EXECUTIVE SUMMARY OF THE THESIS

A Reduced Order Model of Glioblastoma Growth and its Neuroimaging-informed Estimation of Patient-Specific Parameters

LAUREA MAGISTRALE IN MATHEMATICAL ENGINEERING - INGEGNERIA MATEMATICA

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1. Introduction

Glioblastoma multiforme (GBM) is one of the most complex and deadly types of brain cancer. In addition to the typical characteristics of cancer (e.g., uncontrolled cellular proliferation, intense resistance to apoptosis, and rife genomic instability), GBM has a high invasive potential and grows along white matter fibres or vessels, imitating the physical structures of the brain extracellular environment. The resulting diffuse infiltration and the inability of many conventional drugs to penetrate the blood-brain barrier make GBM particularly aggressive and difficult to treat: even after extensive surgery and therapies, the median patient survival does not exceed 10 to 16 months and the five-year survival rate is approximately 5%. For this reason, mathematical models able to describe its proliferation are of fundamental importance. Indeed, they represent an in *in silico* counterpart of the patient, which can be used to predict the evolution of the disease and the effects of treatments.

To describe the tumour spreading, in this work, we have coupled a Cahn-Hilliard type equation , added with a growth term and coupled with a reaction-diffusion equation describing its nutriment behaviour [1]. This lead to a highly non-linear PDE system that takes a non-trivial computational effort if we want to solve the problem over a realistic 3D domain.

This can be a huge issue if we consider in addition that the tumour development, and consequently the parameter of the model are strongly patient-specific. So without further elaboration, the usefulness of the model itself remains limited for clinical applications.

To overcome this computational bottlneck, we use Proper Orthogonal Decomposition (POD) to reduce the computational complexity. In a nutshell, the idea of this method is to build up from the model, here the Full Order Model (FOM), a reduced version, the Reduced Order Model (ROM), that keeps all the most relevant information needed to describe the evolution of the tumour over time. Indeed, it is possible to properly construct a basis of much fewer elements than the one of the FOM and still reconstruct the solution,in the following referred to as *snapshot*, approximately well.

This simplification is of primary importance especially for performing parameters estimation from patient-specific data. Indeed many optimization algorithms and other mathematical methods need the solution to be computed mul-

tiple times in order to retrieve the optimal parameters.

Here, we exploit artificial neural networks to provide the required results in a negligible time once the networks are sufficiently trained. Both the problem of finding the coefficient of the ROM solution at each time-step and the following parameter estimation from acouple of snapshots retrieved from Magnetic Resonance Imaging (MRI) are mapped through a neural network.

The computational effort of the simulations, which can start as soon as we get information on the actual status of the patient and which includes enough simulation to train the neural networks, is balanced by the rapidity of a patient-specific prediction once we collect a second information on the evolution of the tumour growth. For this reason, the method presented in this work makes it possible in a realistic case to predict the future growth of the tumour making the therapy more effective.

2. A diffuse interface model of GBM growth

In this work, we assume that the brain tissue can be assimilated as a mixture of a cellular phase, representing the tumour, and a liquid phase, which describes the health host tissue. According to mixture theory, the space in a mixture may be co-occupied at every location by its components, each of which can be seen as a continuum in its own right [3]. So, at each point, we can define the spatial concentration of each constituent, i.e. the volume fraction of the tumour $\phi_c(\mathbf{x}, t)$ and the volume fraction of the healthy tissue $\phi_l(\mathbf{x}, t)$. We assume that the mixture is fully saturated, so that $\phi_c + \phi_l = 1$ at each point of the mixture and at any time $t \in [0, T]$. From this, it is possible to define a new variable $\phi := \phi_c - \phi_l$ that assumes value 1 where there are only tumour cells and -1 on completely healthy areas.

