

EXPBrain: Exponential Integrators for Glioblastoma Brain Tumor Simulations

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Abstract. In this paper we discuss a MATLAB implementation of the exponential integrators method employed for simulating of the brain tumor progression. As the input data we utilize publicly available T1-weighted magnetic resonance imaging dataset ds003826, representing healthy individuals. The data from these datasets are originally stored using NIFTI format. We select randomly one anonymized individual from the considered dataset. We normalize the brain scan data using min-max normalization to a range of 0 to 255. In the data from the dataset ds003826 the voxel resolution is not isotropic in all directions, so we interpolate the data from dimensions $176 \times 248 \times 256$ into $194 \times 248 \times 256$ in order to have proper proportions of the human brain. We set the data as a sequence of 256 PNG files with the resolution of 194×248 . Having the MRI scan data, we run the exponential integrators method simulating the glioblastoma tumor growth using the Fisher-Kolmogorov diffusion-reaction model with logistic growth. We assume the initial tumor location and run the simulation predicting two years forward tumor growth. For the spatial discretization we employ the finite difference method, and for the temporal discretization we use the ultra-fast exponential integrators method. Our simulator generates the simulational results suitable for visualization using the ParaView tool.

Keywords: T1-weighted magnetic resonance, MATLAB code, brain tumor simulations, exponential integrators, Fisher-Kolmogorov diffusion-reaction model with logistic growth, ParaView visualization

1 Introduction

In this paper, we present the EXPBrain code that performs simulations of the glioblastoma brain tumor on the patient’s MRI scan data using the exponential integrators method [7]. Glioblastoma is a malignant brain tumor with a high mortality rate [6]. This tumor is highly aggressive, and it generates microvascular proliferation that is not visible on MRI scans [25]. Thus, computer-based

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simulation predictions of the evolution of the brain tumor are essential in planning treatment and surgery. The state-of-the-art three dimensional finite element or finite difference simulators are computationally intense [10, 12, 11, 9], and the Physics Informed Neural Networks simulators can deal well with two-dimensional simulations only [28].

The exponential integrators considered in our code method allows for high-speed and accurate simulations of time-dependent problems. We employ this method to simulate the three-dimensional glioblastoma brain tumor growth. Our exponential integrators method is based on the Fisher-Kolmogorov diffusion-reaction equation with logistic growth [26].

In our research, we utilized publicly T1-weighted magnetic resonance imaging dataset, named *ds003826* [27] which consists of the collected data from 136 healthy individuals. The age of them varies from 18 to 35 years. All the subjects were scanned using a 3T scanner called Magnetom Skyra provided by Siemens [14]. It uses a 20-channel or 64-channel head/neck coil. To obtain the T1-weighted images, an MPRAGE sequence was employed, using 176 sagittal slices with $1 \times 1 \times 1.1$ millimeter cube [mm³] voxel size, with TR = 2300 milisecond [ms] and TE = 2.98 milisecond [ms]. Data from the dataset were originally saved in NIfTI format. For our analysis, one subject was randomly selected from the dataset. The data were then normalized using min-max normalization to a range of 0 to 255, which enabled proper saving in PNG format. In the case of our dataset *ds003826* the voxel resolution was not isotropic in all directions, so it was necessary to interpolate the data from spatial dimensions $176 \times 248 \times 256$ into the spatial dimensions $194 \times 248 \times 256$ in order to maintain the brain proportions consistent with reality. Finally, the randomly selected individual's data was saved as a set of PNG files, with each file corresponding to one axial slice of the brain.

We use the exponential Euler method which is first order and we employ the routine presented in [2] for computing the action of the corresponding φ -functions over the vector. The output from the simulation is stored in the ParaView format for the visualization. We test our code using the 256 slices with resolution of 194×248 each, selecting the initial location of the tumor and simulating two years forward tumor growth prediction. The numerical results show that we can perform 100 iterations over $128 \times 128 \times 128$ computational mesh in less than 5 minutes on a single computing node from Athena computer [3]. Thus, this simulator can be employed "on the fly".

The efficiency comes from the fact that the exponential routines are extremely efficient on operators coming from a semidiscretization in space employing finite differences. Moreover, the exponential time integrators [7, 15, 5] are designed to solve semilinear problems that the one presented in this article. They are suitable for long-time simulations and they are unconditionally stable. The computational model and numerical methods have been already explained with all the details in [16]. In this paper we focus on the MATLAB implementation, its efficiency and limitations.

The structure of the paper is the following. Section 2 explains the motivation for development of the EXPBrain code and its significance. The next Section 3

introduces the finite difference spatial discretization for the Fisher-Kolmogorov brain tumor model. In Section 4, we derive the exponential integrators method for the temporal discretization. The following Section 5 presents a MATLAB code description, including the software architecture, the sample code snippets, and the installation manual. We summarize the paper in Section 6 presenting exemplary numerical experiments. The conclusions are presented in Section 7.

