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Summary

As cancer evolution is challenging to evaluate, there is dire need of novel approaches offering clinicians a better insight on the disease. For instance, having an estimation of the growth of slowly evolving tumors that have to be monitored or of the risk of relapse after treatment may be invaluable for clinicians. In this article, two approaches (statistical learning and mechanistic modelling) are presented that aim at addressing these clinical questions. As we wish to use data available in the clinical routine for solid tumors, medical images will be a major source of insight on the disease.

Introduction

In order to evaluate the evolution of a tumor, different approaches may be used depending on the type of data available. When longitudinal data is available, it can be used to build a mechanistic model of the evolution of this disease. This model could then give a quantitative estimate or a prediction of this evolution. When only one single time point is available, statistical approaches are more suited. One tries to correlate different observed features of the disease with clinical outcome by using statistical learning techniques. *In this article, these two different kinds of approaches are presented through two examples from a clinical context.*

In the first example, we show how a mechanistic model describing the growth of meningioma (a type of intracranial tumor) may be useful to have an estimation of the future size, volume, location of the targeted lesion. This information could help clinicians adjust a patient's follow-up or plan a surgery if a specific area of the brain is at risk to be deformed by the increase of volume of the tumor. The derivation of mechanistic models is based on the biological knowledge and the available observations. Mathematical models have become popular tools to analyze longitudinal data in oncology where we want to obtain patient-specific prognoses for which purely statistical models are not adequate. Earliest models were describing the evolution of tumor diameters on mice for preclinical studies. These models - *e.g.* those based on Gompertz's law - have few parameters and were shown adequate to fit experimental data and in some cases, even have a certain predictive value. However, when coupled with imaging data, these models neglect most spatial information even if they describe tumor area or volume and not only the diameter of the lesion. To fully exploit medical images, it is therefore key to develop mathematical models describing the spatial evolution of the tumor at the scale of these images (which makes them essentially phenomenological). These allow more information to be kept from the data and one can expect to have a better insight on the tumor.

In our second example, we show how radiomics approaches [1] may be helpful in evaluating the risk of relapse of low-grade gliomas. This example illustrates how to combine information at different scales to obtain this evaluation. Whereas the former approach studied each patient individually (by personalizing a model), this approach uses the whole cohort to

determine a statistical correlation between various clinical, omics and imaging features and the clinical outcome of the patient. A significant number of patients is required in order to identify a significant correlation.

Approach and application example

Meningioma are rather benign intracranial tumors. One major clinical challenge is to evaluate their growth to help surgeons deciding if they should be resected (as the intervention may be risky depending on the location of the lesion) or carefully monitored. More precisely, the question we are trying to address is the following one: given two MRIs of a patient where the meningioma has been delineated, are we able to predict the location, shape and volume of the lesion at a given later time?

Different approaches are possible to model spatial tumor growth. Basically, two large classes of models may be distinguished. In the so-called *discrete model class*, the evolution of each cancer or healthy cell is described individually (hence at the microscopic scale). Agent based models (like in [2]) describe the evolution of individual cells. This class of models is well adapted to describe the smaller scales. However, these models are computationally very expensive and rendering mechanical effects might be difficult (for instance, one has to consider the interaction of each cell with its neighbors). On the other hand, in *continuous or macroscopic models*, one describes densities of cells, *i.e.* averages over a large number of cells or typically in a voxel of a medical image. Voxel-based models are often based on a set of partial differential equations (PDE) and describe cellular densities in each voxel as well as - in some cases - nutrients concentration or blood flow. This is the class of models we use for describing meningioma.

In this study in collaboration with CHU Bordeaux, meningioma are not treated and are growing naturally. In close collaboration with clinicians, key features of the disease (the tumor grows slowly from the arachnoid, is rather homogeneous) were translated into a mechanistic model based on a set of Partial Differential Equations [3]. This simple model describes the evolution of the density of cancer cells and of a growth factor that is decreasing over time. By dividing, cancer cells push their neighbors and creates a global passive movement that is described by a velocity assumed to follow Darcy's Law. This model has two parameters that are patient specific.

A key factor to the use of mathematical models for clinical applications is the recovery of their parameters. Indeed, several parameters involved in these models do not have any physical meaning nor can be measured experimentally. A way has to be found to overcome this difficulty. Once they are recovered, one can run the mathematical model and compute the future evolution of the tumor. If the mathematical model is biologically accurate, this computed evolution will not be much different from the real one and can be seen as a prognosis.