The resulting system of partial differential equations describing the dynamics of GBM growth is composed of a Cahn-Hilliard equation and a reaction-diffusion equation for the nutrient concentration n [5]:

$$
\begin{cases}
\dfrac{\partial \phi}{\partial t} = \nabla \cdot \left(\dfrac{1}{M_0} \mathsf{T} \nabla \mu \right) + \nu (n - \delta) h(\phi), & \text{(1a)} \\[2ex]
\mu = \kappa \Psi'(\phi) - \epsilon^2 \Delta \phi, & \text{(1b)} \\[2ex]
\dfrac{\partial n}{\partial t} = S_n \left(1 - \dfrac{n}{n_s} \right) \dfrac{n_s}{3}(2 - \phi) & \text{(1c)} \\[1ex]
\quad + \nabla \cdot (\mathsf{D} \nabla n) - \delta_n n h(\phi). &
\end{cases}
$$

In these equations, the auxiliary variable μ represents the chemical potential while the parameters are: the tumour cells proliferation rate ν, the tumour inter-phase friction M_0, the brain Young modulus κ, the diffuse interface thickness ϵ, the oxygen concentration in vessels n_s, the hypoxia threshold δ, the oxygen consumption rate δ_n and the oxygen supply rate S_n. Furthermore, T denotes the preferential mobility tensor that takes into account the spatial anisotropy in the diffusion of tumour cells, while D is the diffusivity tensor of the nutrient that embodies the preferential direction for oxygen diffusion. Finally, $\Psi(\phi)$ is the cell-cell interaction potential, a function with a double-well shape, such that its minima are attained in $\phi = 1$ and $\phi = -1$, corresponding to the two pure phases. A simple admissible choice is given by $\Psi(\phi) = \frac{1}{4}(1 - \phi^2)^2$. Eventually, is a function that should turn off tumour cell proliferation when $\phi = -1$, i.e. where the tumour concentration vanishes. A possible choice for h is given by $h(\phi) = \max(\min(1, \frac{1}{2}(1 + \phi)), 0)$. Homogeneous Neumann boundary condition are imposed for each physical variable.

3. Reduced Order Model via Proper Orthogonal Decomposition

In this section, we focus on a possible reduction of the Full Order Model that is required for improving computational time efficiency. Starting from the system Eq. (1), we perform a Proper Orthogonal Decomposition (POD). The construction of a basis for the final reduced-order space consists of two similar phases. We first perform a Singular Value Decomposition (SVD) over the snapshot matrix associated with the variable $f = \{\phi, \mu, n\}$ associated with a particular choice of the parameters $\mathcal{P}_k = [\nu_k, M_{0l}, \kappa_k, \delta_k, \delta_{nk}, S_{nk}]$. The matrix columns are the nodal values of the solution at a

specific time-step $F_f^1 = [f_k^0, ..., f_k^N]$, where $N+1$ is the number of time-steps. From this, we obtain a basis $\left\{\xi_{kl}^f\right\}_{l=1,...,N_{\text{POD}}^k}$ from each set of parameters $\mathcal{P}_k$, where N_{POD^k} is chosen such that information that the POD basis should cover, indicated as $ic \in (0,1]$, is about $ic = 0.95$ for each variable. Until this point, the bases contain most of the information on the evolution of the tumour through time for a singular set of parameters each. Then, we perform another SVD, this time starting from the matrix collecting the M bases obtained in the previous step, i.e.

$$F_f^2 = \left[\xi_{11}^f, ..., \xi_{1N_{\text{POD}}^1}^f, ..., \xi_{M1}^f, ..., \xi_{MN_{\text{POD}}^M}^f\right].$$

The final result is a basis $\left\{\xi_l^f\right\}_{l=1,...,N_{\text{POD}}}$ of the reduced-order space for each variable $f = \{\phi, \mu, n\}$. N_{POD} is chosen such that information that the POD basis should cover $ic \in (0,1]$ is about $ic = 0.95$ for each variable.

To sum up, the steps that we perform for each phase are [2]:

- prescribe the amount of required information that the POD basis should cover $ic \in (0,1]$;
- compute the trace $tr(F_f^t F_f)$ of the correlation matrix $F_f^t F_f = (f^m, f^l)_{ml}$;
- evaluate the pair eigenvalues-eigenvectors $\{\lambda_{fi}, \nu_f^i\}_{i=1,...,N_f^{\text{POD}}}$ of $F_f^t F_f$;
- $N_f^{\text{POD}} = \min\left\{m, \left(\sum_{i \leq m} \lambda_i\right)/tr(F^t F) \leq ic\right\}$, that is the number of elements in the basis, is set;
- $N^{\text{POD}} = \max\left\{N_\phi^{\text{POD}}, N_\mu^{\text{POD}}, N_n^{\text{POD}}\right\}$
- set $\xi_s^f = \frac{1}{\sqrt{\lambda_{fs}}} \sum_j (\nu_f^s)_j f^j$ where $(1 \leq s \leq N^{\text{POD}})$.

