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Spatial mechanistic modeling for prediction of the growth of asymptomatic meningiomas.

Annabelle Collin^{1*}, Cédric Copol¹, Vivien Pianet², Thierry Colin², Julien Engelhardt³, Guy Kantor⁴, Hugues Loiseau^{3,5}, Olivier Saut¹, Benjamin Taton^{1,6}

1 Univ. Bordeaux, Inria Bordeaux-Sud-Ouest, Bordeaux INP, CNRS, IMB, UMR 5251, F-33400, Talence, France

2 Sophia Genetics, Cité de la Photonique, F-33600, Pessac, France

3 Service de Neurochirurgie B, Groupe Hospitalier Pellegrin, CHU Bordeaux, F-33000, Bordeaux, France

4 Département de Radiothérapie, Institut Bergonié, F-33076 Bordeaux, France

5 EA 7435 - IMOTION, Univ. Bordeaux, F-33076, Bordeaux, France

6 Service de Néphrologie - Transplantation - Dialyse - Aphérèses, Groupe Hospitalier Pellegrin, CHU Bordeaux, F-33000, Bordeaux, France

Abstract

Background and Objective: Mathematical modeling of tumor growth draws interest from the medical community as they have the potential to improve patients' care and the use of public health resources. The main objectives of this work are to model the growth of meningiomas – slow-growing benign tumors requiring extended imaging follow-up – and to predict tumor volume and shape at a later desired time using only two times examinations. **Methods:** We develop two variants of a 3D partial differential system of equations (PDE) which yield after a spatial integration systems of ordinary differential equations (ODE) that relate tumor volume with time. Estimation of models parameters is a crucial step to obtain a personalized model for a patient that can be used for descriptive or predictive purposes. As PDE and ODE systems share the same parameters, they are both estimated by fitting the ODE systems to the tumor volumes obtained from MRI examinations acquired at different times. A population approach allows to compensate for sparse sampling times and measurement uncertainties by constraining the variability of the parameters in the population.

Results: Description capabilities of the models are investigated in 39 patients with benign asymptomatic meningiomas who had had at least three surveillance MRI examinations. The two models can fit to the data accurately and more realistically than a naive linear regression. Prediction performances are validated for 33 patients using a population approach. Mean relative errors in volume predictions are less than 10% with ODE systems versus 12.5% with the naive linear model using only two times examinations. Concerning the shape, the mean Sørensen-Dice coefficients are 85% with the PDE systems in a subset of 10 representative patients.

Conclusions: Our strategy – based on personalization of mathematical model – provides a good insight on meningioma growth and may help decide whether to extend the follow-up or to treat the tumor.

Keywords: Inverse problem; PDE Modeling; Meningiomas; Tumor Growth

1 Introduction

Mathematical modeling of tumor growth has recently drawn interest from the medical community. Indeed, since the pioneering work on glioblastomas [45], the development of

such reliable models has helped to better understand biological mechanisms and clinical behaviors of several types of tumor such as lung metastases [10], renal cell carcinoma [4], and glioblastoma [43, 45] or the effects of treatments [5, 40, 41]. Such applications are made possible mainly thanks to the development of realistic mathematical models which are personalized using patients' imaging.

In this work, we have set our sights on intracranial meningiomas. Arising from arachnoidal cap cells, they account for a third of primary adult intracranial tumors [3, 36]. They become a major public health issue: (1) an annual increasing incidence ranging from 2-4.5% has been reported [2, 3, 36] and (2) one third of these tumors are asymptomatic at the time of diagnosis [2, 3, 16, 33, 36]. While most meningiomas are slow-growing tumors (about 80% are classified grade I, namely benign meningioma), some may exhibit important growth over a short period of time— called for example in [38] atypical meningiomas. Recent data have shown that asymptomatic meningiomas are observed in 1% to 2% of the population, especially in women over 60 years of age [21, 23, 46]. Surgery or radiation therapy remain the cornerstone of the treatment for meningiomas, and, following the diagnosis of asymptomatic lesions, clinicians struggle with the decision of either immediately treating the lesion using these invasive procedures, or simply planning periodical radiological examinations [7, 15, 18, 22, 31, 42, 48]. In most cases, the frequency of such a monitoring is based on empirical strategies [13, 16, 19, 20, 31, 32, 34, 37, 42, 44, 47, 48, 17]. This is not optimal due to the potential toxicity of repeated Gadolinium infusions [28] and from a medico-economic point of view. Consequently, predicting the progression of asymptomatic lesions is paramount to inform decision-making. However, to our knowledge, only one predictive tool [8, 29, 30] is available to assess the growth rate of untreated meningiomas and help clinicians in selecting which patients to treat or simply monitor. This tool was developed based on statistical predictions (logistic regression) using various clinical and imaging findings collected at the time of diagnosis as covariates. In this context, mathematical modeling of the underlying physiopathological processes can offer an accurate alternative in terms of prediction of growth.

Using a single-center prospective cohort of 39 patients diagnosed with asymptomatic meningioma data, we want to answer two questions:

- Can we model the dynamics of meningioma evolution?
- Using only two MRI examinations, can we predict the volume and the shape of the tumor, at a later time?

To answer the first question, we build two 3D mechanical models of tumor growth. These models depend on parameters which have to be estimated for each patient. As these models can be reduced to ODE systems corresponding to the volume evolution with respect to time and depending on the same parameters as the PDE systems, the estimation process can be performed on these 0D equations (leading to a very efficient method in terms of computational times). Our models – depending on two parameters – allow to represent all patterns of growth: very slower growth, linear and faster growth (to focus on the growth of atypical meningiomas see [38] for a superlinear growth model). To validate the models, the full cohort with all the available times will be used to fit the ODE systems to the data and then assess their descriptive power. To answer the second question, we use only the two first available MRI examinations to estimate the parameters of the models and then predict the volume and the shape of the tumor at a later time corresponding to the time of the third available examination. We compensate the lack of available times of a given patient by an available population of many patients using the mixed-effect approach to estimate the parameters. To resume, our strategy – based on 0D reduction – allows to make predictions of shape and volume of the meningiomas at a later time chosen by the clinician in a very reasonable time (few minutes if all steps are automated, much less if the code was optimized). These predictions could prove valuable to inform medical decisions, adapt follow-up and hence optimize the use of public health resources.

The outline of the paper is as follows. In Section 2.1, the patients cohort and the associated data are presented. In Section 2.2, different models are presented. We consider spatio-temporal evolution of populations of tumor cells locally controlled by a “carrying

capacity” parameter. In this work, spatially distributed and spatially independent carrying capacities will be confronted and then two models will be derived. These two models have the form of partial differential equation (PDE) systems. They can be reduced to ordinary differential equation (ODE) systems that will be used to adapt the model to each patient by estimating the parameters, see Section 2.3. In Section 3.1, a validation of ODE and PDE models is done using the full cohort with all the available times. The objective of this section is to assess the descriptive power in terms of tumor volume and shape of our models. In Section 3.2, we will assess the predictive power (also in terms of tumor volume and shape) of our models in order to see if using only two MRI examinations, we can predict the volume and the shape of the tumor, at a later time. Finally, in Section 4, we discuss our results and the limitations of our work.

2 Methods

2.1 Patients

A single-center prospective cohort of patients diagnosed with asymptomatic meningioma has been studied. Patients did not receive any treatment during the study period. Patients were included in the study if at least three gadolinium-enhanced T1-weighted MRI (acquired on various devices) were available. Patients with neurofibromatosis type II were excluded ($n = 2$) because their natural history is different from the one of sporadic meningiomas. Similarly, patients under cyproterone acetate at the time of diagnosis were excluded ($n = 10$) because meningiomas in most cases regress when treatment is stopped, a phenomenon not accounted for in the proposed models. The study and the use of the MRI images were approved by our institutional review board. Informed consents for data collection used in research were waived for all patients, in accordance with the related policy of Bordeaux University Hospital.

Clinical information (age, gender and meningioma position) of the cohort and times and volumes of available MRI examinations are given in Table 1. The cohort is composed of 38 patients with between three and six MRI acquired during follow-up. Two patients (29-30 and 33-34) have two meningiomas. We have excluded Patient 24 because it was not possible to properly quantify the evolution of his meningioma, due to poor quality of his MRI examinations.