Here, the main source of information on the disease is obtained from images. From these images, we use the delineated tumor and compared its evolution with the simulation run with our model. In our case, the model can be integrated and the system of PDE transformed into an equation describing the evolution of the tumor volume. This equation has the same parameters as the full model. A Bayesian technique is then used to recover reasonable values of the parameters. The personalized model is then validated on a retrospective study from the Bordeaux Hospital with a very satisfactory accuracy [3]. Yet this technique does not work for tumors with complex shape evolutions (like brain metastases or gliomas). For this matter, more advanced data assimilation techniques have to be used like sequential approaches and state observers (that may also account for uncertainties in the observations). We have recently extended the approach of [4] with very promising results.

On the other hand, when no longitudinal information is available, other techniques have to be used. For instance, in a collaboration with Humanitas Research Hospital, we tried to evaluate the risk of relapse of patients with low-grade gliomas (a type of brain tumor). These patients had their tumor resected and the challenge for the clinicians is to determine whether they will relapse before or after 30 months (in order to adapt their follow-up). For a cohort of more than 100 patients, we had clinical information (sex, age, …), histo-molecular data (IDH1 status, codeletion) as well as information extracted from images (PET-MET scans and MRIs). From the images we compute various features (tumor volume, enhancement volume, SUVMax, SUVMean…) as well as a novel PET heterogeneity marker described in [5]. For each patient we know her/his clinical outcome, so we can determine if a relapse occurred before or after 30 months.

On this data, we trained a statistical learning algorithm to correlate the features to clinical outcome. This is achieved with a 10-fold cross-validation. The number of features is reduced through standard feature selection and dimensionality reduction algorithms. Several classical algorithms are then tested. With the best classifier the mean accuracy is around 82% and the AUC is at 0.82 which is very satisfactory. In particular, as shown in Figure 18, it gives a better stratification of patients than a classification by histological grade or by the IDH1 status (which is not entirely striking as our algorithm uses these features - and others - to discriminate patients).

Discussion and perspectives

We have presented two different approaches to obtain a better evaluation of the evolution of some intracranial tumors. The first one is purely patient-specific and relies on a mechanistic model that is personalized for each patient. The second one relies on a patient cohort and statistics to evaluate a risk of relapse. Both approaches are well adapted for the challenges they are trying to overcome. They show that mathematics could offer meaningful insights for clinicians in their routine.

Yet there are several shortcomings that may prevent the use of these approaches in other pathologies or contexts. There is obviously no generic model for cancer progression or response to therapy. A novel model has to be developed for each type of cancer targeted **and** the available data. This requires a strong collaboration between mathematicians, computer scientists, biologists and clinicians. Given the complexity of the cancer mechanisms, modelling is always a trade-off between accuracy (precise description of the biology) and applicability (the effective use of the model for our applications).

The personalization process takes time as it requires exploring the parameter space [6]. Yet this calibration could a be shortened with reduced-order models derived from the original models. These models - that are much faster to compute that the ones from which they are build - reduce the time taken by data assimilation algorithms that require many evaluations of the model for different sets of parameters. These reduced-order models may for instance be built analytically (as in the presented example), through proper-orthogonal decomposition [7] or with machine learning techniques.

A promising perspective is the development of hybrid approaches combining cohort information and individual evolutions. For simpler mechanistic models (based on ordinary differential equations), mixed-effect models can be used but their extension to spatial models based on partial differential equations is far from being straightforward [8]. Another approach that we are currently investigating, is to include model parameters as patient-specific features in a machine-learning approach.