Physical variables can be written as:
$$\phi_h^t = \sum_{i=1}^{N_{\text{POD}}} a_{\phi i}^t \xi_i^\phi, \quad \mu_h^t = \sum_{i=1}^{N_{\text{POD}}} a_{\mu i}^t \xi_i^\mu, \quad n_h^t = \sum_{i=1}^{N_{\text{POD}}} a_{ni}^t \xi_i^n.$$

To construct a Reduced Order Model the projection of the non-linear operators is required. When a general non-linearity is present, the cost to evaluate the projected nonlinear function still depends on the dimension of the original system, resulting in simulation times that hardly improve over the original system. A possible approach to overcome this issue is the usage of a greedy algorithm using DEIM interpolation. In this work, an alternative approach, exploiting neural networks is preferred in order to reduce the computational cost significantly.

Indeed, the reduction of the problem to a few degrees of freedom, equal to the dimensionality of the reduced space N_{POD} and corresponding to the coefficient of the ROM basis, makes it possible to train a simple neural network which maps the parameters space onto the space of the ROM coefficients.

4. Surrogate of POD with the usage of Neural Network

As introduced in the previous section, we rely on a Neural Network for solving the ROM [4]. Indeed, given a set of parameters $\mathcal{P} = [\nu, M_0, \kappa, \delta, \delta_n, S_n]$ of cardinality $N_\mathcal{P}$, in addition with a temporal step t, we train the neural network $\mathbf{NN}_\phi : \mathbb{R}^{N_\mathcal{P}+1} \to \mathbb{R}^{N_{\text{POD}}}$ to compute the coefficients $\{a_{\phi i}^t\} \in \mathbb{R}^{N_{\text{POD}}}$ for the ROM basis of the tumor concentration variable ϕ. Thus, $\mathbf{NN}_\phi$ is an approximation of the function that map points $[\nu, M_0, \kappa, \delta, \delta_n, S_n, t]$, that correspond to a tumour distribution at a given instant t, to the space of coefficients $\{a_{\phi i}^t\}_{i=1,...,N_{\text{POD}}}$ of the projected solution in the ROM space at the same time instant. We choose not to make ϵ vary since it related to the thickness of the diffusive interface that is fixed *a priori*, while the tensors T and D are extracted from the used imaging technique. For training the neural network we draw parameters out of the biological range exhibited in Tab. 1. For all the cases we exhibit, we choose the weighted sum as the propagation function, the LeakyReLU as the activation function and just the identity for the output function. Moreover, the loss function used is the mean squared error $\mathbf{e}$. The minimization algorithm is L-BFGS. To obtain adequate accuracy the training is performed on a data set of $N_{\text{Data}} = 45000$ input-output pair, comprehensive of 750 set parameters, that is split into a train set with $N_{\text{Train}} = 33000$ elements and a test set with $N_{\text{Test}} = 12000$ elements. Each simulation comprises 60 temporal steps, each of them representing 0.5 days. The absolute mean square error obtained during the training phase is shown in Fig. 1a. Once the Reduced Order Model is properly set, it is possible to obtain a virtual solution from a factitious set of parameters via $\mathbf{NN}_\phi$ in a negligible amount of time (see Tab. 2).

	Parameter description	Range of values
M_0	Tumour inter-phase friction	$1377.9 - 5032.2 \ \frac{\text{(Pa day)}}{\text{mm}^2}$
ν	Tumour cells proliferation rate	$0.012 - 0.5 \ \text{day}^{-1}$
S_n	Oxygen supply rate	$10^3 - 10^5 \ \text{day}^{-1}$
δ_n	Oxygen consumption rate	$10^3 - 10^5 \ \text{day}^{-1}$
κ	Brain Young modulus	$106.66 - 1533.3 \ \text{Pa}$
δ	Hypoxia threshold	$0.1 - 0.33$

Table 1: Biological range found in literature for the parameters of the model.

Simulation	Elapsed time
Full Order Model	920 s
Reduced Order Model	5190 s
ROM - Neural Network	5 s

Table 2: Computational time for the different used techniques.

