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Source Localization of Reaction-Diffusion Models for Brain Tumors

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Abstract. We propose a mathematically well-founded approach for locating the source (initial state) of density functions evolved within a nonlinear reaction-diffusion model. The reconstruction of the initial source is an ill-posed inverse problem since the solution is highly unstable with respect to measurement noise. To address this instability problem, we introduce a regularization procedure based on the nonlinear Landweber method for the stable determination of the source location. This amounts to solving a sequence of well-posed forward reaction-diffusion problems. The developed framework is general, and as a special instance we consider the problem of source localization of brain tumors. We show numerically that the source of the initial densities of tumor cells are reconstructed well on both imaging data consisting of simple and complex geometric structures.

1 Introduction

Brain cancer is one of the most common cancers worldwide. A brain tumor is an abnormal growth of tissue cells partly due to genetic events. Treatment of brain tumors includes surgery, radiotherapy and chemotherapy and is based on a number of factors, with the location in the brain where the tumor formed being of pivotal importance. Studies have been conducted showing that the source of a tumor is correlated with characteristics such as genetic signature [17,30]. These characteristics can influence the behaviour of the tumor including its diffusion and proliferation properties and can therefore be an important marker for diagnosis. The influence of the source location on the diffusion and proliferation properties is herein neglected for simplicity, and future work can focus on incorporating priors on the multimap between the source location and the diffusion and proliferation properties due to genetics.
In this work, largely motivated by the potential impact of tumor source localization, we address the problem of reconstructing the source of cell densities evolved within a reaction-diffusion model commonly used to describe tumor growth. Unlike the majority of research done in the area of tumor source localization, which aim at approximating the nonlinear PDE models by systems of ODEs (for example with the Eikonal equation [21]), we propose here a novel and altogether different mathematical approach. We take advantage of the theory of inverse problems to reconstruct initial data in parabolic equations, that is we recast the reconstruction of the source as a backward parabolic problem (for an overview of backward problems, see Chap. 9 in [10]). In doing this, we remove sources of uncertainty introduced when reducing the model to ODEs, i.e., we work with the reaction-diffusion model directly.
Our approach formulates an iterative procedure for solving well-posed forward

PDEs at each iteration step, with the aim of adjusting the initial state to match the given data. On an abstract level, this procedure can be seen as a nonlinear Landweber method [23] for an operator equation. The proposed approach assumes that the initial tumor cell density (needed as input data) is measurable; typically it would be extracted from medical imagery.

1.1 Overview

In Sect. 2, we give an overview of some current mathematical models describing tumor growth, i.e., the forward-problem. In Sect. 3, we describe the reactiondiffusion model and state the corresponding inverse problem; the iterative procedure is outlined in Sect. 3.1 together with its connection to the non-linear Landweber method. In Sect. 3.2, some details are given to motivate the wellposedness of the forward problems and the uniqueness of a solution to the inverse problem as well as the convergence of the procedure. In Sect. 4, we describe numerical implementation of the procedure and perform numerical experiments on the Shepp-Logan phantom as well as on MRI data, showing the accuracy of the approach for source localization with different source terms. Finally, some conclusions and remarks are given in Sect. 5.

2 Reaction-Diffusion Models and Related Works

One of the first PDE models for tumor growth was proposed by Murray in the early 1990s [3,5,26]. This model consists of a reaction-diffusion type parabolic PDE with the reaction term representing the proliferation and the diffusion term representing the infiltration [18]:

$$
\begin{cases}
\partial_t u - \operatorname{div}(D\,\nabla u) - f(u) = 0 \text{ in } \Omega \times (0, T) \\
u(0) = \phi \text{ in } \Omega \\
D\,\nabla u \cdot n = 0 \text{ on } \partial\Omega \times (0, T)
\end{cases}
\tag{1}
$$

Here, u is the tumor cell density at time t at the spatial position x, with D the diffusion tensor for tumor cells and f a reaction term describing the cell

growth as a function of the current cell concentration. Different models have been suggested for the proliferation rate f, e.g., $f(u) = \rho u$ referred to as the exponential source term and $f(u) = \rho u(1 - u)$ as the logistic source term where $\rho > 0$, see [27] and [16] for specific applications.[1] The interpretation of the term $\operatorname{div}(D\,\nabla u)$ in (1) is that it describes the invasion of tumor cells as a diffusive flux along the concentration gradient. The initial tumor cell density ϕ is given at time $t = 0$, and the boundary condition on $\partial\Omega$ states that tumor cells do not diffuse outside the brain region.