All MRI examinations are T1-weighted sequences with gadolinium-based contrast media. However the MRI acquisition protocol was not standardized: patients were asked to have their examination performed in their usual radiology practice, which is the standard of care for the follow-up of meningiomas in our institution. The maximal voxel sizes for all MRI examinations of each patient are given in Table 1. Slice thickness ranges from 0.7 to 5 mm (most of them between 1 and 1.6 mm though), the sizes of acquisition matrices also vary but range between 180 and 352 in width or height (most often between 256 and 320). As the tumors are rather homogeneous, the segmentation step is relatively easy.

The lesion, as well as the skull are segmented using homemade software developed by B. Taton that relies on a deformable model in the principle of [25]. Illustrations of the segmentation process are given in Fig 1. Using this tool, we have extracted for each patient of the cohort the volumes and the shapes of the tumor at each time.

2.2 Modeling of meningiomas evolution

In this section, we describe the spatio-temporal evolution of populations of tumor cells that is locally controlled by a “carrying capacity” parameter (in the spirit of [6]). In this work, spatially distributed and spatially independent carrying capacities are investigated hence deriving two different models. These two models are based on systems of partial differential equation (PDE) as shown in Section 2.2.1. These systems can be reduced to ordinary differential equation (ODE) systems, see Section 2.2.2, that are used to parametrize the model.

Pat.	Age	G	Voxel sizes	Pos.	Times [months]	Volumes [cm ³]
1	52	F	(0.94,0.94,0.8)	ER	0 5 13 25	0.67 0.83 0.95 1.68
2	48	M	(0.95,0.95,0.9)	BLPS	0 6 14	6.15 6.26 6.42
3	50	F	(0.46,0.46,0.7)	BRPM	0 31 67 93	2.25 3.45 3.69 3.99
4	53	F	(1.0,1.0,0.5)	BMPS	0 5 21 44	4.42 4.67 5.62 7.70
5	33	F	(0.38,0.38,1.0)	BLPI	0 20 32 50	1.53 2.73 3.59 5.70
6	44	F	(0.49,0.49,1.2)	IMAM	0 28 40 52	1.68 2.32 2.70 3.20
7	34	F	(0.49,0.49,1.0)	BLAS	0 12 24	1.15 1.89 2.68
8	70	F	(0.94,0.94,0.6)	ELI	0 5 10	1.04 2.04 3.41
9	77	F	(1.0,1.0,0.7)	BLPI	0 23 42	0.56 1.46 3.31
10	50	F	(0.42,0.42,0.7)	IRAS	0 39 62 95	13.4 15.5 15.9 16.3
11	52	M	(0.9,0.9,1.3)	BRAS	0 32 62	1.29 1.73 1.76
12	60	F	(0.47,0.47,6.5)	BRAS	0 74 86	4.87 7.59 7.71
13	64	F	(0.49,2.0,0.49)	ER	0 6 12 29 53	2.30 2.52 2.94 3.57 4.18
14	34	F	(0.43,0.43,2.9)	EL	0 11 37 61 68 81	2.78 3.04 4.02 6.00 6.18 6.85
15	57	F	(0.78,0.78,5.5)	BRMI	0 38 83	1.51 2.20 2.55
16	39	F	(0.89,0.89,0.7)	BMAS	0 7 14 22 34	1.00 1.73 2.07 2.05 2.20
17	66	F	(0.47,0.47,0.6)	BRMS	0 13 33 59	4.25 4.01 4.03 4.43
18	52	F	(0.47,0.47,4.4)	BLMS	0 7 21	3.51 4.85 6.86
19	62	F	(0.78,0.78,0.5)	ER	0 30 46 60	2.48 3.12 3.62 3.94
20	53	F	(0.5,0.5,1.0)	BRPM	0 7 21	0.65 0.77 0.82
21	69	F	(1.0,1.0,1.0)	IMMS	0 6 23 39	10.4 10.4 12.2 13.1
22	80	F	(0.94,0.94,0.6)	ELI	0 8 10	2.52 5.64 7.08
23	45	M	(0.48,0.48,0.62)	IMAS	0 7 15	5.48 5.69 6.30
25	49	F	(0.38,0.38,1.0)	EM	0 7 14 26	2.59 3.07 3.57 3.54
26	46	F	(1.0,1.0,0.75)	BRAS	0 6 21 37	1.92 1.95 2.15 2.30
27	58	F	(0.51,0.51,1.2)	ER	0 6 13 40	2.48 2.49 2.62 2.74
28	81	F	(0.78,0.78,0.5)	BMPI	0 20 43 64	1.89 3.31 5.82 7.62
29	40	F	(0.47,0.47,0.8)	ER	0 5 13 33	0.37 0.42 0.48 0.81
30	40	F	(0.47,0.47,0.8)	ER	0 5 13 33	0.05 0.09 0.22 1.17
31	44	F	(0.47,0.47,0.6)	IMPS	0 4 7 33	0.50 0.58 0.62 0.81
32	69	F	(0.47,0.47,0.6)	BLAS	0 7 14	1.58 1.72 1.99
33	39	F	(1.0,1.1,1.1)	EL	0 7 23	1.74 1.95 1.93
34	39	F	(1.0,1.1,1.1)	EL	0 7 23	2.77 2.69 3.14
35	64	F	(0.9,0.9,0.8)	BLAS	0 27 46	5.58 5.83 6.11
36	47	F	(0.78,0.78,0.95)	EL	0 6 12	1.23 1.25 1.85
37	66	F	(0.94,0.94,0.7)	ER	0 5 12	0.91 0.91 1.15
38	52	F	(1.0,1.0,0.7)	BMPS	0 5 13	1.75 1.71 2.14
39	79	F	(1.0,1.0,1.0)	IMMS	0 10 25	1.30 1.30 1.62
40	48	F	(1.0,1.0,1.0)	BMPM	0 18 29	2.10 3.05 3.87

Table 1: Presentation of the patient cohort: age at diagnostic, gender, maximal voxel sizes, meningioma position, times and volumes of available examinations. The position is summarized by 2 or 4 letters where letters indicate at the first position, B border, I interior, E eye, and at the other positions: L left, R right, A anterior, P posterior, I inferior, S superior and M middle.

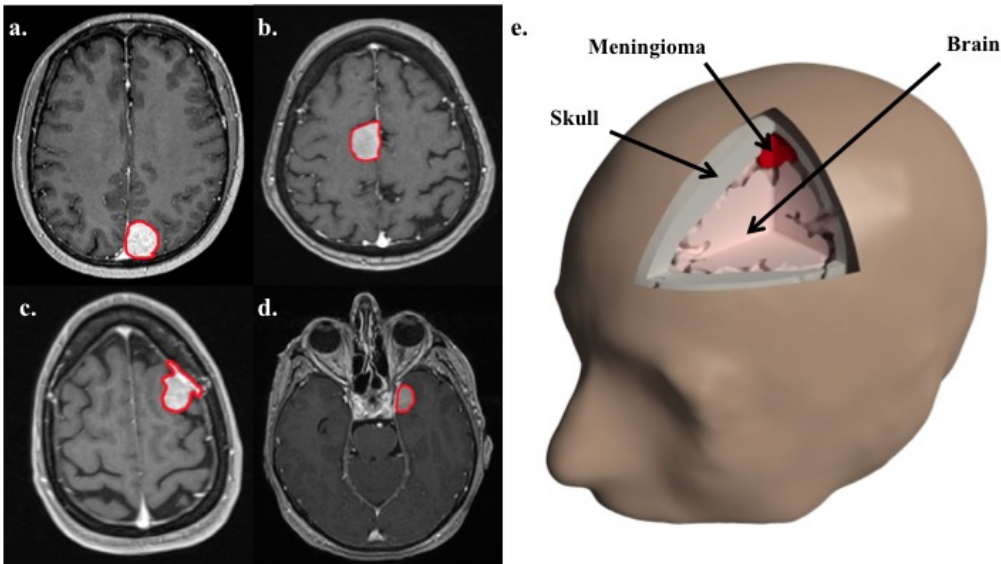


Figure 1: Examples of meningioma geometry (a,b,c,d) from MRI T1-weighted sequences with gadolinium-based contrast media. Tumor boundaries are highlighted in red. (e) Anatomical view of a meningioma: 3D reconstruction with a homemade segmentation tool from the medical images. The head, skull, brain and meningioma geometries are delineated in 3D from the MRI examination.

