Mathematical models for the dynamics of low-grade gliomas and their response to therapies

PhD dissertation summary

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In this dissertation, we developed macroscopic mathematical models describing several aspects of the growth dynamics of low-grade gliomas and their response to chemotherapy. Low-grade gliomas (abbreviated as LGGs) are brain tumours having a poor prognosis and causing a premature death for almost all patients. The clinical course of this disease is usually very difficult to predict. Some of these tumours remain stable for years, while others progress rapidly into their more malignant counterparts known as high-grade gliomas, which induce the appearance of major neurological deficits and, eventually, death. Unfortunately, it is extremely difficult to verify an arbitrary number of possible therapy schemes *in vivo* as, apart from ethical reasons, it is very time-consuming. Due to the long time of disease evolution in some of LGGs patients, clinical trials on LGGs require many years to test a single hypothesis.

Some of the questions coming from medicine could be potentially addressed using mathematical frameworks [6]. However, up to now only few studies have been intended to describe LGG growth and its response to therapies using a mathematical modelling techniques. Some of the mathematical models presented so far take into account a large number of quantities which are very difficult, or impossible, to measure or estimate, see *e.g.* the review [7].

Models proposed in this thesis are based on biological and clinical studies concerning LGGs and all models' parameters have a clear biological meaning. Most of them were estimated from the appropriate data or literature and at most four parameters were considered to be patient-specific. Such a "minimalistic approach" enabled to fit the models' solutions to reflect the growth kinetics of individual patients, obtaining very good results. We validated our models using LGGs patients' data provided by our collaborators from Bern University Hospital. Importantly, we performed mathematical analysis of our models and studied various quantities of potential practical interest.

In **Chapter 2** we formulated a mathematical model describing LGGs growth and their response to temozolomide, a specific chemotherapeutic drug currently used to treat these tumours. The model was developed in the form of two ODEs describing the evolution of two populations of LGG cells:

$$\begin{aligned} \dot{P} &= \rho P \cdot f\left(\frac{P+D}{K}\right) - \alpha P C, \\ \dot{D} &= -\frac{\rho}{k} D \cdot f\left(\frac{P+D}{K}\right) + \alpha P C, \end{aligned} \tag{1}$$

with initial conditions

$$P(0) = P_0, \quad D(0) = 0, \tag{2}$$

where P denotes the population of proliferating cells, D – population of cells damaged by chemotherapy. Such an approach was chosen to characterise the prolonged response of LGGs to cytotoxic treatments, which lasts months or sometimes even years after the end of therapy [8, 9]. A drug dynamics was modelled directly by an impulsive ODE:

$$\begin{aligned} \dot{C}(t) &= -\lambda C, \\ C(0) &= C_0, \\ C(t_j) &= C(t_j^-) + C_j, \end{aligned} \tag{3}$$

where $t \in \mathbb{R}_0^+$, t_j are the times of subsequent doses administration and C_j are the fractions of the given doses that reaches the tumour tissue, $j = 1, \ldots, n$. This model of drug kinetics allowed to realistically model the way chemotherapy drugs are administered in the clinical practice. Recall that other mathematical models for glioma response to chemotherapy did not focus on a very realistic description of chemotherapy drug administration, see *e.g.* [10].

We investigated the mathematical properties of the proposed model with a general form of tumour growth function f. In particular, we proved the existence and uniqueness of solutions. We showed that there exists a compact set invariant with respect to the evolution of the model in a case when initial conditions and model parameters fulfil given conditions. We showed that the long-term behaviour of the model is similar for different choices of the specific growth function. To be specific, we showed that in the case of constant treatment, the conditions for stability of existing steady states are the same for Gompertz type and logistic type of tumour growth function, *cf.* Theorem 2.8. In addition, we also considered drug concentration to be described by an asymptotically periodic function, which is a generalisation of the previously proposed one [2]. In Theorem 2.12. we indicated the condition under which the trivial steady state is asymptotically stable in the case of asymptotically periodic treatment. Based on this result, we provided estimations of suggested minimal effective doses for individual LGG patients. Finally, we showed that in some cases of periodic treatment there exist periodic solutions.