2 Motivation and significance

- The EXPBrain code performs simulations of the glioblastoma brain tumor on the patient’s MRI scan data. Glioblastoma is a malignant brain tumor with a high mortality rate [6]. This tumor is highly aggressive, and it generates microvascular proliferation that is not visible on MRI scans [25]. Thus, computer-based simulation predictions of the evolution of the brain tumor are important in planning treatment and surgery.
- The exponential integrators method allows for very fast and accurate simulations of time-dependent problems. We employ this method to simulate for the first time the brain tumor growth. The mathematical details of the brain tumor model and numerical formulation are described in [16].
- In order to run the brain tumor simulator, the user needs to provide patient-specific MRI scan data, set up the assumed initial location of the brain tumor, run the simulator, and post-process the ParaView output files.
- The Physics Informed Neural Networks originally proposed by Karniadakis [22] instantiated for the brain tumor simulation in [28] can predict the future behavior of the glioblastoma tumor evolution within one hour for the patient-specific case. We employ the exponential time integrators [8, 15, 5] designed to solve semilinear problems. While there are many brain tumor simulation methods, the novelty of our method lies in the novel implementation using the exponential integrators method. From the authors understanding, there is only one work in the literature using the exponential integrators method to simulate the tumor growth [13].

3 Finite differences

The simulation is based on the Fisher-Kolmogorov diffusion-reaction equation with logistic growth,

$$\begin{cases} \frac{\partial u}{\partial t} = \underbrace{\nabla \cdot (D(\mathbf{x}) \nabla u)}_{\text{Tumor cell diffusion}} + \underbrace{\rho u(1-u)}_{\text{Tumor cell proliferation}}, & \text{in } \Omega \times I, \\ \nabla u \cdot \mathbf{n} = 0, & \text{on } \partial\Omega \times I, \\ u(\mathbf{x}, 0) = u_0, & \text{on } \Omega \times \{0\}, \end{cases} \quad (1)$$

where $u(x, y, z; t)$ represents the tumor cell density, $D(x, y, z)$ is the diffusion coefficient estimated for different materials based on the MRI scan data, and ρ is the tumor cells proliferation rate (patient-specific).

We first semi-discretize (1) in space employing finite differences. Namely, we introduce a regular grid with equidistant points in each espatial direction:

$$\{x_{i,j,k} = ((i-1)h, (j-1)h, (k-1)h)\}_{i=1,\dots,N_x; j=1,\dots,N_y; k=1,\dots,N_z}, \quad (2)$$

and we represent the values of the tumor cell densities at these point at time moment t as

$$\{u_{i,j,k}^t = u(x_{i,j,k}; t)\}_{i=1,\dots,N_x; j=1,\dots,N_y; k=1,\dots,N_z}. \quad (3)$$

We discretize the equation at time moment t using finite differences as follows

$$\begin{aligned} \frac{\partial u_{i,j,k}^t}{\partial t} = & \frac{\partial D(x_{i,j,k})}{\partial x_1} \frac{\partial u_{i,j,k}^t}{\partial x_1} + D(x_{i,j,k}) \frac{\partial^2 u_{i,j,k}^t}{\partial x_1^2} + \\ & \frac{\partial D(x_{i,j,k})}{\partial x_2} \frac{\partial u_{i,j,k}^t}{\partial x_2} + D(x_{i,j,k}) \frac{\partial^2 u_{i,j,k}^t}{\partial x_2^2} \\ & \frac{\partial D(x_{i,j,k})}{\partial x_3} \frac{\partial u_{i,j,k}^t}{\partial x_3} + D(x_{i,j,k}) \frac{\partial^2 u_{i,j,k}^t}{\partial x_3^2} + \rho u_{i,j,k}^t (1 - u_{i,j,k}^t), \end{aligned} \quad (4)$$

with

$$\begin{aligned} \frac{\partial u_{i,j,k}^t}{\partial x_1} &= \frac{u_{i+1,j,k}^t - u_{i,j,k}^t}{h}, \\ \frac{\partial u_{i,j,k}^t}{\partial x_2} &= \frac{u_{i,j+1,k}^t - u_{i,j,k}^t}{h}, \\ \frac{\partial u_{i,j,k}^t}{\partial x_3} &= \frac{u_{i,j,k+1}^t - u_{i,j,k}^t}{h}, \\ \frac{\partial^2 u_{i,j,k}^t}{\partial x_1^2} &= \frac{u_{i+1,j,k}^t - 2u_{i,j,k}^t + u_{i-1,j,k}^t}{h^2}, \\ \frac{\partial^2 u_{i,j,k}^t}{\partial x_2^2} &= \frac{u_{i,j+1,k}^t - 2u_{i,j,k}^t + u_{i,j-1,k}^t}{h^2}, \\ \frac{\partial^2 u_{i,j,k}^t}{\partial x_3^2} &= \frac{u_{i,j,k+1}^t - 2u_{i,j,k}^t + u_{i,j,k-1}^t}{h^2}, \end{aligned} \quad (5)$$