2.2.1 Spatial modeling

PDE systems Let \mathcal{B} be a bounded and smooth domain of \mathbb{R}^3 . The evolution of the density T of proliferative cells is supposed to satisfy the following equation:

$$\partial_t T + \nabla \cdot (\vec{v}T) = MT, \quad \mathcal{B} \quad (1)$$

where \vec{v} denotes the velocity field that describes the motion of tumor cells. The growth rate is denoted by $M(t, X)$. In this work, two different dynamics of the growth rate are considered:

$$M = M_0 e^{-\alpha t} \text{ (equivalent to } \partial_t M = -\alpha M)$$

and

$$\partial_t M = -\alpha MT$$

where in both cases α^{-1} corresponds to the characteristic time at which the tumor growth capacity decreases and M_0 is a constant corresponding to the initial growth rate. In the first case, the growth rate only depends on t - which could be seen as an oversimplifying assumption -, in the second case it also depends on the space variable X .

We denote by $S(t, X) = 1 - T(t, X)$ the density of healthy tissue and we assume that $S(t, X)$ is only advected at the velocity \vec{v} due to cellular division of tumor cells. This is clearly not true (for example, there is a biological action of the tumor on the extracellular matrix), but in our setting, this assumption means that the global evolution of the tumor is not modified by the extra-tumoral medium. This reads

$$\partial_t S + \nabla \cdot (\vec{v}S) = 0, \quad \mathcal{B}. \quad (2)$$

Using $T + S = 1$ (it is a saturation hypothesis) leads to (using Eq (1))

$$\nabla \cdot \vec{v} = MT, \quad \mathcal{B}. \quad (3)$$

Eq (3) is clearly not enough to close the system and we assume in addition the following Darcy's law

$$\vec{v} = -\nabla \pi, \quad \mathcal{B}, \quad (4)$$

where π is the pressure. Eqs (3) and (4) lead to

$$-\Delta \pi = MT, \quad \mathcal{B}. \quad (5)$$

Eq (5) is solved in \mathcal{B} that is the intersection of the inside of the skull with a cube centered on the tumor. The boundary of the cube is denoted by $\Gamma = \partial \mathcal{B}$. The part of the skull that is included in the cube is denoted by Γ_1 . The boundary condition on Γ_1 is

$$\frac{\partial \pi}{\partial n} = 0 \quad (6)$$

and is implemented by a penalty method. On $\Gamma \setminus \Gamma_1$ we impose

$$\pi = 0. \quad (7)$$

The PDE system is summarized in the case of time and space dependent (resp. only time dependent) growth rate by

$$\begin{cases} \partial_t T + \nabla \cdot (\vec{v}T) & = & MT, & \mathcal{B} \\ \partial_t M & = & -\alpha MT \text{ (resp. } -\alpha M), & \mathcal{B} \\ \vec{v} & = & -\nabla \pi, & \mathcal{B} \\ -\Delta \pi & = & MT, & \mathcal{B}. \end{cases} \quad (8)$$

To obtain these PDE models, many assumptions have been done as for example: the dependence of M and α on the material properties is ignored ; the motion is assumed to be

only due to Darcy flow (*i.e.* the natural diffusion of tumor cells is ignored) and the Darcy permeability is assumed to be constant. These hypothesis – which can be discussed – have been done in order to obtain models whose the parameters are identifiable with very few examinations.

The domain \mathcal{B} is chosen large enough in order to ensure that (7) has no significant influence on the growth. Mechanically speaking, Eqs (4) and (5) imply that the increase in volume due to the tumor growth generates locally an increase in pressure. The pressure gradient creates a movement at velocity \vec{v} in its opposite direction. Developing Eq. (1) yields

$$\partial_t T + \vec{v} \cdot \nabla T = MT(1 - T). \quad (9)$$

Let the initial condition of T equal to $T(0, x) = 1$ inside the tumor and 0 elsewhere, one can easily see that $T(t, X) = 1$ inside the tumor and 0 elsewhere at any time. Eq. (9) then becomes:

$$\partial_t T + \vec{v} \cdot \nabla T = 0.$$

We define by $\Omega(t) = \{x, T(t, x) > 0\}$ the domain corresponding to the tumor at time t .

It is clear than one could probably write a model for tumor growth closer to biology but the major advantage of these two models is that they depend only on two parameters: M_0 and α . We choose to keep the models simple to ensure that they can effectively be personalized for each patient using the sparse observations that are available in the clinical routine.

Numerical resolution The meningioma growth in the skull can be simulated in 3D by the numerical resolution of the two PDE systems presented in the last paragraph.

The inputs of the simulation are the initial tumor cell density $T(0, X)$ – obtained via the segmentation of the first MRI examination – and the α or β and M_0 parameters – hence the estimation is the major issue of this work, see Sections 2.2.2 and 2.3. Simulation boundary conditions consist in the assumption that the meningioma growth is limited by the arachnoid tissue. The boundary conditions are obtained via the segmentation of the last available MRI examinations (see Fig 1).

The simulation is done using the following split-step scheme:

- Computes the potential π by solving the Poisson’s equation (5) at time t .
- Estimates the cell transport velocity \vec{v} via the Darcy’s law (4) and the velocity divergence $\nabla \cdot \vec{v}$ (3) at time $t + \Delta t$.
- Computes the tumor cell density transport over the time step Δt .
- Computes the growth capacity M at time $t + \Delta t$.

The resolution of the tumor cell transport at each time is performed thanks to a second order splitting method with a fifth order WENO transport scheme. The simulation time step Δt used in the resolution is computed at each iteration to satisfy two conditions: (i) to be small enough to ensure the stability of the transport solution and (ii) not to exceed one day per simulation step.

In what follows, the similarity between simulations and registered MRI segmentations is measured with the Sørensen-Dice coefficient (SDC). Given two sets, X and Y of discrete data, the SDC is defined by

$$\text{SDC} = \frac{2|X \cap Y|}{|X| + |Y|} \times 100, \quad (10)$$

where $|X|$ and $|Y|$ are the cardinalities of the two sets. It is a classical metric used to gauge the similarity of two samples.

2.2.2 ODE systems embedded in PDE systems

Let us denote by $V(t)$ the volume of the lesion $\Omega(t)$ at time t . We have

$$V(t) = \int_{\mathcal{B}} T(t, X) dX = \int_{\Omega(t)} dX$$

by definition of T . One can prove the two following propositions (see Appendix for the proofs).

Proposition 1. *If $M = M_0 e^{-\alpha t}$, we have:*

$$V(t) = V_0 e^{\frac{M_0}{\alpha}(1-e^{-\alpha t})}. \quad (11)$$

Proposition 2. *If $\partial_t M = -\alpha M T$, we have:*

$$V(t) = V_0 + M_0 V_0 \frac{e^{(M_0 - \alpha)t} - 1}{M_0 - \alpha}. \quad (12)$$

For the estimation process, we define $\beta = M_0 - \alpha$. Let us note that the volume evolution V is linear if and only if $M_0 = \alpha$ and in this case

$$V(t) = V_0 + V_0 M_0 t. \quad (13)$$

As we have $\frac{e^{(M_0 - \alpha)t} - 1}{M_0 - \alpha} > 1$ (resp. $\frac{e^{(M_0 - \alpha)t} - 1}{M_0 - \alpha} < 1$) if $M_0 > \alpha$ (resp. $M_0 < \alpha$), three behaviors for V are possible:

- $M_0 = \alpha$: V is linear,
- $M_0 > \alpha$: V is exponential (strictly convex),
- $M_0 < \alpha$: V is strictly concave.

For the parametrization process, instead of estimating α , we will estimate $\beta = M_0 - \alpha$ using as *a-priori* $\beta = 0$.

2.3 Parameter estimation method

The parameter estimation method is the major issue of this work. This section is devoted to present our estimation strategies.