We used numerical analysis methods to solve our system and analyse the dependence of the model dynamics on parameters values. It turned out that our ODE model with logistic growth function not only reflected the fundamental phenomena on LGGs growth and response to chemotherapy but also fitted well to volumetric data of LGG patients treated with chemotherapy. We also studied various quantities of practical meaning, among others the time to radiological progression, defined as the time when a tumour attains its minimum volume after the chemotherapy and subsequently starts regrowing. Investigating a wide range of possible values of parameters, we concluded that virtual tumours having a shorter time to radiological progression after chemotherapy may be more aggressive. Such a behaviour was also noticeable in LGGs patients data and has been previously observed likewise for LGGs treated with

radiotherapy [1, 11]. We suggested that estimated time to radiological progression can be useful as a measure of tumour aggressiveness and a possible indicator of tumour prognosis.

Through simplifications made to the original model, we managed to estimate the time to radiological progression as a function of the relevant biological and therapeutic parameters. The obtained formula given by Eq. (2.46) may be helpful in designing improved personalised treatment schedules, due to its dependence on tumour-specific parameters.

On the basis of our mathematical model, we also proposed a probing procedure which could be considered in clinical practice. We suggested applying a small number of chemotherapeutic drug doses and monitoring the tumour response to verify tumour's characteristics. The latter treatment decisions would depend on the observed time of maximal response. Tumours attaining their minimal volume early after a short course of chemotherapy treatment may be more aggressive, thus the remaining drug doses should be finished as soon as possible and other therapeutic options (further surgery if feasible or radiotherapy) should be considered. In the opposite case of slowly-responding tumours, it seems that after such a probing procedure the rest of treatment might be delayed (as these tumours seem to be less aggressive).

In **Chapter 3** we described mathematically the process of malignant transformation, *i.e.* the switch of low-grade gliomas to high-grade gliomas. Based on biological observations, we raised the hypothesis that malignant transformation may be induced by changes in tumour microenvironment happening as a result of increased tumoural density [4]. Such assumption led us to a formulation of a system of two reaction-diffusion equations coupled by a switch function describing the transition from low-grade glioma phenotype to a more malignant one, characterised by larger both proliferation and motility rates. The full mathematical model for the evolution of both tumour cells populations is given by the following system of Fisher–Kolmogorov–type equations [12]:

$$\begin{aligned} \frac{\partial L}{\partial t} &= \rho_L L\left(1-\frac{L+H}{K}\right)+D_L\Delta L-\frac{1}{\tau}S\left(\frac{L+H}{K}\right)L, \\ \frac{\partial H}{\partial t} &= \rho_H H\left(1-\frac{L+H}{K}\right)+D_H\Delta H+\frac{1}{\tau}S\left(\frac{L+H}{K}\right)L, \end{aligned} \tag{4}$$

with initial conditions:

$$L(0,x)=L_0(x)\in C^2\left(\bar{\Omega}\right), \quad H(0,x)=0, \tag{5}$$

and homogeneous von Neumann boundary conditions:

$$\left.\frac{\partial L}{\partial n}\right|_{\partial\Omega}=\left.\frac{\partial H}{\partial n}\right|_{\partial\Omega}=0. \tag{6}$$

We showed the existence, uniqueness and non-negativity of solutions of the proposed model. We demonstrated the local stability of homogeneous steady states of the system in

the case of zero and non-zero diffusion coefficient. We also investigated the stability of space homogeneous steady states and showed in Theorem 3.5 that no diffusion-driven instabilities occur in the system, which is a biologically viable result.

As the model was developed with a minimal number of adjustable parameters, we were able to successfully fit its solutions to data describing the evolution of tumours which underwent malignant transformation. Subsequently, using numerical simulations and performing sensitivity analysis, we studied how the patient-specific parameters influence the long-term prognosis. We found out that the initial cell density at the centre of a tumour and rate of LGG cells growth are the parameters which have the biggest influence on both time to malignant transformation and overall survival.

These results suggest that the main goal of LGGs care should be the possible prevention or delay in appearing malignant transformation. Thus, we focused on studying analytically the tumour dynamics in the time horizon before the onset of malignant transformation. We discussed a possible model simplification in this period of time. Using a solution of Skellam equation we derived explicit formulae for the evolution of radius of the detectable part of a tumour and the velocity of its growth. Due to practical motivations, we also determined an analytic formula for the time of malignant transformation onset as a function of patient-specific parameters. Finally, we discussed the possible ways to apply some of these results in clinical oncology practice. We believe that by coupling detailed radiological imaging information with mathematical estimation derived in Chapter 3, malignant transformation could be predicted in a non-invasive way. Such a prediction could have a huge impact on treatment planning for low-grade glioma patients.