Let us briefly give some works on (1) to show that it is an established model with known and validated parameters.

Clinical imaging data offers the benefit of non-invasive, in vivo and timely measurement of parameters needed in (1). Under the influence of experimental results of Giese et al. [8] regarding the differential motility of tumor cells on grey and white matters, Swanson et al. [25] assumed an infiltrative growth of the tumor cells, while considering differences in cell diffusion in white and gray matter. They suggested that the diffusion tensor D in (1) is spatially dependent: $D = d(x)I$, where I is the identity matrix and $d(x)$ is the diffusion coefficient. Moreover, this diffusion coefficient should only take two different values; in the white matter (myelin) of the brain it is dw, and in the grey matter it is dg, with $dw >> dg > 0$, corresponding to the observation that tumor cells move faster on myelin. Furthermore, in [25] medical images necessary for the diagnosis (CT and MR images) of brain tumors were used to calibrate the parameters ρ and D. Extending the work [25] regarding the differential motility of tumor cells on different tissues, Jbabdi et al. [11] assumed that tumor cells not only move faster on myelin, but also that they follow the white matter fiber tracts that are present in the brain. Simulations using (1) incorporating this extension corroborated well with real tumor growth obtained from MR images.

Other extensions can be done, for example, the invasive nature of tumor

growth. Clatz et al. [6] did this by assuming that brain tissue is a linear viscoelastic material.

Let us mention that Konukoglu et al. proposed an altogether different tool for radiotherapy in [13], which extrapolates the extents of the tumor invasion not visible in MR images from the visible part. Based on the reaction-diffusion formalism, they deduced the anisotropic eikonal equation:

$$\sqrt{\nabla u \cdot (D \nabla \sqrt{u})}$$

$\rho u = 1$, $u(\partial\Omega) =$ u_0, describing the extents of the tumor starting from the visible tumor contour in the MR image. With this, one can obtain ordinary differential equations to solve for the cell density rather than a partial differential equation.

However, as explained above, (1) is well-established for tumor growth, and although challenging to solve due to its nonlinear term, we shall base our reconstruction of the tumor source on this model.

1 Note that the PDE models considered in this work have their origin in ordinary differential equation (ODE) models and the terminology is adopted from ODE models with corresponding source terms as their solution. For example, $u_t = \rho u$ has the *exponential function* $u = Ce^{\rho t}$ as a solution. Furthermore, the logistic equation $u_t = u(1 - u)$ has the *logistic function* $u = 1/(1 + e^{-t})$ as a solution.

3 Source Location

The model (1) describes the tumor cell density u over time. Given knowledge of this density at a fixed time $T > 0$, that is $u = \psi$ at $t = T$, to find the initial distribution (source) amounts to solving

$$\begin{cases} \partial_t u - \operatorname{div}(D(x)\nabla u) - f(u) = 0 \text{ in } \Omega \times (0, T) \\ u(T) = \psi \text{ in } \Omega \\ D\nabla u \cdot n = 0 \text{ on } \partial\Omega \times (0, T) \end{cases} \quad (2)$$

Compared with (1), we have now a final condition imposed (at $t = T$) instead of an initial one (when $t = 0$), and (2) is known as a backward parabolic problem having the additional challenge of being ill-posed with respect to measurement noise in the data, see further [10, Chap. 9] for details on backward problems.

To obtain a regularizing procedure for the stable determination of the initial source ϕ, we note that the backward problem in (2) can be rewritten as:

Determine ϕ in (1) matching the given data

$u(x, T) = \psi(x)$. (3)

The determination of ϕ from this data is our inverse problem (IP) and amounts to solving (2).

3.1 Nonlinear Landweber Method

The inverse problem consisting of finding the initial condition in (1) to match (3) can be reduced to a nonlinear operator equation. This takes the form

$A(\phi) = \psi$. (4)

The definition of $A\phi$ is $u_T(\phi)$, with $u_T(\phi)$ the restriction of the solution of (1) to $t = T$ for a given initial state ϕ.