and we obtain the following system of semilinear Ordinary Differential Equations

$$\begin{cases} \dot{U}(t) = AU(t) + F(U(t)), & \text{in } I, \\ U(0) = U_0, \end{cases} \quad (6)$$

where $U(t) = \{u_{i,j,k}^t\}_{i=1,\dots,N_x; j=1,\dots,N_y; k=1,\dots,N_z}$ is the time-dependent vector of the degrees of freedom in space. To derive the A operator, we simplify the

derivation, assuming $\frac{\partial D_{i,j,k}}{\partial x_i} = 0$,

$$\begin{aligned} \frac{\partial u_{i,j,k}^t}{\partial t} &= D(x_{i,j,k}) \frac{u_{i+1,j,k}^t - 2u_{i,j,k}^t + u_{i-1,j,k}^t}{h^2} \\ &+ D(x_{i,j,k}) \frac{u_{i,j+1,k}^t - 2u_{i,j,k}^t + u_{i,j-1,k}^t}{h^2} \\ &+ D(x_{i,j,k}) \frac{u_{i,j,k+1}^t - 2u_{i,j,k}^t + u_{i,j,k-1}^t}{h^2} + \rho u_{i,j,k}^t (1 - u_{i,j,k}^t), \end{aligned} \quad (7)$$

and we group the terms

$$\begin{aligned} h^2 \frac{\partial u_{i,j,k}^t}{\partial t} &= -6D(x_{i,j,k}) u_{i,j,k}^t + D(x_{i,j,k}) u_{i-1,j,k}^t \\ &+ D(x_{i,j,k}) u_{i,j-1,k}^t + D(x_{i,j,k}) u_{i,j,k-1}^t \\ &+ D(x_{i,j,k}) u_{i+1,j,k}^t + D(x_{i,j,k}) u_{i,j+1,k}^t \\ &+ D(x_{i,j,k}) u_{i,j,k+1}^t + h^2 \rho u_{i,j,k}^t (1 - u_{i,j,k}^t), \end{aligned} \quad (8)$$

The entries of matrix A are

$$A_{i,j,k;l,m,n} = \begin{cases} -6D(x_{i,j,k}), & (i,j,k) == (l,m,n), \\ D(x_{i-1,j,k}), & (l,m,n) \in \{(i-1,j,k), (i+1,j,k), \\ & (i,j-1,k), (i-1,j+1,k), \\ & (i-1,j,k-1), (i-1,j,k+1)\}, \\ 0, & \text{otherwise.} \end{cases} \quad (9)$$

We employ $\{1, \dots, N_x\} \times \{1, \dots, N_y\} \times \{1, \dots, N_z\} \ni (i,j,k) \rightarrow \text{global}(i,j,k) = i + (j-1)N_y + (j-1)(k-1)N_yN_z$ is the mapping from the integer coordinates into the global rows / columns numbering. The F operator is given by $F(U(t)) = \rho U(t)(1 - U(t))$.

4 Exponential integrators

For the time discretization, we consider a uniform partition of the time interval as

$$0 = t_0 < t_1 < \dots < t_{N-1} < t_N = T, \quad (10)$$

we define $I_n = (t_n, t_{n+1})$ and $\tau = t_{n+1} - t_n$, $\forall n = 0, \dots, N-1$. Let U_n be the numerical approximation to the solution of (6) at t_n , we know that the integral representation of the solution of (6) at t_{n+1} , also known as the *variation-of-constants* formula, reads

$$U_{n+1} = e^{\tau A} U_n + h \int_0^1 e^{(1-\theta)\tau A} F(U(t_n + \tau\theta)) d\theta. \quad (11)$$

Different approximations of the nonlinear term in (11) lead to different exponential time integration methods [8]. All these methods are expressed in terms of the so-called φ -functions defined as

$$\begin{cases} \varphi_0(z) = e^z, \\ \varphi_p(z) = \int_0^1 e^{(1-\theta)z} \frac{\theta^{p-1}}{(p-1)!} d\theta, \quad \forall p \geq 1, \end{cases} \quad (12)$$

which satisfy the following recurrence relation

$$\varphi_{p+1}(z) = \frac{1}{z} \left(\varphi_p(z) - \frac{1}{p!} \right). \quad (13)$$