Motivated by the above results, in **Chapter 4** we studied a reaction-diffusion system capable of describing both the process of malignant transformation and the tumour response to chemotherapy. It was based on both models presented in Chapters 3 and 4 and developed in the following form:

$$\begin{aligned} \frac{\partial P}{\partial t} &= \delta \Delta P + \rho P \left(1 - \frac{P+D}{K}\right) - \alpha C P, \\ \frac{\partial D}{\partial t} &= \delta \Delta D - \frac{\rho}{k} D \left(1 - \frac{P+D}{K}\right) + \alpha C P. \end{aligned} \tag{7}$$

System (7) is complemented with non-negative initial conditions and homogeneous von Neumann boundary conditions. We studied the system analytically proving the existence and uniqueness of solutions. In the case of constant chemotherapy, using Fredholm alternative theorem, among others, we also showed that travelling wave solutions exist for some parameters values, see Theorem 4.3.

Afterwards, we used that model to investigate possibly improved chemotherapy fractionations. Usually, while studying theoretically the possible more effective treatment schedules, researchers aim at minimising the total tumour size or the total number of cells. However, in

the case of LGGs, the total tumour size does not have to be related with the tumour aggressiveness or responsiveness to treatments. There have been reported cases of large tumours that remain stable for long periods of time and small tumours growing very fast. However, it seems unquestionable that after the malignant transformation onset the mean velocity of tumour growth increases significantly. Thus, it appears that the possible delaying of malignant transformation is an alternative goal potentially applicable in selecting treatment schemes for LGGs patients.

We proceeded to estimate the time of malignant transformation onset for virtual patients treated with a fixed number of chemotherapeutic drug doses. In order to do so, we considered the evolution of local tumour density L at the centre of a tumour:

$$\begin{aligned} \dot{L}(t) &= \rho L\,(1-L) - \alpha C L, \\ L(t_1) &= L_1 > 0, \end{aligned} \tag{8}$$

where function C describing chemotherapy concentration satisfies:

$$\begin{aligned} \dot{C}(t) &= -\lambda C, \\ C(t_1) &= C_0 > 0, \\ C(t_i) &= C(t_i^-) + C_0 \quad \text{for } i \in \{2, \ldots, n\}, \end{aligned} \tag{9}$$

compare system (3). In order to obtain a possibly simple form of the solution of system (8), we simplified the description of chemotherapy, arriving at

$$\begin{aligned} \frac{\mathrm{d}L}{\mathrm{d}t} &= \begin{cases} \rho L(1-L) - \alpha \bar{C} L & \text{for } t \in [t_i, t_i + \epsilon), \\ \rho L(1-L) & \text{for } t \in [t_i + \epsilon, t_{i+1}) \text{ and } t \geq t_n + \epsilon, \end{cases} \\ L(t_1) &= L_1, \end{aligned} \tag{10}$$

where ϵ is the time when the drug is acting on a tumour and $\bar{C}$ is the mean value of drug concentration in that period of time. In Theorem 4.4 we derived the solution of the resulting ODE system. We also studied the long-term dynamics of the obtained difference equation describing the density of tumour cells at the centre of a tumour at times of the drug administration, see Theorem 4.6. Afterwards, we proposed an estimate of the onset of malignant transformation for virtual patients treated with a fixed number of chemotherapeutic drug doses. We investigated the dependence of obtained estimate on model parameters and treatment scheme. Based on numerical simulations, we suggested that a better treatment outcome could be possibly attained only by increasing the break between subsequent doses. We also discussed the feasibility of such a solution.

We conclude that therapy schemes designed on the basis of tumour-specific characteristics may lead to significant improvements (even of the order of a year) in therapy effectiveness. We hope that optimised cancer treatment protocols on the basis of mathematical models,

such as the ones presented in this dissertation, may become in the future a standard element of personalised medicine.

In each chapter, we presented results suggesting some novel strategies for LGG care. However, they require meticulous verification in an experimental setting. Both *in vitro* and *in vivo* experiments are being planned to verify the outcomes of this thesis and study their possible use in practice. In the future, having more specific experimental or clinical data would enable to include in our mathematical models more phenomena (such as acquiring drug resistance or toxicity) and address other clinically-driven questions.

The results of this dissertation were published in four scientific articles in peer-reviewed high-ranked international journals [1–3, 5] and in a number of proceedings of national and international conferences (*e.g.* in AIMS Conference on Dynamical Systems, Differential Equations and Applications, Quadrennial Meeting of the World Federation of Neuro-Oncology Societies, International Seminar on Statistics and Clinical Practice, BIOMAT International Symposium on Mathematical and Computational Biology). In the nearest future, the results presented in Chapter 4 will be submitted to other peer-reviewed journals.

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