5.   Parameters Estimation

A proper construction of a Reduced Order Model is of primary importance when we want to perform an estimation of patient-specific parameters. The reduction of the degrees of freedom is, in fact, essential to the construction of a second simple neural network that allows predicting the parameters from a pair of snapshots distant in time. By simulating various scenarios, we can build up a dataset for the inverse problem (the estimation of the parameters) that is big enough. The trained neural network is a map $\mathbf{NN}_{\text{inv}} : \mathbb{R}^{2N^{\text{POD}}} \rightarrow \mathbb{R}^{N_{\mathcal{P}}}$ that goes from a couple of snapshots, identified with their projection coefficients, to a set of parameters, i.e. $(\nu, M_0, \kappa, \delta, \delta_n, S_n) = \mathbf{NN}_{\text{inv}} \left(a_{\phi 1}^{t_0}, ..., a_{\phi N_{\text{POD}}}^{t_0}, a_{\phi 1}^{t_1}, ..., a_{\phi N_{\text{POD}}}^{t_1} \right)$ where $(t_0, t_1) \in [0, T]$. Instant t_1 and t_0 represent the time interval that elapses from the first and the second MRI. The mean square error over epochs obtained in the training phase is shown in Fig. 1b. Rearranging the data set used for the training of reducing map $\mathbf{NN}_\phi$, we obtain $N_{\text{Data}} = 15000$ input-output pair, that is split into a train set with $N_{\text{Train}} = 11000$ elements and a test set with $N_{\text{Test}} = 4000$ elements.

6.   Numerical Results

This section is devoted to the presentation of the numerical results in a realistic geometry. We compute numerical simulations over a re-
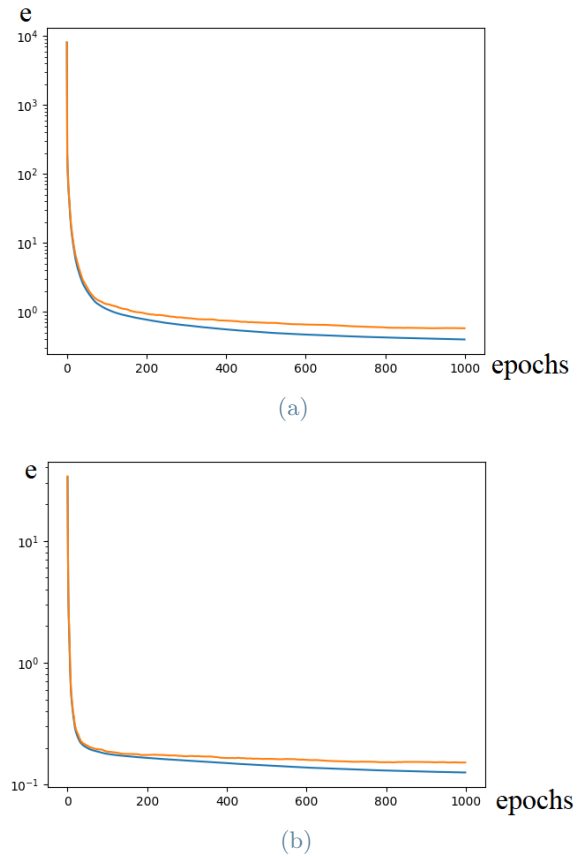

(a)

(b)

Figure 1: Mean square error **e** over the epochs in the training of the neural network $\mathbf{NN}_\phi$ (a) and of the neural network $\mathbf{NN}_{\text{inv}}$ (b). The error over the train set is coloured in blue while the error over the test set is coloured in orange. The error for the neural network $\mathbf{NN}_{\text{inv}}$ is computed from a normalized values for parameters upon the chosen biological range.

alistic brain-shaped mesh with 32293 vertices and 196778 tetrahedral elements. A sagittal section of brain mesh is represented in Fig. 2. This domain represents a real clinical case obtained via MRI. A refinement of the mesh is performed in the neighbourhood of the tumour initial placement. For each simulation, a piecewise linear basis function is chosen, so that the degrees of freedom of the solution correspond to the number of vertices. The overall implementation framework exploits the functionalities given by the platform `FEniCSx`, a popular open-source environment for solving partial differential equations. The implementation of the used code heavily relies on two of its components: `Dolfinx`, a C++/Python library providing data structures and algorithms for finite element meshes, automated finite element assembly, and numerical linear algebra, and Uni-

fied Form Language `UFL` which is a domain-specific language for declaration of finite element discretizations of variational forms. The construction of the ROM basis is obtained through `RBniCSx`, a library useful to implement reduced-order modelling techniques.