Equation (4) inherits the ill-posedness of the backward parabolic problem (2). Therefore, to obtain a stable solution, the nonlinear Landweber method given, for example, in [23] can be applied. In this method, the initial source is updated according to

$$\phi_{k+1} = \phi_k - A'^*(A\phi_k - \psi), \quad (5)$$

where ϕ_0 is an arbitrary initial guess of the source (belonging to the standard space of square integrable functions, $L_2(\Omega)$), and A'^* is the adjoint of the Fr´echet derivative of the operator A. Convergence rates and stability results can be found in [23]. In particular, for noisy data, the iterations has to be ceased at some point otherwise the errors will start to magnify. In the linear case, an approach of this

form to find the initial distribution together with a source term, was used in [12]. Thus, it is natural to generalize this to the nonlinear setting.

To calculate the action of the operator A on the element ϕ_k amounts to solving (1) with data ϕ_k, resulting in an approximate cell density distribution u_k. Moreover, the action of the operator $A'(\phi_k)^*$ on the element $(A\phi_k - \psi)$ is obtained by solving a corresponding adjoint linear problem to (1).

Lemma 1. *The adjoint linear equation corresponding to the governing equation in* (1)*, that is*

$$\partial_t u - \operatorname{div}(D(x)\,\nabla u) - f(u) = 0, \quad (6)$$

is given by

$$\partial_t v + \operatorname{div}(D(x)\,\nabla v) + f'_u(u)v = 0. \quad (7)$$

Proof. Briefly, without entering into full details, the change of sign in Eq. (7) is obtained by multiplying the Eq. (6) by a suitable (test) function v and integrating by parts over the time interval $(0, T)$. Moreover, the linear elliptic part in (7) is obtained by observing that A has a Fr´echet derivative, and that the Gateaux derivative of $-\operatorname{div}(D(x)\,\nabla u) - f(u)$ at u in the direction of v, can be used to evaluate it,

$$\frac{d}{d\varepsilon}\left[-\operatorname{div}(D(x)(\nabla u + \varepsilon \nabla v)) - f(u + \varepsilon v)\right]\Big|_{\varepsilon=0} = -\operatorname{div}(D(x)\,\nabla v) - f'_u(u)v, \quad (8)$$

and the result follows. __

To solve the inverse problem (1) and (3), following the scheme (5), we start by solving

$$\begin{cases} \partial_t u_1 - \operatorname{div}(D(x)\,\nabla u_1) - f(u_1) = 0, \text{ in } \Omega \times (0, T) \\ \partial_n u_1 = 0, \text{ on } \partial\Omega \times (0, T) \\ u_1(0) = \phi_0, \text{ in } \Omega \end{cases} \quad (9)$$

Given that u_k, $k \geq 1$, has been constructed, we proceed by solving the linear adjoint problem

$$\begin{cases} \partial_t v_k + \operatorname{div}(D(x)\,\nabla v_k) + f'_u(u_k)v_k = 0, \text{ in } \Omega \times (0, T) \\ \partial_n v_k = 0, \text{ on } \partial\Omega \times (0, T) \\ v_k(T) = u_k(T) - \psi, \text{ in } \Omega \end{cases} \quad (10)$$

to obtain v_k. Then u_{k+1} is constructed as the solution to

$$\begin{cases} \partial_t u_{k+1} - \operatorname{div}(D(x)\,\nabla u_{k+1}) - f(u_{k+1}) = 0, \text{ in } \Omega \times (0, T) \\ \partial_n u_{k+1} = 0, \text{ on } \partial\Omega \times (0, T) \\ u_{k+1}(0) = u_k(0) - v_k(0), \text{ in } \Omega \end{cases} \quad (11)$$

We iterate the last two steps until the desired level of accuracy has been obtained. Using Lemma 1, it is straightforward to verify that the above procedure corresponds to the nonlinear Landweber method (5) for solving (4).

3.2 Well-Posedness of the Forward Problem (1)

It is possible to introduce a weak formulation and with a rather direct approach prove that (1) is well-posed in standard Sobolev spaces for parabolic equations (for such spaces, see [15, Chap. 4.2]). However, to save space, we refer to general theory for abstract parabolic equations and note that (1) can be written

$$\_u\__t + Bu = f(u(t))$$
$$u(0) = \phi$$

Equations of this form and further abstractions have been studied in depth in the literature in various spaces, see for example, [29, Chap. 30].