Mixed-effect approach To estimate the two constant parameters α (resp. β) and M_0 of the 0D model (11) (resp. (12)), a population approach has been chosen. The mixed-effect approach [39] consists of pooling all the patients together and estimating a global distribution of the model parameters in the population. More precisely, the individual parameters α^j , β^j and M_0^j (where j denotes the individual) are assumed to be realizations of a random variable decomposed into two parts:

$$\begin{aligned} \{\alpha, \beta\}^j &= \{\alpha, \beta\}^{pop} + \{\tilde{\alpha}, \tilde{\beta}\}^j, \forall j \in [1, N_p], \\ M_0^j &= M_0^{pop} + \tilde{M}_0^j, \forall j \in [1, N_p], \end{aligned}$$

where N_p is the number of considered patients, α^{pop} , β^{pop} and M_0^{pop} correspond to the fixed effects where as $\tilde{\alpha}^j$, $\tilde{\beta}^j$ and \tilde{M}_0^j correspond to the random effects and have been assumed with mean zero. The parameters that we want to estimate are not physiological, there are no priors for their means and standard deviations. Then, we assume that

$$\alpha^{pop}, \beta^{pop} \sim \mathcal{N}(0, 0.01^2) \text{ and } M_0^{pop} \sim \mathcal{N}(0, 0.01^2),$$

emphasizing that these assumptions do not seem too restrictive. The estimation strategy is not sensitive to these priors.

Models (11) (time-dependent M) and (12) (space- and time-dependent M) also depend on the initial volume V_0 . This value can be fixed with the volume computed using the first MRI examination but doing that does not allow to consider the uncertainty of the segmentation process. That is why we consider V_0^j of each patient $j \in [1, N_p]$ as a covariate of the estimated volume at the initial time:

$$V_0^j = V_0^{j, MRI} + e_0^j,$$

where $e_0^j \sim \mathcal{N}(0, 0.1^2)$.

We assume that the measurement error for all volumes is proportional

$$V^{j,MRI}(t) = V^{j,estim}(t)(1 + e),$$

where $V_k^{j,estim}$ corresponds to the estimated volume using ODE systems and e the measurement error. We assume that it follows a Gaussian law $\mathcal{N}(0, 0.05^2)$. The standard deviation of 5% is not arbitrary. It is the same order of magnitude found in [12] for homogeneous tumors (lung or liver metastasis) similar to meningiomas. This standard deviation is estimated σ_e and is used to define the 95% confidence interval: $[V^{j,estim}(t)(1 - 1.96\sigma_e); V^{j,estim}(t)(1 + 1.96\sigma_e)]$.

This estimation strategy is implemented in a software called `Monolix` [1], which maximizes the likelihood using the stochastic approximation expectation maximization (SAEM) algorithm [24]. For all the results obtained with `Monolix` in this paper, the convergence of the algorithm has been reached.

As the growth of meningioma is quite slow, a comparison with a linear model (for example Model (12) when $\beta = 0$) will be done using the same hypothesis.

Prediction This paragraph is devoted to present our estimation strategy to answer the following question: using only two MRI examinations given at time t_0 and t_1 , can we predict the volume and the shape of the tumor, at a later time t_2 ? It is a very difficult question because the patient variability cannot be perfectly explained using a model with less than two parameters. In particular, using only one time point (as the first time point is used to estimate the initial volume), it is impossible to determine the behavior of the volume evolution, namely whether the volume evolution is linear, strictly convex or strictly concave. Indeed, determining α (or β), V_0 and M_0 using only the volumes at time t_0 and t_1 is an underdetermined problem. Using clinical characteristics (meningioma location, patient's age and gender) and the times and volumes data, we have tried to classify the patients using machine learning techniques but found no interesting results.

Then to answer this difficult question, we develop the following strategy. Let a patient denoted by p for which only two times data are available, we assume that a population of patients with at least 3 times is available and we will use this population to estimate the parameters of the patient p using the mixed-effect approach. Our strategy can be seen as a way to compensate the lack of available times of the given patient p by an available population of $N_p - 1$ patients.

3 Results

3.1 Descriptive power of the models

To validate the models, the full cohort with all the available times is used to fit the ODE systems to the data and then assess their descriptive power. We start by investigating the prediction of the tumor volume then its shape.

Tumor volume Fig 2 presents all the graphical representations of the results using the estimation process. Each figure gathers all the fits performed for a given patient: the tumor volumes obtained using MRI segmentations are represented by black circles. The red (resp. blue and green) curves correspond to the model with time-dependent growth rate (11) (resp. to the model with space- and time-dependent growth rate (12) and to the linear model (13)). The 95% confidence intervals are also represented as shaded areas. It corresponds to the uncertainty on the volume prediction and is computed by the SAEM algorithm. Since different models yield different distributions for the random variables, the corresponding 95% confidence intervals also differ. One can remark that the results obtained using the ODE models are similar. The 95% confidence intervals of the linear model are

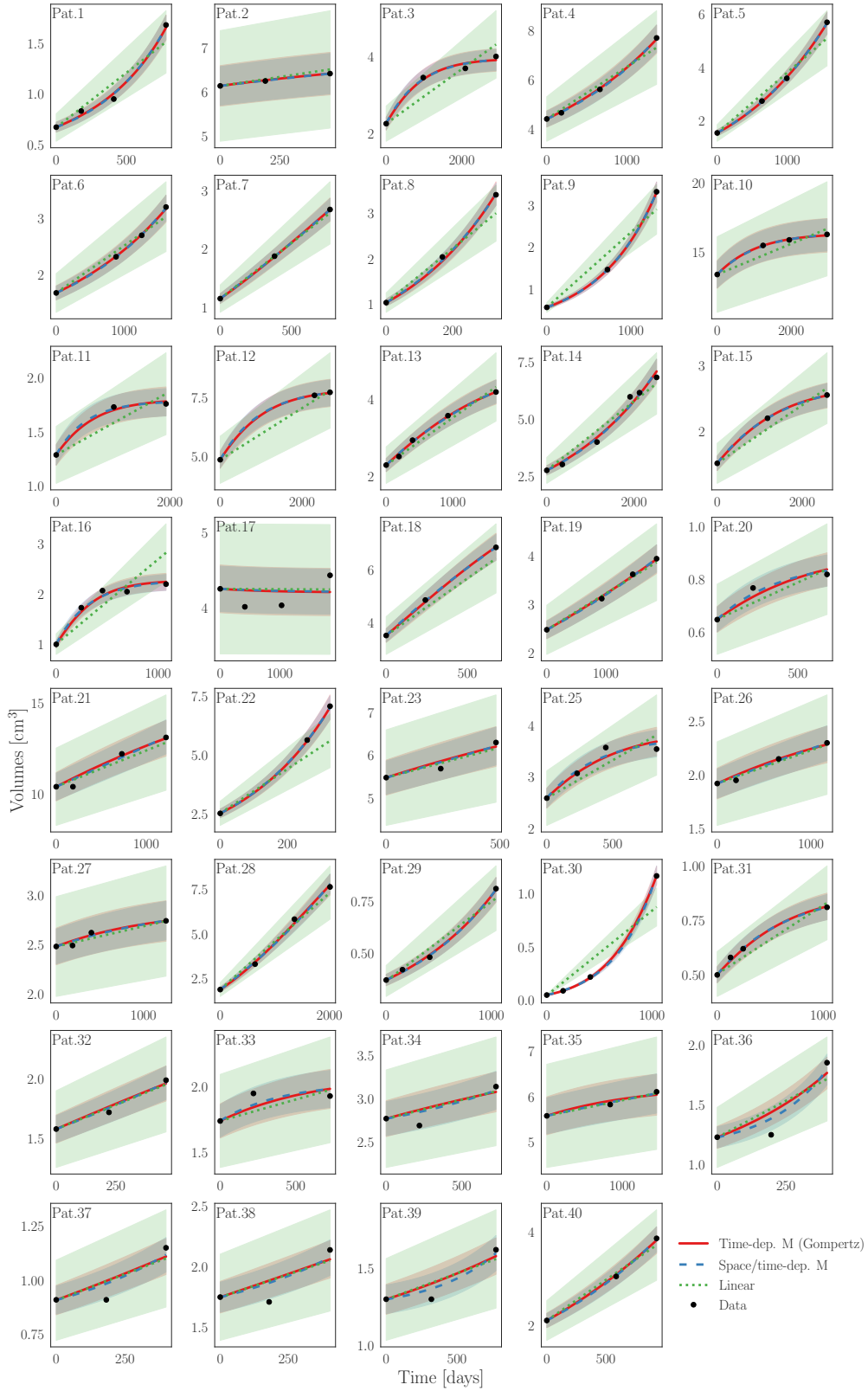


Figure 2: **Descriptive power - Estimated volumes compared to the data for the full cohort. The tumor volumes obtained using MRI segmentations are represented by black circles. The red (resp. blue and green) curves correspond to the model with time-dependent growth rate (11) (resp. to the model with space- and time-dependent growth rate (12) and to the linear model (13)).**

Pat.	SDC (Time-d. M)	SDC (Space/time-d. M)
2	95%	95%
4	93%	93%
7	83%	83%
8	83%	86%
9	67%	67%
11	87%	87%
18	87%	86%
20	93%	93%
22	85%	85%
23	88%	88%

Table 2: **Descriptive power - Sørensen-Dice coefficient SDC** (see Eq. (10)) as a comparison between the solution of the tumor growth model and the MRI segmentation at the last available time.