All codes are parallelized and the time specifics showed in Tab. 2 rely on a multi-thread CPU with 20 cores. Supposing a patient is related to
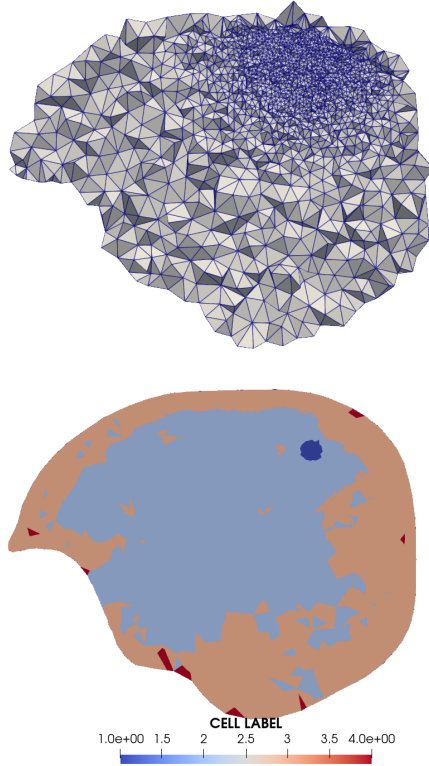

Figure 2: Sagittal section of the brain refined geometrical mesh. On the top, a view of the refinement applied in the neighbourhood of the tumour placement. At the bottom, the mesh labelled according to the different occupation zones. The area in blue (1.0) is that occupied by the tumour, in light blue (2.0) by the white matter, in ochre (3.0) by the grey matter and in red (4.0) by the cerebrospinal fluid.

this specific set of parameters:

$$(\nu, M_0, \kappa, \delta, \delta_n, S_n) = (0.356, 3860.7, 700.4, \quad (2)$$
$$0.24, 21041, 41978).$$

with unit measure that can be found in Tab. 1 . We perform several FOM computations, with $M = 64$ different sets of parameters, to build up an adequate basis that can retain most of the energy present in all of the original variables. In this case, a basis with $N_{\text{POD}} = 40$ elements is

big enough to have a restrained error between the FOM solution and the ROM one (Fig. 5). From this, it is possible to create a data set for the neural networks for the map of the direct problem $\mathbf{NN}_\phi$ that relies on 750 different possible evolution of the tumour starting from the same initial condition $\phi_0(x, y, z) = 2e^{-100((x-193)^2+(y-308)^2+(z-30)^2)^2} - 1$ where spatial quantities are measured in mm. The results of the training in terms of mean square error over epochs are exhibited in Fig. 1a. Since the ROM solution using POD without the neural network variation takes much more time to be computed, as can be seen in Tab. 2, we prefer to simulate the FOM and then project over the reduced basis. Once the training is performed, the gain is of getting the reduced solution in about 100 times less computational time.

Coupling a pair of snapshots in the reduced space, that is enough distant in time in other to discriminate between different possible evolutive scenarios with more accuracy, it is then possible to set up a data set whose input-output pair is formed by the vector containing the pair of coefficients for the reduced solution and the patient-specific parameters. The mean square errors over epochs for the neural network $\mathbf{NN}_{\text{inv}}$, computed for normalized over the biological range parameters, are shown in Fig. 1b. Although this result appears to be non-optimal in order to catch the exact parameter of a patient (the computed error is about 15%), the simulations performed show that the specific behaviour is actually well captured.