Here, we will focus on the simplest exponential integrator method, the *Exponential Euler* method, which is first order in time. For higher-order methods we refer to [8, 15]. For that, we approximate in (11) the non-linear term with its value at t_n that it is known, i.e., $F(U(t_n + \tau\theta)) \approx F(U_n)$. Integrating exactly in (11), we obtain

$$U_{n+1} = \varphi_0(\tau A)U_n + \tau \varphi_1(\tau A)F(U_n). \quad (14)$$

which is given in terms of the φ -functions (12). Finally, employing the recurrence formula (13), we rewrite (14) as

$$U_{n+1} = U_n + \tau \varphi_1(\tau A)(F(U_n) + \tau A U_n). \quad (15)$$

For the numerical results, we employ the *MATLAB* routines from [?] for computing the action of φ -functions over vectors. In this routine the authors employ the scaling and squaring method together with a truncated Taylor series approximation to the exponential of a matrix. As we show in the numerical results, this routine applied to operator τA coming from finite difference semidiscretization in space is extremely efficient. Moreover, exponential integrators are suitable for long-time simulations as they are unconditionally stable.

Thus, in the exponential integrators method we compute the sequence

$$\begin{aligned} U_1 &= U_0 + \tau \int_0^1 e^{(1-\theta)(\tau A)} d\theta (\rho U_0(1 - U_0) + \tau A U_0), \\ U_2 &= U_1 + \tau \int_0^1 e^{(1-\theta)(\tau A)} d\theta (\rho U_1(1 - U_1) + \tau A U_1), \\ &\dots \\ U_{n+1} &= U_n + \tau \int_0^1 e^{(1-\theta)(\tau A)} d\theta (\rho U_n(1 - U_n) + \tau A U_n). \end{aligned} \quad (16)$$

5 Software description

The EXPBrain code runs the exponential integrator simulations of the glioblastoma tumor growth within the 3D domain. The code parameters are described

in Table 1. The dimensions of the domain $x2 - x1, y2 - y1, z2 - z1$ [mm] define the human head size. It allows simulation to be performed within a prescribed time interval, starting from $t0$ and ending at the final time moment T . It assumes initial brain tumor location at point xic, yic, zic [mm]. The exponential integrators simulation in time is based on the finite difference approximation in space using the computational mesh with $nelx, nely, nelz$ elements.

The simulation is performed within the human head model based on MRI scan data loaded into the directory `brain_scan` out `_*.png`.

The simulation output is a sequence of ParaView files generated into the directory `paraview_files` tumor `_*.vti`.

Parameter	Description
$\rho = 0.025$;	tumor proliferation rate
$x1 = 0; y1 = 0; z1 = 0$;	left-front-bottom domain corner
$x2 = 193; y2 = 193; z2 = 193$;	right-rear-top domain corner
$t0 = 150$;	initial time moment
$T = 750$;	final time moment
$steps=100$;	number of time steps
$\tau = (T - t0)/steps$;	time step size
$xic = 102; yic = 138; zic = 96$;	initial location of tumor
$nelx = 32; nely = 32; nelz = 32$;	number of mesh elements
hx, hy, hz	element diameters
$hx2, hy2, hz2$	element diameters squared
$nx = nelx + 1; ny = nely + 1; nz = nelz + 1$;	number of grid points

Table 1: Code parameters

5.1 Software architecture

The software metadata are summarized in Table 2. The primary executable is `Tumor_growth_3D.m` file. First, in the *Initializing* step, it initializes the simulation parameters as described in Table 1.

Next, the *Reading MRI scan* step calls the `get_diffusion3d(nx,ny,nz)` routine that reads the MRI scan data and sets the diffusion coefficient for white matter, gray matter, cerebrospinal fluid, air, and bones. The routine assumes that the MRI scan provides 256 bitmaps of 194×248 pixels (this step can be adjusted to another MRI scan resolution in the routine if needed).

The *Generating finite difference matrix* step constructs a finite difference discretization in space with nx, ny, nz elements. The finite difference matrix A is created. The initial tumor configuration is set up with $xc, yc, and zc$ coordinates.

Next, we are *Setting up exponential integrators* method, deciding on the number of time *steps*, and their time length *tau*.

The *Computing exponential integrators* step runs the numerical simulation, followed by dumping out the ParaView files in `write_solution_to_files` routine,

Nr.	Code metadata description	Please fill in this column
C1	Current code version	v1
C2	Permanent link to code/repository used for this code version	https://github.com/Magdamini/EXPBrain
C4	Legal Code License	GNU General Public License (GPL)
C5	Code versioning system used	git
C6	Software code languages, tools, and services used	Matlab, ParaView.
C7	Compilation requirements, operating environments & dependencies	Matlab, https://github.com/higham/expmv/expmv.m , normAm.m, select_taylor_degree.m, select_taylor_degree.m, theta_taylor.mat, theta_taylor_half.mat, theta_taylor_single.mat
C9	Support email for questions	maciej.paszynski@agh.edu.pl

Table 2: Code metadata

5.2 Sample code snippets analysis

The simulation starts from the initially assumed configuration $u_0(x, y, z)$ of the brain tumor cells. It generates a sequence of ParaView files, allowing for the generation of a sequence of pictures or a movie from the simulation.