	Time-d. M	Space/time-d. M	Linear mod.
\mathcal{E}_p	9.9 %	9.8%	12.5%
\mathcal{B}_p	0.007	-0.007	0.024

Table 3: **Predictive power - Relative error \mathcal{E}_p and bias \mathcal{B}_p at time t_2** (see Eq. (15))

larger. The following relative error is computed

$$\mathcal{E}_d = 100 \frac{1}{N_p} \sum_{p=1}^{N_p} \frac{1}{N_{p,e}} \sum_{e=1}^{N_{p,e}} \frac{|V(t_e) - V_e^{meas}|}{V_e^{meas}}, \quad (14)$$

for each model where $N_{p,e}$ corresponds to the number of available examinations for each patient p , $V(t_e)$ to the estimated volume at time t_e corresponding to the e -th MRI examination, V_e^{meas} to the measurement volume at time t_e . We obtain respectively an error of 1.7%, 1.5% and 5.2% for the model with time-dependent growth rate (11), the model with space- and time-dependent growth rate (12) and the linear model (13).

Tumor shape As presented in Section 2.2, the meningioma growth in the skull can be simulated in 3D by the numerical resolution of two PDE systems (one with space- and time-dependent growth rate and one with time-dependent growth rate) leading after volume integration to the two ODE systems studied in the previous section.

The 3D simulation of the spatial growth of meningiomas has been performed in 10 cases – selected to represent the full cohort. We compare using the Sørensen-Dice coefficient (SDC) the overlap between the spatial extension of the simulated tumor and the segmentation of the MRI data at the last available time. Results are presented in Table 2.

3.2 Predictive power of the models

This section illustrates the strategy – presented in Section 2.3 – to answer the following question: using only two MRI examinations given at time t_0 and t_1 , can we predict the volume and the shape of the tumor, at a later time t_2 ? We recall that it is a very difficult question because – as seen in the last section – the patient variability cannot be perfectly explained using a model with less than two parameters.

Volume prediction Fig 3 illustrates our strategy on Patient 15. All the time data of Patients from 1 to 14 and from 16 to 39 are used by the estimation process. Each figure

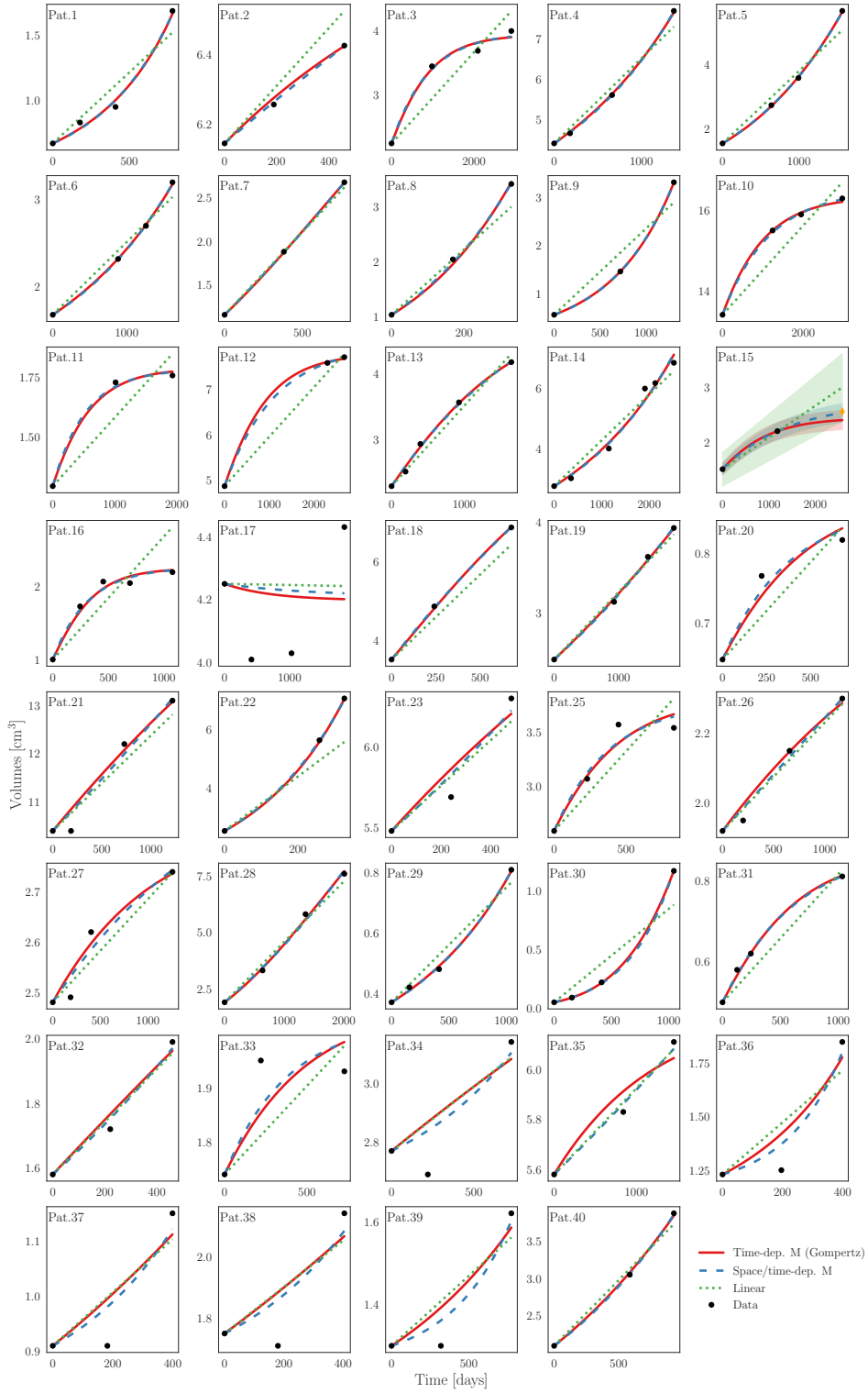


Figure 3: Predictive power (see Patient 15) - Estimated volumes compared to the data for the full cohort. The tumor volumes obtained using MRI segmentations and used by the estimation process are represented by black circles. The orange diamond (see Patient 15) corresponds to the volume at time t_2 which is not used to estimate the parameters. The red (resp. blue and green) curves correspond to the model with time-dependent growth rate (11) (resp. to the model with space- and time-dependent growth rate (12) and to the linear model (13)).