Giving as input the snapshots of the evolution of the tumour starting from the parameters specified in Eq. (2), we obtain the following result:

$$(\nu, M_0, \kappa, \delta, \delta_n, S_n) = (0.369, 3950.4, 776.8, \quad (3)$$
$$0.25, 25142, 36982).$$

In Fig. 4 the evolution of the tumour with the actual set of parameters and the evolution with the predicted set is exhibited. As we can see in Fig. 3, the volume fraction is well-tracked over time entailing a good estimation both in terms of tumour morphology. The elapsed time for the estimation of the parameters is of the order of seconds (Tab. 2) since it only requires the evaluation of the trained map at a specific point given by the projected couple of snapshots onto the ROM space.
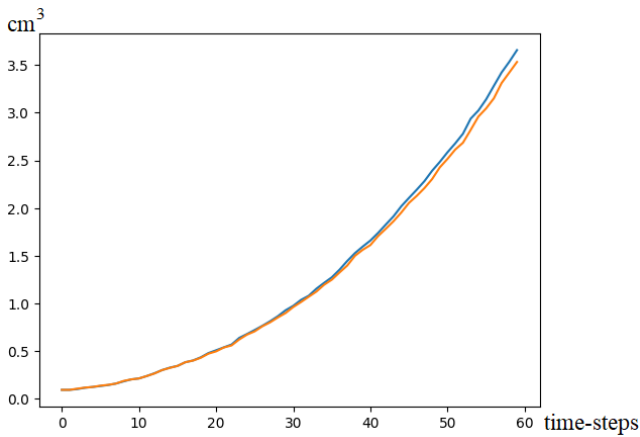
Figure 3: The volume fraction of tumour over time. In blue, the actual evolution starting from parameters Eq. (2); in orange, the predicted one starting from parameters Eq. (3).

7. Conclusion

Although discrete, hybrid, and continuous models of GBM growth have been proposed in the mathematical literature, they are not yet clinically applicable due to the difficulty of constructing a patient-specific model that is accurate and predictive enough to aid clinical decision-making.

In this work, we presented a continuous physics-based model and its computational application for simulating the personalized growth and progression of GBM. The diffuse–interface model consists of a Cahn–Hilliard equation with a double-well potential for the volume fraction of cancer cells coupled with a reaction-diffusion equation for the nutrient. Starting from medical images, it is possible to model the evolution of GBM through this partial differential system. The Cahn-Hilliard type equation contains nonlinear terms that make the Full Order Model (FOM) expansive from a computational point of view.

To reduce the degrees of freedom of the problem it is possible to find in the mathematical literature different techniques. Here, we have studied the impact of the Proper Orthogonal Decomposition method in the construction of the Reduced Order Model (ROM), which reduces the dimensionality of a system by transforming the original variables into a new set of uncorrelated variables (called POD modes, or principal components). In this way, the first few modes ideally retain most of the energy present in all of the original
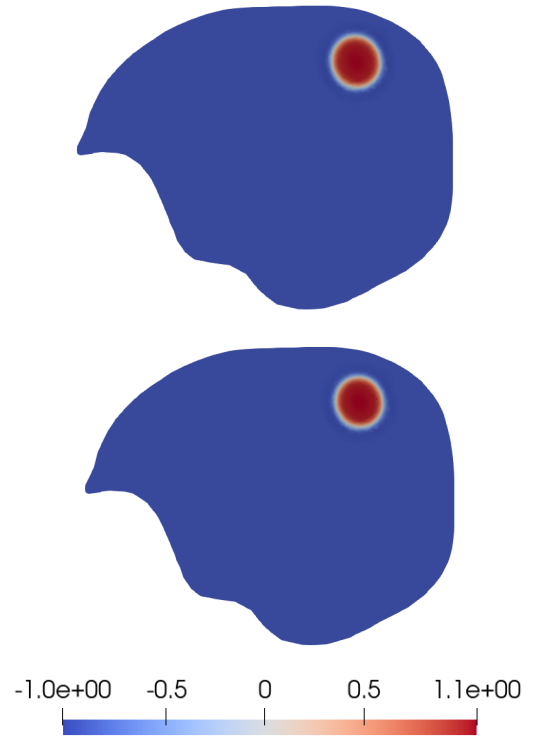

Figure 4: Evolution of a GMB. The solutions for the physical variable ϕ at t=30 days are shown. At the top, the solution computed starting from actual parameters Eq. (2); at the bottom, the solution computed from the predicted parameters Eq. (3) obtained in the inverse problem.

variables. Thus, it is possible to cut down the number of degrees of freedom (d.o.f) from thousands d.o.f (32293 for the brain mesh presented here) to tens d.o.f (40 as shown in Sec. 6).