In our case of (1), B is the divergence term, and B generates a semi-group, see [20, Theorem 7.2.5]. From this, and since we work with functions f being at least Lipschitz continuous, we have from [20, Theorem 6.1.2],

Theorem 1. *Let $\phi \in L_2(\Omega)$. Then there exists a unique* (*weak or mild*) *solution $u \in L_2(0, T; H_1(\Omega))$ to the reaction-diffusion problem* (1)*, and this element u depends continuously on the data.*

The similar result holds for classical solutions in spaces of H¨older continuous and differentiable functions, see Theorem 7.4, p. 491, in [14]. The adjoint and linear problem (10) is also well-posed.

More general reaction-diffusion models containing, for example, convection terms and having non-linearities in the divergence term, can be considered, see [22, Chap. 8.6]. Thus, our approach is not limited to (1).

For the reconstructions, it is important to know that there is only one solution to the backward problem (2). Formally, the solution to the backward problem can be represented as

$$u(t) = S(t - T)\psi - \__t^T S(t - s)f(u(s))\, ds$$

with S being the semi-group generated by the divergence term in (1). Using this representation, one can build on the results for source reconstructions, see [4,7], to obtain that the backward problem has a unique solution. This holds for functions f that are locally Lipschitz, see further [28]. Thus, we can state

Theorem 2. *The backward problem* (2) *has a unique solution.*

We assume that data are given and compatible such that (2) has a solution. For the convergence of the nonlinear Landweber type method outlined in the steps (9)–(11), we assume that the initial guess is chosen such that in a neighbourhood of it there is the estimate

$$\_A(\phi) - A(\phi_0) - A\_(\phi_0)(\phi - \phi_0)\_ \leq \eta\_A(\phi) - A(\phi_0)\_$$

with $0 < \eta < 1/2$, and A from (4). Given this, the nonlinear Landweber method converges, see Theorem 2.4 in [9].

4 Evaluation

We evaluate the proposed solution scheme (9)–(11) on two types of data with synthetically generated tumors obtained via the forward model (2). The parameters values are equal in the forward and backward model.

Fig. 1. Source localization for the Shepp-Logan phantom image with different source terms and proliferation rates: logistic in (d), (e) and exponential source term in (f), (g). In (d)–(g): right figures show the final source location in red and the initial distribution in yellow; left figures show the tumour distribution at time T in yellow and the tumor boundary in green. Panel (c) illustrates the randomly generated seed-points. (Color figure online)

4.1 Discretization

We adopt a generic forward Euler discretization strategy using finite differences approximating derivatives in the parabolic PDEs [19]. Since Ω is the (curved) boundary of the brain (union of white and gray matter segments), special care needs to be taken when computing the Neumann boundary condition on irregular grids. We approach this problem by replicating the boundary pixels in the outward normal direction of Ω sequentially (left-right, up-down, right-left and down-up). Any inconsistency for diagonal flow vectors could not be observed, and this straightforward strategy performs remarkably well.

Table 1. Mean L1 pixel distance and standard deviation for 100 seed-points between

the ground truth seed center location and the estimated tumor source for the Shepp-Logan and the MRI images.

	Shepp-Logan phantom $f = \rho u(1 - u)$		$f = \rho u$	
ρ	0.001	0.01	0.001	0.01
Landweber	1.35 ± 1.40	2.73 ± 1.56	1.37 ± 1.36	2.67 ± 1.56
Centroid	1.65 ± 2.05	3.16 ± 1.91	1.35 ± 1.37	2.65 ± 1.55
MRI T1				
Landweber	1.54 ± 2.01	3.52 ± 1.84	0.77 ± 0.98	2.17 ± 1.35
Centroid	1.98 ± 2.30	5.34 ± 2.12	0.77 ± 0.98	2.16 ± 1.34

4.2 Evaluation Setup

We use two different settings to evaluate the proposed source reconstruction of tumors: the first is usage of the standard Shepp-Logan phantom [24] describing a comparably simple geometry, the second setting describes a more involved geometry and consists of an MRI T1-weighted brain scan [2] from the Internet Brain Segmentation Repository (IBSR) [1]. In the synthetic setting of the Shepp-Logan phantom, we manually selected hypothetical white and gray matter regions whereas in the second configuration the data has ground truth segmentation provided by experts. These imaging data are illustrated in Figs. 1(a), (b) and 2(a), (b), respectively.