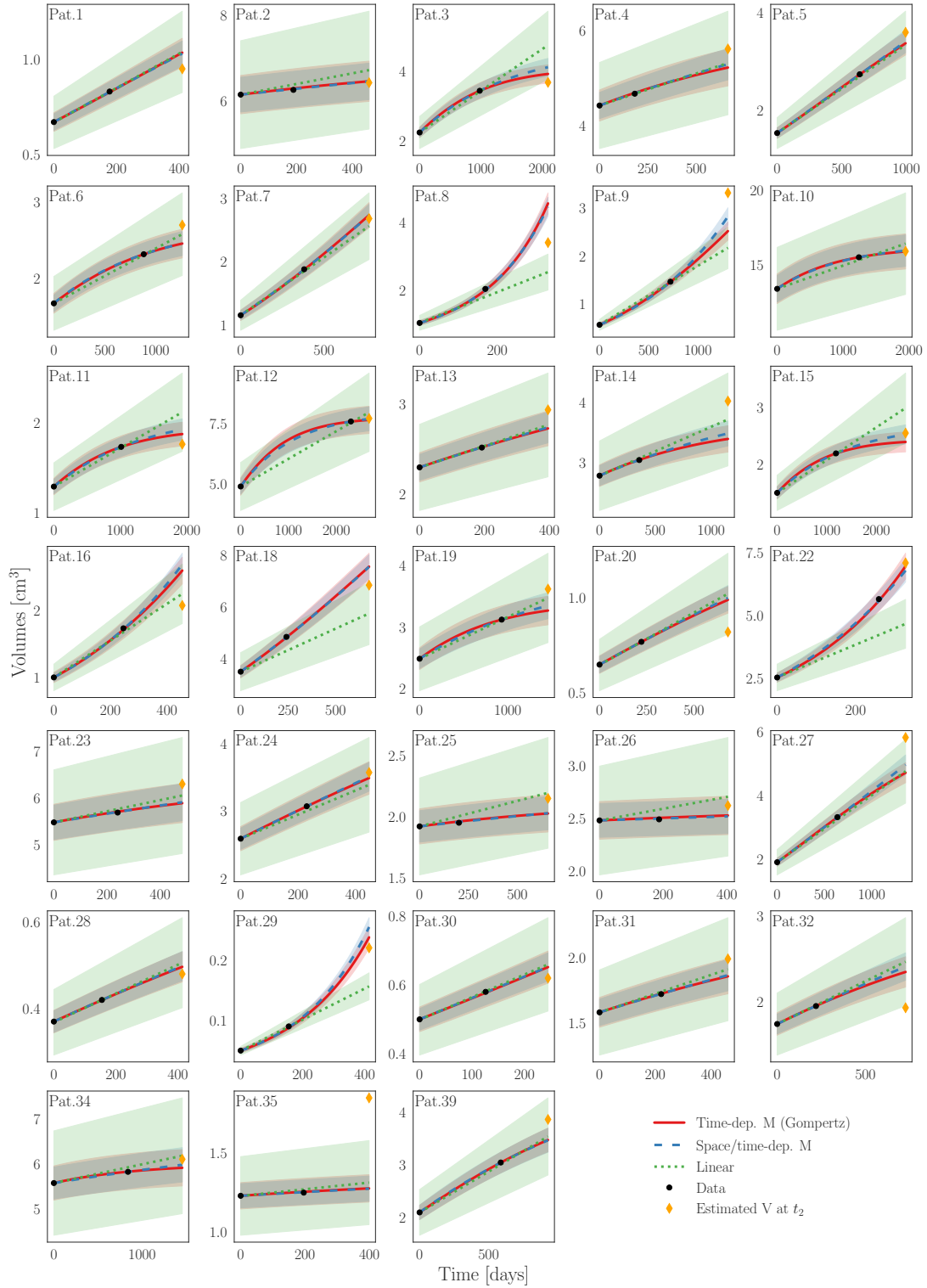


Figure 4: **Predictive power - Results obtained by applying the strategy presented in Section 3.2 to 33 patients.** The tumor volumes obtained using MRI segmentations and used by the estimation process are represented by black circles. The orange diamond corresponds to the volume at time t_2 which is not used to estimate the parameters. The red (resp. blue and green) curves correspond to the model with time-dependent growth rate (11) (resp. to the model with space- and time-dependent growth rate (12) and to the linear model (13)).

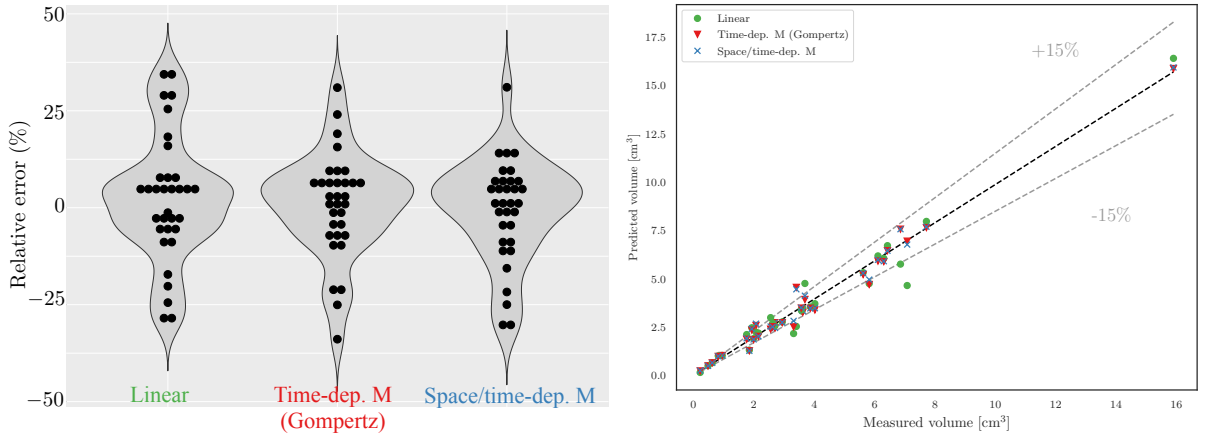


Figure 5: **Predictive power - Results obtained by applying the strategy presented in Section 3.2 to 33 patients. Left: Comparison of errors \mathcal{B}_p . Right: Comparison of the tumor volume predictions and measurements.**

gathers all the fits performed for each patient: the tumor volumes used for estimating the parameters are represented by black circles. The initial volume is not estimated in this strategy in order to increase the determination of the problem and to be compatible with 3D assessments. The red (resp. blue and green) curves correspond to the model with time-dependent growth rate (11) (resp. to the model with space- and time-dependent growth rate (12) and to the linear model (13)). The orange diamond (see figure of Patient 15) corresponds to the volume at time t_2 which is not used to estimate the parameters.

The strategy is applied for all the patients whose tumor volume at time t_1 is strictly superior to the volume at time t_0 (33 patients on 39), see Fig 4. Table 3 gives the error and the bias computed as

$$\mathcal{E}_p = 100 \frac{1}{N_p^s} \sum_{p=1}^{N_p^s} \frac{|V(t_2) - V_2^{meas}|}{V_2^{meas}} \quad \text{and} \quad \mathcal{B}_p = \frac{1}{N_p^s} \sum_{p=1}^{N_p^s} \frac{V(t_2) - V_2^{meas}}{V_2^{meas}}, \quad (15)$$

where N_p^s corresponds to the number of patients whose the volume at time t_1 is strictly superior to the volume at time t_0 ($N_p^s = 33$). Fig 5-left shows the relative error $\frac{V(t_2) - V_2^{meas}}{V_2^{meas}}$ for each patient for the three models. In Fig 5-right, a comparison of the predicted volume with the measured volume at t_2 has been done for the 33 patients. The grey lines permit the identification of outliers.

Shape prediction We perform 3D simulations for 10 patients in order to assess the shape prediction of PDE models. We compare the solutions of PDE models with the shape obtained by doing an expansion of the shape of the initial tumor using a redistancing process. To do that, we consider the level set of the initial shape with a volume equals to the volume predicted using the linear 0D model. Table 4 gives the Sørensen-Dice coefficient (SDC) measuring the similarity between simulations and registered MRI segmentations. Fig 6 presents 3D views of the solution of the model tumor growth with space- and time-dependent growth rate (red) compared to the MRI segmentation (blue) at the last available time. The supportive arachnoid tissue is represented by the grey surface. Fig 7 presents 2D slice views of the solution of the model tumor growth with space- and time-dependent growth rate (red) compared to the MRI segmentation (blue) for the three time steps (t_0 , t_1 and t_2) for 5 patients. The slices correspond to the ones with maximal tumor area.