As we can see from the results, without the usage of a discrete empirical interpolation method, which has to be appropriately adapted in order to deal with highly nonlinear parabolic partial differential equations, the resolution of a ROM is actually more demanding from a computational standpoint, taking almost 7-8 times more computational effort in terms of elapsed time (see Tab. 2).

In this work, we propose an alternative approach that relies on the power of the Neural Networks (NN) to cut computational costs after proper training. Indeed coupling the POD method for constructing the basis with a neural network (POD-NN) to map the space of the parameters into the space of the coefficient for the reduced order basis, we move all the computational effort at the starting analysis of the tumour evolution. In such a way, we have built up a net-
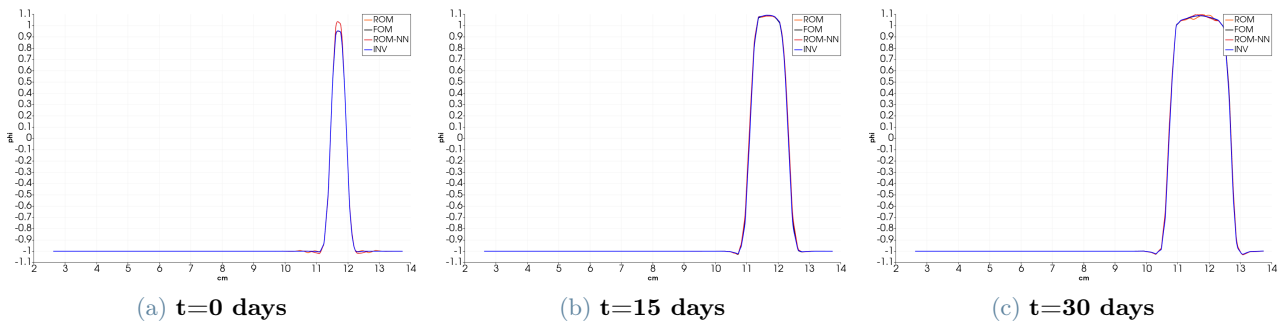
(a) **t=0 days**   (b) **t=15 days**   (c) **t=30 days**

Figure 5: Evolution of a GMB. Plot of the solution ϕ along a straight line intersecting the tumour. From left to right, the plot for each used method at t$=0, 15, 30$ days is shown. In black, the solution computed via the Full Order Model; in orange, the solution computed via the classical Proper Orthogonal Decomposition; in red, the solution computed via the Neural Network variation of the POD; in blue, the solution computed via FOM starting from the parameter obtained in the inverse problem. FOM solution is indistinguishable from the one obtained via the inverse problem, entailing a good estimation of the parameter.

work that predicts all the possible evolutions from a physiological point of view. The gain, in terms of computational time, is about 100:1 when we compare the elapsed time for computing the reduced solution using POD and its NN-based variation, once the training is performed. This simplification is of primary importance when we want to perform an estimation of patient-specific parameters. The reduction of the degrees of freedom is, in fact, essential to the construction of a second simple neural network that allows predicting the parameters from a pair of snapshots distant in time. Indeed, we train a map that goes from the space of the pairs of reduced coefficients of the solution to the space of parameters. From the training phase of this network, we obtain a relative mean square error of about 15% on the parameters prediction, for the realistic domain case. This result seems not to affect the difference between the actual and predicted evolution.

The computational effort of the simulations phase, which can start as soon as we get information on the actual status of the patient and which includes enough simulation to train the neural networks, is balanced by the rapidity of a patient-specific prediction once we collect a second piece of information on the evolution of the tumour growth. The elapsed time for the estimation of the parameters is, indeed, of the order of seconds ($5\,s$ in our simulations) since it only requests the evaluation of the trained map at a specific point given by the projected couple of snapshots onto the ROM space.

In a real clinical case, thus, starting from a first image of the actual status of the patient, we can retrace all the steps previously described in order to set a predicted growth, specific to the patient, once a second image is obtained.

Future developments in the approach presented in this work can be the addition in the mathematical model of factors taking into account the adjuvant therapy. Moreover, since this method is heavily dependent on the initial conditions and on the used mesh geometry, another interesting evolution could be the creation of a data set able to map the patient-specific parameters over different initial conditions and mesh geometries without re-training networks for each patient.

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