The spatial discretization involves finite difference method

```

for i = 2:nx-1
    for j = 2:ny-1
        for k = 2:nz-1
            l = i + (j-1)*nx + (k-1)*nx*ny;
            values(idx) = (diff(i+1,j,k)-diff(i,j,k))/
                hx2
                + 2.0 * diff(i,j,k)/hx2
                + (diff(i,j+1,k)-diff(i,j,k))/hy2
                + 2.0 * diff(i,j,k)/hy2
                + (diff(i,j,k+1)-diff(i,j,k))/hz2
                + 2.0 * diff(i,j,k)/hz2;
            row_idx(idx) = 1; col_idx(idx) = 1;
            values(idx + 1) = - diff(i,j,k)/hx2;
            row_idx(idx + 1) = 1; col_idx(idx + 1) = 1
                -1;
            values(idx + 2) =
                (- diff(i+1,j,k)+diff(i,j,k))/hx2
                - diff(i,j,k)/hx2;
            row_idx(idx + 2) = 1; col_idx(idx + 2) = 1
                +1;
            values(idx + 3) = - diff(i,j,k)/hy2;

```



```

        row_idx(idx + 3) = 1; col_idx(idx + 3) = 1
        -nx;
        values(idx + 4) = (-diff(i,j+1,k)+diff(i,j
        ,k))/hy2
        - diff(i,j,k)/hy2;
        row_idx(idx + 4) = 1; col_idx(idx + 4) = 1
        +nx;
        values(idx + 5) = - diff(i,j,k)/hz2;
        row_idx(idx + 5) = 1; col_idx(idx + 5) = 1
        -nx*ny;
        values(idx + 6) =
        ( -diff(i,j,k+1)+diff(i,j,k))/hz2
        - diff(i,j,k)/hz2;
        row_idx(idx + 6) = 1; col_idx(idx + 6) = 1
        +nx*ny;
        idx = idx + 7;
    end
end
end
% Create the sparse matrix A
A = sparse(row_idx(1:idx-1), col_idx(1:idx-1),
        values(1:idx-1), nx*ny*nz, nx*ny*nz);

```

The exponential integrators simulation is very elegant

```

%Time grid and step size
fprintf("Setting up exponential integrators...\n");
steps = 100;
tau = (T-t0)/steps;
t = t0:tau:T;

%Exponential Euler method
fprintf("Computing exponential integrators...\n");

U = zeros(dimx,steps+1);
U(:,1) = U0;
for i = 1:steps
    Fu = rho*U(:,i).*(1-U(:,i));
    U(:,i+1) = U(:,i)+tau*phiB(-tau*A,Fu-A*U(:,i));
    show_progress(i, steps);
end
write_solution_to_files;

```

it involves phiB routine from <https://github.com/higham/expmv> library, performing fast exponential integrators operations.

5.3 Code installation and usage

The code can be downloaded from repository
<https://github.com/Magdamini/EXPBrain>

The code is available under GNU General Public License (GPL).

The code is implemented in Matlab and it uses a ParaView for visualizations. It requires Matlab and the following libraries (included in the github repository)

```
https://github.com/higham/expmv/expmv.m,
https://github.com/higham/expmv/normAm.m,
https://github.com/higham/expmv/select_taylor_degree.m,
https://github.com/higham/expmv/select_taylor_degree.m,
https://github.com/higham/expmv/theta_taylor.mat,
https://github.com/higham/expmv/theta_taylor_half.mat,
https://github.com/higham/expmv/theta_taylor_single.mat
```

6 Illustrative examples

After running the computations, the code generates a sequence of *.vti files [23]. To visualize computed data, open the ParaView application [1, 4]. Then click “Open” from the “File” menu in the upper left corner. Choose the file brain.vti. It should be in the paraview_files directory. Once the file is selected, click on the “OK” button in the dialog box. To display the data, in the “Properties” tab, click the green “Apply” button and set the representation to “Volume”. After this step, the brain image should be visible on the screen. Then, repeat the above instructions to open files containing tumor data. While opening those files, Paraview should see them as a group of files named tumor_*.vti and open them all at once. After setting up those files, choose the brain.vti file in the “Pipeline Browser”. Then focus on the right tab, named “Color Map Editor”. Find the bar “Select a color map from default presets” or the small icon with a heart and choose one of the proposed color maps. Use the slider to decrease the opacity. Now, both tumor and brain data should be visible on the screen. Use the mouse to rotate the image. To display (or hide) the scale, select the chosen object and click on the colorful “Toggle Color Legend Visibility” icon located in the upper left corner. To start the animation, choose the tumor_1.vti file, and on the right bar, set the “Automatic Rescale Range Mode” on “Grow and update every timestep”. Then click the play button in the top part of the window. The tumor image can also be seen at a particular time. To visualize it, change the time option next to the play button and adjust the scale by clicking the “Rescale to Data Range” button.