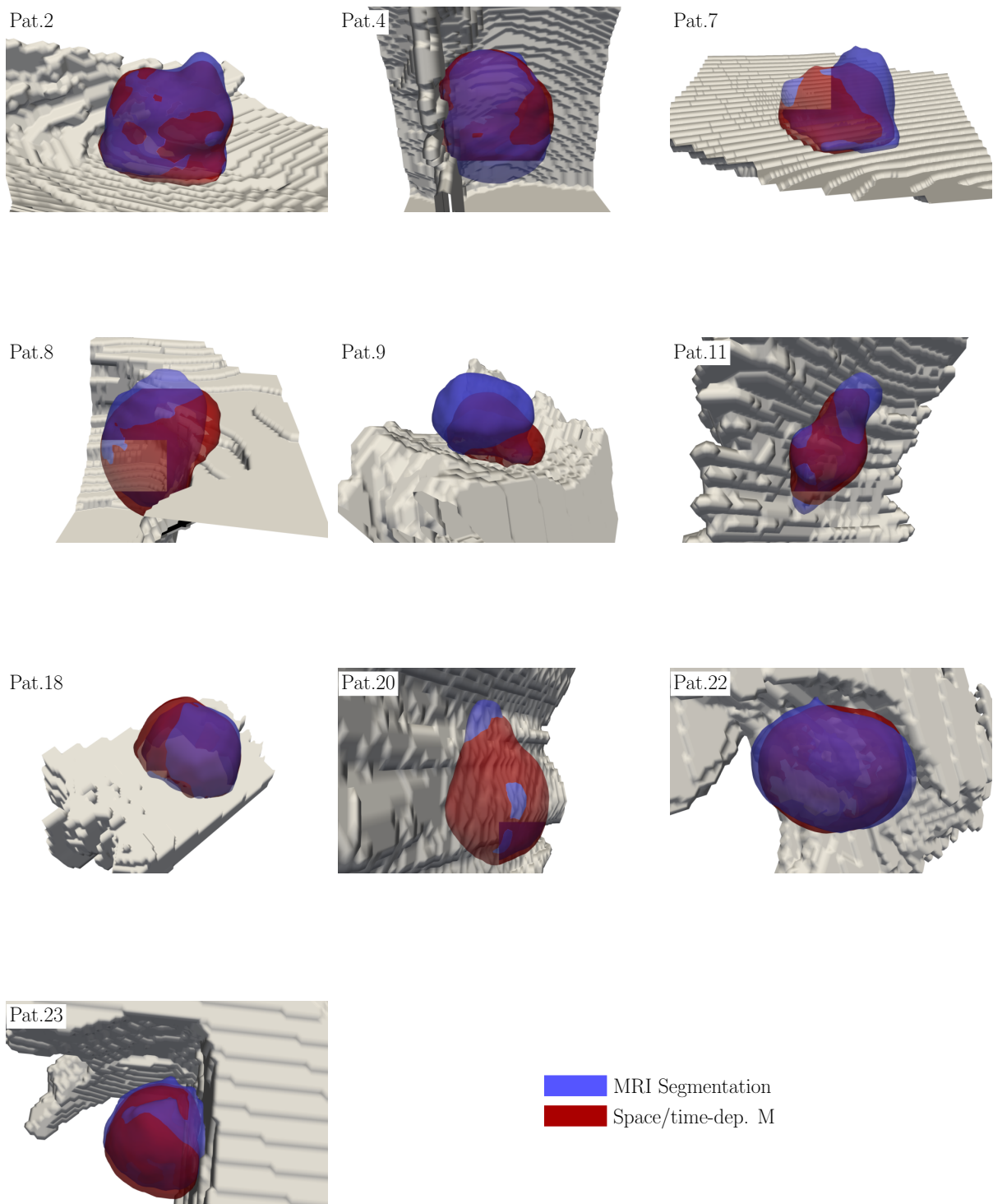


Figure 6: **Predictive power - 3D views of the solution of the model tumor growth with space- and time-dependent growth rate (red) compared to the MRI segmentation (blue) at the last available time for 10 patients. The supportive arachnoid tissue is represented by the grey surface.**

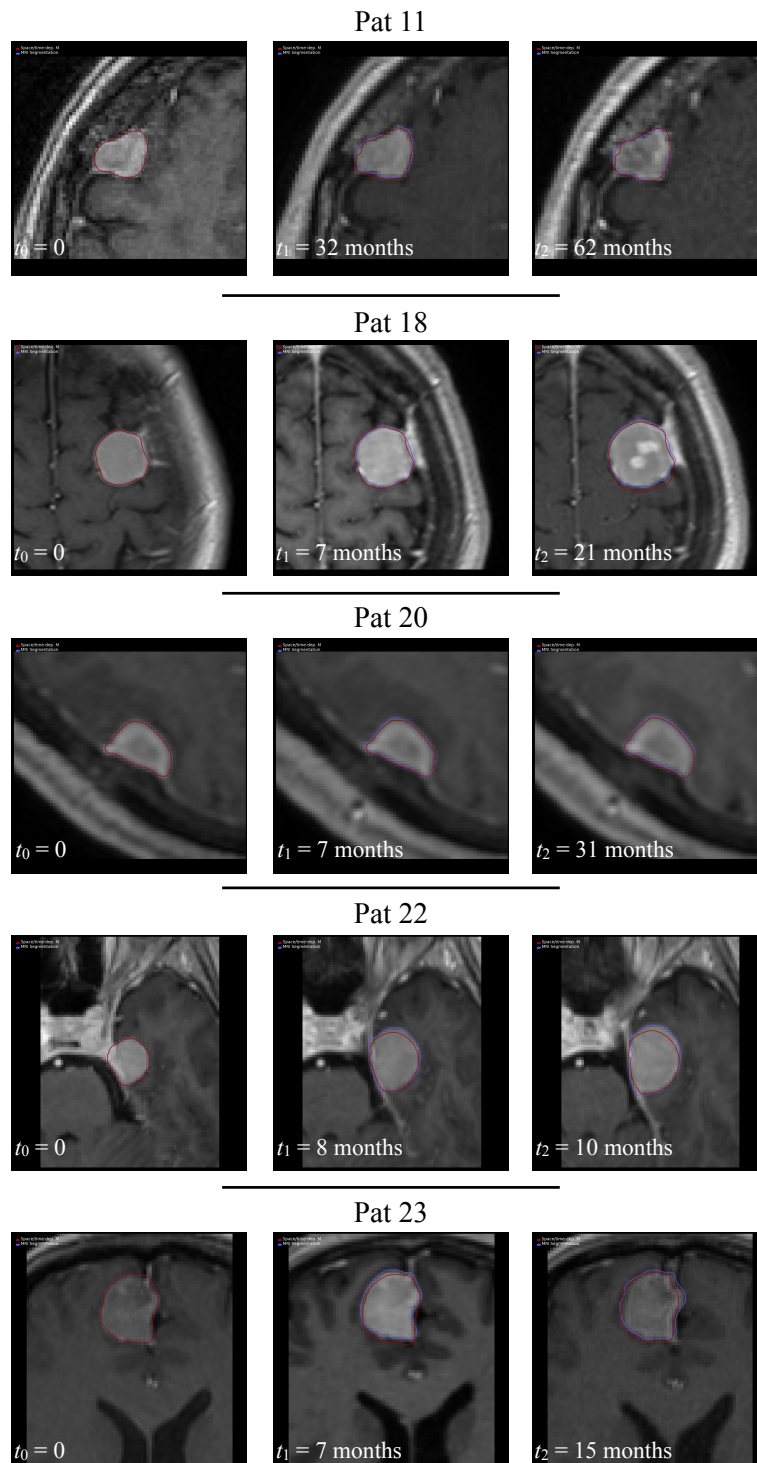


Figure 7: Predictive power - 2D slice views of the solution of the model tumor growth with space- and time-dependent growth rate (red) compared to the MRI segmentation (blue) for the three time steps (t_0 , t_1 and t_2) for five patients.

Pat.	SDC (Time-d. M)	SDC (Space/time-d. M)	SDC (Redist.)
2	95%	95%	94%
4	93%	93%	93%
7	83%	83%	74%
8	87%	85%	69%
9	65%	63%	52%
11	85%	86%	82%
18	86%	86%	86%
20	90%	90%	87%
22	85%	84%	66%
23	87%	87%	88%

Table 4: **Predictive power - Sørensen-Dice coefficient SDC (see Eq. (10)) as a comparison between the solution of the tumor growth model and the MRI segmentation at the last available time. Second (resp. third) column: model with only time dependent (resp. time and space dependent) growth rate. Last column: linear model with the redistancing process.**

4 Discussion

We recall that our objective is to use a single-center prospective cohort of patients diagnosed with asymptomatic meningioma, we want to answer two questions:

- Can we model the dynamics of meningioma evolution?
- Using only two MRI examinations, can we predict the volume and the shape of the tumor, at a later time?

To answer the first question, two 3D mechanical models of tumor growth – able to represent all patterns of growth: very slower growth, linear and faster growth – have been built. As these models can be reduced to ODE systems corresponding to the volume evolution with respect to time and depending on the same parameters as the PDE systems, the estimation process can be performed on these 0D equations. To validate the models, the full cohort with all the available times have been used to fit the ODE systems to the data and then assess their descriptive power.

