  at different time levels using  $N = 25921$  uniform nodes for  $s = (2.75 + c) g/(L.day)$  with a mild heterogeneity  $c$ .

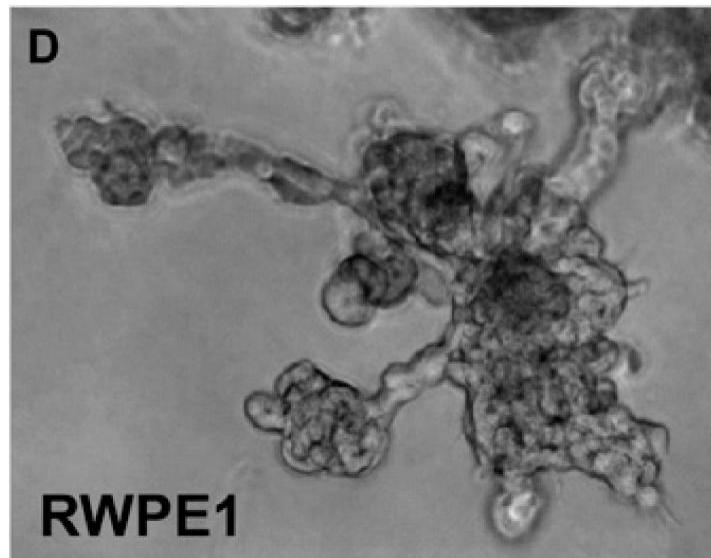


Figure 19: The fingered tumor growth patterns as observed in clinical practice and experiments ( $\lambda = 5 \times 10^{-11} \text{ cm}^2/s$  and  $\epsilon = 2 \times 10^{-9} \text{ cm}^2/s$ ). This picture is taken from [41], which authors of [41] had borrowed from [33].