The exemplary MRI scan data files, are presented in Figure 1. There are 256 scans with a resolution of 194×248 pixels. Running the EXPBrain code starting from $t_0 = 150$ for 100-time steps until time moment $T = 750$, using $128 \times 128 \times 128$ finite difference mesh with the initial location of tumor defined as $x_{ic} = 102$; $y_{ic} = 138$; $z_{ic} = 96$; results in a sequence of output ParaView files illustrated in Figures 2-3. The exponential integrators simulation takes 287 [s] = less than 5 minutes on a single node from Athena supercomputer [3]. It predicts two years forward of the tumor evolution.

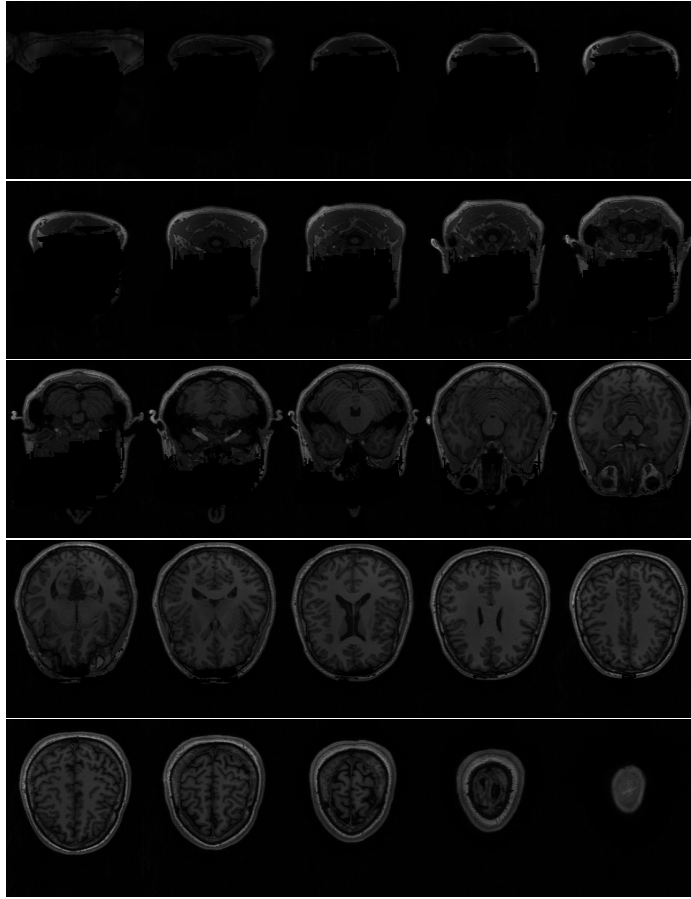


Fig. 1: MRI scans of the human head.

7 Conclusions

- The EXPBrain code performs ultra-fast simulations of the glioblastoma brain tumor on the patient's MRI scan data. It can predict two years of future brain tumor growth within 5 minute on a single computing node, including the output ParaView files generation. Alternative highly efficient simulators using finite difference or finite element method for the tumor growth simulations take several minutes to compute a single time step [10, 12, 11, 9]. The efficiency of our method comes from the fact that the exponential routines are extremely efficient on operators coming from a semi discretization in space employing finite differences.
- Fast tumor growth simulators are important for patient-specific modeling. Tumor growth models include several patient-specific parameters, and data assimilation techniques fitting model parameters to patient-specific data re-