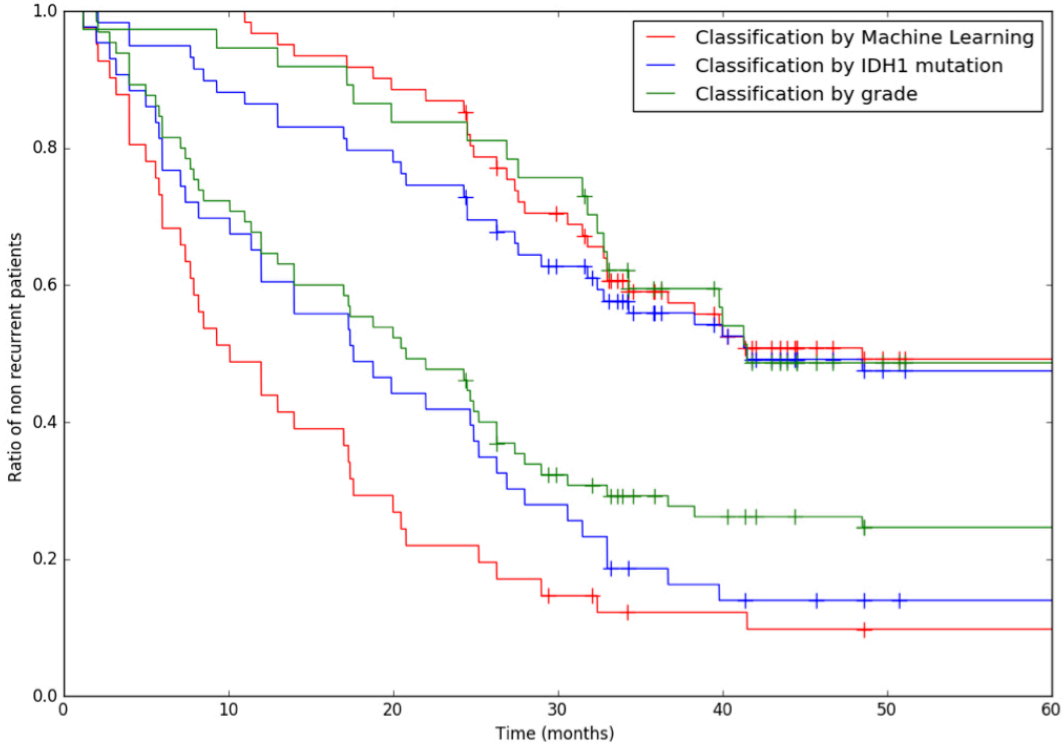
Finally, as the ultimate goal is to develop decision-helping tools for clinicians, great care should be taken to ensure the robustness of these tools. The answer they offer should not be sensible to noise and uncertainty (even in delineations [9]),

model prediction [10], data variability (between medical centers and medical devices) for instance. This has to be investigated seriously for any useful clinical application.

References

1. Parmar, C., Grossmann, P., Bussink, J., Lambin, P., & Aerts, H. J. (2015). Machine Learning methods for Quantitative Radiomic Biomarkers. Scientific reports, 5, 13087.
2. Mansury Y., Kimura M., Lobo J., Deisboeck T.S., Emerging Patterns in Tumor Systems: Simulating the Dynamics of Multicellular Clusters with an Agent-based Spatial Agglomeration Model, Journal of Theoretical Biology, Volume 219, Issue 3, 2002,
3. Pianet, V & Colin, Thierry & Loiseau, H & Joie, J & Lafourcade, J & Kantor, G & Bigourdan, A & Taton, Benjamin & Saut, Olivier. (2017). P12.23 Tumor growth model applied for meningiomas: first clinical validation. Neuro-Oncology. 19. iii99-iii100.
4. A. Collin, D. Chapelle, P. Moireau, A Luenberger observer for reaction–diffusion models with front position data, Journal of Computational Physics, Volume 300, 2015.
5. T. Kritter, M. Rossi, T. Colin, F.H. Cornelis, L. Egesta, L. Bello, A. Chiti, C. Poignard and O. Saut, PhD Heterogeneity Index: a methionine PET based prognostic factor in low grade gliomas, submitted.
6. M. Lê, H.Delingette, J. Kalpathy-Cramer, E. Gerstner, T. Batchelor, J. Unkelbach, N. Ayache, MRI Based Bayesian Personalization of a Tumor Growth Model, in IEEE Transactions on Medical Imaging, vol. 35, no. 10, pp. 2329-2339, Oct. 2016.
7. T. Colin, F. Cornelis, J. Jouganous, J. Palussière, O. Saut, Patient specific simulation of tumor growth, response to the treatment and relapse of a lung metastasis: a clinical case, Journal of Computational Surgery 2015, 2:1.
8. Grenier, E., Louvet, V., & Vigneaux, P. (2014). Parameter estimation in non-linear mixed effects models with SAEM algorithm: Extension from ODE to PDE. ESAIM: Mathematical Modelling and Numerical Analysis, 48(5), 1303-1329.
9. Cornelis, F.H., Martin, M., Saut, O. et al. Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumor response assessment using RECIST 1.1, Eur Radiol Exp (2017) 1: 16.
10. Andrea Hawkins-Daarud, Sandra K. Johnston, Kristin R. Swanson, Quantifying Uncertainty and Robustness in a Biomathematical Model Based Patient-Specific Response Metric for Glioblastoma, bioRxiv 325340; doi: https://doi.org/10.1101/325340

Figure 18. Kaplain Meier curves on the cohort from Humanitas Hospital (in collaboration with L. Bello and M. Rossi). Three different stratifications are evaluated: by grade (where risk of relapse is directly related to grade), by IDH1 status (where we split patient regarding the IDH1 mutation status) and by our machine learning algorithm (which uses grade, IDH1 status as well as other clinical, omic or imaging features). Our approach yields a much better stratification of patients.


Classification by Machine Learning
Classification by IDH1 mutation
Classification by grade
Ratio of non recurrent patients
Time (months)
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60