For each of the data, we use 100 seed-points shown in panels (c) of respectively figure. For each seed-point we run the forward model to obtain a synthetic tumor at time a $T > 0$ for a particular parameter configuration. In the Shepp-Logan phantom we used diffusivity speed 1 in the white matter and 0.05 in the gray matter segment. For the MRI image we set diffusivity speed 1 in the white matter region and 0.1 in the gray matter region. In all of the experiments, we let the update step in the Euler scheme be 10^{-1}, ρ either 0.001 or 0.01 influencing the degree of the nonlinearity for the exponential and logistic source terms in the PDE model (1). The forward problem was iterated 100 times for the Shepp-Logan phantom and 500 for the MRI image, these data were used as ϕ_0 in (9). The problem (9) is iterated 20 times and the resulting u_1 is used as initial data to (10) and (11), each iterated two and one time respectively. Finally, the overall problem (10)-(11) is iterated 10 times.We found no improvement in source localization by performing additional iterations of the outer loop. For comparison, we segment the tumor and compute its centroid (or “center of mass”), and let this point represent a baseline method for source localization. The next section discusses the results.

4.3 Results

Figures 1 and 2 display examples of source localization for the Shepp-Logan phantom and the MRI image in (a). Panel (b) depicts the regions of hypothetical

Fig. 2. Panel (a) shows a T1-weighted MRI brain scan from IBSR. Its ground truth segmentation provided by experts is shown in panel (b). Panel (c) illustrates the randomly generated seed-points and each point constitutes one experiment. (d), (e), (f) and (g) shows different source localization for different proliferation rates. In (d)–(g): right figures show the final source location in red and the initial distribution in yellow; left figures show the tumour distribution at time T in yellow and the tumor boundary in green. (Color figure online)

white and gray matter regions. In (d)–(f), left panels, show the tumors cell densities obtained with the forward model and the initial seed-points depicted in yellow in the right panels. When the tumor density is nearly homogeneous the source localization works well with a minor error as visualized in the right panels. If the tumor source is located close to the boundary Ω it is more difficult to reconstruct as the inverse scheme needs to handle a severely anisotropic growth pattern.

Both Figs. 1 and 2 show experiments of source localization for the Shepp-Logan phantom image and the MRI data image with different source terms and

proliferation rates. In panels (d), (e) of Fig. 1 and panels (d), (e) of Fig. 2, we use a logistic source term $f = \rho u(1 - u)$ for a small proliferation rate $\rho = 0.001$ and a larger one $\rho = 0.01$. Moreover, in panels (f) and (g) of Fig. 1 and panels (f) and (g) of Fig. 2, we did the similar simulations but with an exponential source term $f = \rho u$. For both source terms we obtain an accurate estimate of the tumor (or

density) source.
Table 1 shows the mean L1 pixel distance of 100 seed-points (illustrated in (c), Figs. 1 and 2) between the ground truth seed center location and the estimated tumor source for the Shepp-Logan image and the MRI T1 image. Since we include two source terms, the logistic and the exponential proliferation, this is also a quantitative evaluation for evaluating the robustness of the scheme for different source terms. The parameter ρ determines the influence of the source term and a larger value yields a tumor cell density which is more anisotropic than with smaller values, making the source localization harder. Therefore, it is expected that the error should increase as the value of ρ increases. We also remark that the source of tumors located close to the boundary will be harder to reconstruct as the proposed regularizing procedure needs to handle a severely anisotropic growth pattern.

5 Conclusion

Motivated by the importance of being able to determine the initial location where a brain tumor formed, we have proposed an iterative regularizing procedure for a nonlinear backward parabolic reaction-diffusion model, and applied it for the stable determination of the initial brain tumor cell density. Mathematical analysis of the procedure, such as well-posedness of the forward problems used in the iterations, were undertaken. Numerical experiments were included on the Shepp-Logan phantom as well as an MRI image for various nonlinear terms in the parabolic equation. These initial experiments show that it is possible to retrieve the initial source in a stable way with the proposed procedure, and with accepted accuracy. Future work includes, for example, other source terms and validation against real data.

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