Descriptive power of the models Our modeling choices (PDE and ODE models) have been validated as they allow to describe the shape and the volume of meningiomas. Indeed, \mathcal{E}_d is very small for the ODE models ($< 2\%$) but also for the linear model (5.2%). For the three models, errors are of the same order as the measurement error so that all these models are acceptable. However, one can see that the patients variability is not well represented using the linear model, see Figure 2. Indeed, the volume evolution when they are strictly convex, as for example for Patients 1, 5 and 9 (resp. concave, as for example for Patients 3, 10 and 11) are not well fitted using the simple linear model. This is also underlined by the fact that the linear model have larger 95% confidence intervals.

One can see in Table 2 that the shape of the tumor is very well estimated with a mean SDC of 86 % for both models. For Patients 2, 4 and 20, the very excellent results can be explained by the fact that the growth is very slow. Minimum (67 %) is obtained for Patient 9. This result is due to the fact that the shape of the tumor evolves heterogeneously over time during the two first times t_0 and t_1 .

Indeed the two PDE systems presented in this work are able to take into account evolving shapes due to the skull boundary but do not allow heterogenous spatial variations. One way to do so, we need to assume that M_0 varies spatially. The estimation strategy has to be adapted as the 0D model reduction is not valid anymore, see [11].

Results are satisfactory but do not permit to select one ODE model as the two ODE models give very similar outcomes.

Predictive power of the models To answer our second question, only two first available MRI examinations have been used to estimate the parameters of the models and then to predict the volume and the shape of the tumor at a later time corresponding to the time of the third available examination. The lack of available times of a given patient has been compensated by an available population of many patients using the mixed-effect approach to estimate the parameters. We recall that these predictions could prove valuable to inform medical decisions, adapt follow-up and hence optimize the use of public health resources.

Our prediction strategy has been validated. Indeed, the results are excellent: using ODE systems, we can predict the volume at t_2 with an error inferior to 10 % *i.e.* with the same order of magnitude of the segmentation error. Concerning the bias, it is smaller using ODE systems than linear model. One can remark that for some patients, the three models give similar results. For some other patients, the measured volume is included in the interval defined by the three predicted volumes. This motivates us to compare the mean of the predicted volumes to the measured volume: we obtain a global error of 9%. This strategy allows us to improve the volume prediction but cannot be used for the shape prediction.

Concerning the shape, one can see that it is very well estimated with a mean of 85 % for PDE systems and 79 % for the linear model. The results are similar to those obtained with the descriptive cases, which is very encouraging. On Fig 6, one can see as the shape of tumor of Patient 9 evolves heterogeneously in time, the difference between the predicted and the real shapes is important. The limitation of the linear model (which is not able to take into account the boundary of the skull) can be seen on the results of Patients 7, 8, 9 and 22. As previously, this section does not allow to select one PDE system. Both give similar results. This means that for meningioma, the hypothesis assuming that the growth rate is spatially independent seems realistic. This can be explained by the fact that the meningioma growth is slow.

5 Conclusion

In this work, we have introduced two PDE systems able to represent tumor growth. The growth rate is either assumed to be spatially dependent (*i.e.* decreases quicker inside the tumor) or assumed to be spatially independent (*i.e.* decreases at the same velocity inside or outside the tumor). The major advantage of these two models is that they depend only on two parameters and then can be adapted for each patient using observations that may be very sparse in time. After integration, these two models lead to two ODE systems that are used to estimate the parameters. In case of spatially-independent growth rate, the ODE system corresponds to the Gompertz model which is a very classical ODE model for tumor growth [6, 9, 14, 26, 27, 35].

The models have been validated retrospectively using a cohort of 39 patients with meningioma. This shows the descriptive power in terms of tumor volume and shape of our models. Then, we develop a strategy to predict the volume and the shape of the tumor at a later time using only two MRI examinations. Applying this strategy requires a population of patients with meningioma with at least three MRI examinations. Our results are very encouraging, provide a good insight on tumor growth and may help decide whether to extend the follow-up or to treat the tumor. Yet they have to be confirmed on a larger cohort. Work is also underway to consider additional covariates (*i.e.* clinical information of patients) to improve the accuracy of the prediction with machine learning to obtain a prior on meningioma behaviors. Three different patterns of growth are distinguishable in our cohort (linear, exponential or strictly concave.). These covariates may help determining the most likely pattern for a given patient and improve the personalization of the model by reducing the parameter search-space.

Acknowledgments

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Appendix

In order to prove Propositions 1 and 2, we will prove the following lemma.

Lemma 1. *Let $\bar{M}(t)$ the mean carrying capacity*

$$\bar{M}(t) = \int_{\Omega(t)} M(t, X) dX,$$

the quantity $V(t)$ satisfies the following ODE:

$$V'(t) = \bar{M}(t).$$

Proof. Let us compute $V'(t)$. Using Reynold's theorem and Eq (1), we get

$$V'(t) = \frac{d}{dt} \int_{\Omega(t)} dX = \int_{\partial\Omega(t)} (\vec{v} \cdot \vec{n}) d\sigma,$$

where \vec{n} is the outward normal to $\partial\Omega(t)$. Green theorem shows that $\int_{\partial\Omega} \vec{v} \cdot \vec{n} d\sigma = \int_{\Omega(t)} \nabla \cdot \vec{v} dX$. Thanks to Eq (3), it follows that

$$V'(t) = \frac{d}{dt} \int_{\Omega(t)} dX = \int_{\Omega(t)} MT dX = \int_{\Omega(t)} M dX,$$

since T is identically equal to 1 inside $\Omega(t)$. This last identity leads to

$$V'(t) = \bar{M}(t). \tag{16}$$

□

Proof. (Proposition 1) We can compute $\bar{M}(t)$

$$\bar{M}(t) = \int_{\Omega(t)} M(t) dX = \int_{\Omega(t)} M_0 e^{-\alpha t} dX = M_0 e^{-\alpha t} V(t).$$

This implies that

$$V'(t) = M_0 e^{-\alpha t} V(t).$$

This is easily solved and one gets

$$V(t) = V_0 e^{\frac{M_0}{\alpha} (1 - e^{-\alpha t})}.$$

One can recognize the formula of the Gompertz model, a very classical growth model, see [6] for a full study and [14, 9, 26, 27, 35] for validations of Gompertz model for tumor growth. □

Proof. (Proposition 2) We can compute $\bar{M}'(t)$ using Reynold's theorem:

$$\begin{aligned} \bar{M}'(t) &= \frac{d}{dt} \int_{\Omega(t)} M(t, X) dX = \int_{\Omega(t)} \partial_t M dX + \int_{\partial\Omega(t)} (\vec{v} \cdot \vec{n}) M d\sigma \\ &= - \int_{\Omega(t)} \alpha M T dX + \int_{\partial\Omega(t)} (\vec{v} \cdot \vec{n}) M d\sigma. \end{aligned}$$

Now, recall that T is identically equal to 1 within the tumor $\Omega(t)$ and M is identically equal to M_0 on the boundary $\partial\Omega(t)$. Therefore

$$\bar{M}'(t) = -\alpha \int_{\Omega(t)} M dX + M_0 \int_{\partial\Omega} (\vec{v} \cdot \vec{n}) d\sigma.$$

As previously, using Green formula and Eq (3), we have

$$\begin{aligned}\bar{M}'(t) &= -\alpha \int_{\Omega(t)} M dX + M_0 \int_{\Omega(t)} MT dX \\ &= (M_0 - \alpha) \int_{\Omega(t)} M dX = (M_0 - \alpha)\bar{M}.\end{aligned}$$

It follows

$$\bar{M}'(t) = (M_0 - \alpha)\bar{M}(t). \quad (17)$$

System Eq (16)-(17) can be solved and one gets

$$\bar{M}(t) = \bar{M}_0 e^{(M_0 - \alpha)t} = M_0 V_0 e^{(M_0 - \alpha)t},$$

and $V'(t) = M_0 V_0 e^{(M_0 - \alpha)t}$ leads to

$$V(t) = V_0 + M_0 V_0 \frac{e^{(M_0 - \alpha)t} - 1}{M_0 - \alpha}.$$

□