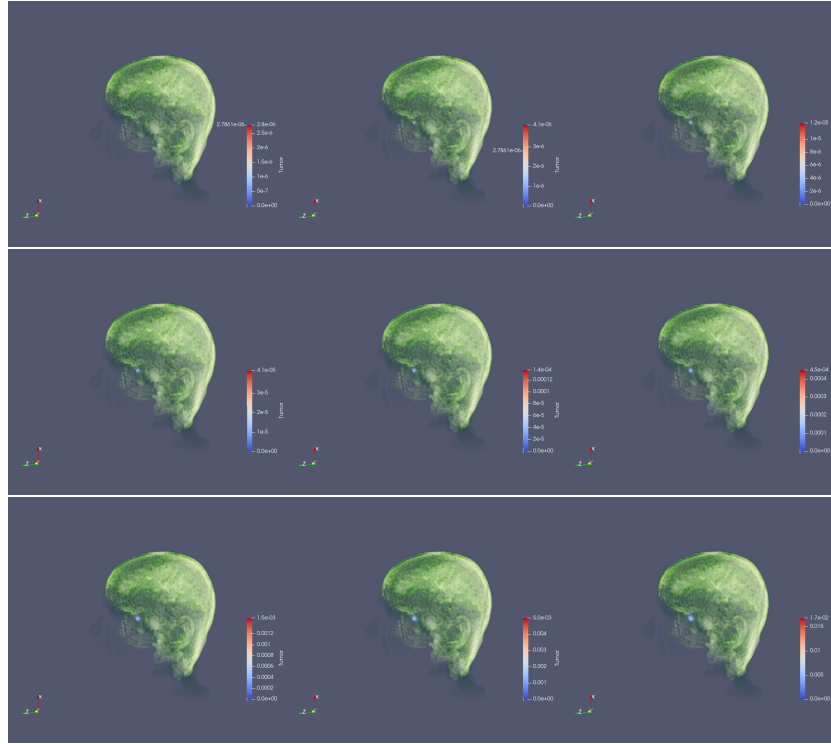


Fig. 2: Glioblastoma brain tumor simulation with exponential integrators method.

quire several runs of the simulator [21, 24]. The EXPBrain simulator can be employed in data assimilation algorithms [21, 24] to assimilate the model parameters, such as the diffusion coefficient D specific for each kind of tissue (describing how the tumor cells expand in a tissue, similarly to the diffusion phenomena), and the proliferation rate of the tumor cells ρ (how fast they multiply).

- The EXPBrain simulator may allow medical doctors to predict the future progression of the brain tumor cells one year in the future.
- The future work may involve development of the adaptive version of the exponential integrators software [17, 18, 20, 19].

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2. A. H. Al-Mohy and N. J. Higham. Computing the action of the matrix exponential, with an application to exponential integrators. *SIAM Journal on Scientific Computing*, 33(2):488–511, 2011.
3. Athena supercomputer <https://www.cyfronet.pl/en/19073,artykul,athena.html> (accessed on December 20, 2024)
4. Utkarsh Ayachit, *The ParaView Guide: A Parallel Visualization Application*, Kitware, 2015
5. Matteo Croci, Judit Muñoz-Matute, Exploiting Kronecker structure in exponential integrators: Fast approximation of the action of ϕ -functions of matrices via quadrature, *Journal of Computational Science*, 67 (2023) 101966.
6. Caroline Hertler, Jörg Felsberg, Dorothee Gramatzki, Emilie Le Rhun, Jennifer Clarke, Riccardo Soffietti, Wolfgang Wick, Olivier Chinot, François Ducray, Patrick Roth, Kerrie McDonald, Peter Hau, Andreas F. Hottinger, Jaap Reijneveld, Oliver Schnell, Christine Marosi, Michael Glantz, Amélie Darlix, Giuseppe Lombardi, Dietmar Krex, Martin Glas, David A. Reardon, Martin van den Bent, Florence Lefranc, Ulrich Herrlinger, Evangelia Razis, Antoine F. Carpentier, Samuel Phillips, Roberta Rudà, Antje Wick, Emeline Tabouret, David Meyronet, Claude-Alain Maurage, Elisabeth Rushing, Robert Rapkins, Elisabeth Bumes, Monika Hegi, Astrid Weyerbrock, Dawit Aregawi, Christian Gonzalez-Gomez, Alessia Pellerino, Martin Klein, Matthias Preusser, Martin Bendszus, Vassilis Goufopoulos, Andreas von Deimling, Thierry Gorlia, Patrick Y. Wen, Guido Reifenberger, Michael Weller, Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY Brain Tumor Funders' Collaborative Consortium (EORTC 1419), *European Journal of Cancer Research*, 189 (2023) 112913
7. M. Hochbruck and A. Ostermann. Explicit exponential Runge–Kutta methods for semilinear parabolic problems. *SIAM Journal on Numerical Analysis*, 43(3):1069–1090, 2005
8. Marlis Hochbruck, Alexander Ostermann, Exponential integrators, *Acta Numerica*, 19 (2010) 209–286.
9. Adrian Kłusek, Marcin Łoś, Maciej Paszyński, Witold Dzwinel, Efficient model of tumor dynamics simulated in multi-GPU environment, *The International Journal of High Performance Computing Applications*, 33(3) (2019) 489–506.
10. Jana Lipková, Panagiotis Angelikopoulos, Stephen Wu, Esther Alberts, Benedikt Wiestler, Christian Diehl, Christine Preibisch, Thomas Pyka, Stephanie Elisabeth Combs, Panagiotis E. Hadjidakas, Koen Van Leemput, Petros Koumoutsakos, John S. Lowengrub, Bjoern H Menze, Personalized Radiotherapy Design for Glioblastoma: Integrating Mathematical Tumor Models, Multimodal Scans, and Bayesian Inference, *IEEE Transactions on Medical Imaging*, 38 (2018) 1875–1884
11. Marcin Łoś, Adrian Kłusek, Muhammad Amber Hassaan, Keshav Pingali, Witold Dzwinel, Maciej Paszyński, Parallel fast isogeometric L2 projection solver with GALOIS system for 3D tumor growth simulations, *Computer Methods in Applied Mechanics and Engineering*, 341 (2019) 1–22.
12. Marcin Łoś, Maciej Paszyński, Adrian Kłusek, Witold Dzwinel, Application of fast isogeometric L2 projection solver for tumor growth simulations, *Computer Methods in Applied Mechanics and Engineering, Special Issue on Isogeometric Analysis: Progress and Challenges*, 316 (2017) 1257–1269.
13. Lucia Maddalena, Stefania Ragni, Existence of solutions and numerical approximation of a non-local tumor growth model, *Mathematical Medicine and Biology: A Journal of the IMA*, 37(1) (2020) 58–82

14. MAGNETOM Skyra 3T MRI scanner <https://www.siemens-healthineers.com/pl/magnetic-resonance-imaging/3t-mri-scanner/magnetom-skyra> (accessed on December 20, 2024)
15. Judit Muñoz-Matute, Leszek Demkowicz, Multistage DPG time-marching scheme for nonlinear problems, *arXiv:2309.00069* (2023)
16. Magdalena Pabisz, Judit Muñoz-Matute, Maciej Paszyński, Augmenting MRI scan data with real-time predictions of glioblastoma brain tumor evolution using faster exponential time integrators, *Journal of Computational Science*, 85 (2025) 102493.
17. Anna Paszyńska, Maciej Paszyński, Konrad Jopek, M Woźniak, Damian Goik, Piotr Gurgul, Hassan AbouEisha, Mikhail Moshkov, Victor Manuel Calo, Andrew Lenharth, Donald Nguyen, Keshav Pingali, Quasi-Optimal Elimination Trees for 2D Grids with Singularities, *Scientific Programming*, 1 (2015) 303024
18. Anna Paszyńska, Maciej Paszyński, Ewa Grabska, Graph Transformations for Modeling hp-Adaptive Finite Element Method with Triangular Elements Lecture Notes in Computer Science, 5103 (2008) 604-613.
19. Damin Goik, Konrad Jopek, Maciej Paszyński, Andrew Lenharth, Donald Nguyen, Keshav Pingali, Graph grammar based multi-thread multi-frontal direct solver with Galois scheduler *Procedia Computer Science* 29 (2014) 960-969
20. Maciej Paszyński, Anna Paszyńska, Graph Transformations for Modeling Parallel hp-Adaptive Finite Element Method, *Parallel Processing and Applied Mathematics: 7th International Conference, PPAM 2007, Gdańsk, Poland, September 9-12 (2007)* 1313-1322.
21. Maciej Paszyński, Leszek Siwik, Witold Dzwiniel, Keshav Pingali, Supermodeling, a convergent data assimilation meta-procedure used in simulation of tumor progression, *Computers & Mathematics with Applications*, 113 (2022) 214-224.
22. Maziar Raissi, Paris Perdikaris, George E. Karniadakis, Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations, *Journal of Computational physics*, 378 (2019) 686-707.
23. Will Schroeder, Ken Martin, Bill Lorensen, *The Visualization Toolkit* (4th ed.) Kitware (2006).
24. Leszek Siwik, Marcin Łoś, Adrian Klusek, Anna Paszyńska, Keshav Pingali, Witold Dzwiniel, Maciej Paszyński, Tuning three-dimensional tumor progression simulations on a cluster of GPGPUs, *Journal of Computational and Applied Mathematics*, 412 (2022) 114308.
25. R. Stupp, M. Brada, M. J. van den Bent, J. C. Tonn, G. Pentheroudakis, High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, *Annals of Oncology*, 25 (2014) 93-101.
26. K. R. Swanson, E. C. Alvord Jr, and J. D. Murray. A quantitative model for differential motility of gliomas in grey and white matter. *Cell Proliferation*, 33(5):317-329, 2000.
27. Zareba, M. R., Fafrowicz, M., Marek, T., Beldzik, E., Oginska, H., Domagalik, A. (2022). Late chronotype is linked to greater cortical thickness in the left fusiform and entorhinal gyri. *Biological Rhythm Research*, 53(10), 1626-1638.
28. Andy Zhu, Accelerating Parameter Inference in Diffusion-Reaction Models of Glioblastoma Using Physics-Informed Neural Networks, *SIAM Undergraduate Resources Online*, (2022)