Problems in gliomas' treatment

In this project we will focus on the most frequent type of brain tumours, namely gliomas, accounting for about 80% of all brain tumours. Gliomas are generally divided into astrocytomas or oligodendroglioma, originating from different glial cells. World Health Organisation (WHO) grade I astrocytoma are very rare and usually curable. WHO grade II gliomas are usually referred to as low-grade gliomas (LGGs), while WHO grade III and IV—as high-grade gliomas (HGGs). The incidence rate of astrocytic tumours in Europe is 4.8 per 100,000 per year, while oligodendroglial tumours has incidence rate 0.4 [3], whereas median untreated survival time for HGGs' patients is about 1 year and the average years of life lost for each patient with HGG is high (20.1 years), thus one British study [1] ranked it as the most malignant out of 17 types of cancer. Even lower grade gliomas with very slow proliferation indexes have very poor prognosis as they can rarely be cured. Despite therapies used, those tumours transform into more aggressive, anaplastic forms. LGGs have a tremendous impact on the community also because of the fact that they usually occur in young patients, therefore being the object of strong clinical interest and main inspiration for following mathematical studies.

In the initial phase of tumour growth, apart of seizures most patients do not have any symptoms. Because of lack of major symptoms and young age of patients, an object of the treatment is not only to prolong time of survival, but also to minimise therapies side effects in such

a way that patients maintain a good quality of life as long as possible. Management decisions (such as whether and when a patient with LGG should receive resection, radiation therapy or chemotherapy) are not fully standardized and depend on many factors, including patient preference, tumour location, age and patients' quality-of-life. Therefore, timing and dosing of radiotherapy, chemotherapy or combination of both requires a careful planning that may benefit from—now absent—rational design based on mathematical modelling.

Unfortunately, it is extremely difficult to verify many possible therapy schemes in vivo as, apart from ethical reasons, it is very time-consuming. Due to long time of disease evolution in some of LGGs patients, clinical trials on LGGs sometimes require about ten years to test a single hypothesis. So far, no one has been able to establish cell line which reproduces in mice or rats the behaviour of human LGGs. This is why research on this type of tumours has been so slow with no substantial progresses in the last few years except from those enabling a more accurate resection of the tumour with minimal damage to functional brain areas.

Mathematical oncology

Mathematical models have a great potential to help in managing medical problems. They might be used to simulate e.g. kinetics and dynamics of tumour cells, drug concentration, course of therapy. The results can aid in individual patients' treatment decisions, finding appropriate therapeutical timings and/or fractionations or even the development of new therapies [4]. We believe that properly constructed mathematical models could assist in personalising medicine, what represents another hallmark of contemporary medicine.

Unfortunately the role of mathematics in generating mechanistic insight into biomedical problems in general is less well known than in case of physics and engineering. An obvious reason for difficulties faced during interdisciplinary work in so-called "mathematical oncology" is the completely different status of knowledge in mathematics with comparison to biology and medicine. Mathematical models have been unintelligible to most biomedical researchers, therefore it is usually mathematicians who have to acquire understanding of main biological processes. The other reason is different scientific goals. Most biologists and physicians do not consider mathematicians as possible

contributors as instead of theorems they look forward to studies designed for therapeutic improvements. Moreover, in case of gliomas one has to face the general lack of large cohorts of patients treated in the same way.

Researchers working in the area of mathematical oncology (or mathematical biology in general) usually have one of the following approaches: either they use biological and medical knowledge only as a source of mathematical problems and do not look for any applications, or they search for issues of major biomedical importance and openminded physicians who would verify whether theoretical results obtained by mathematician might be exploited for practical, therapeutic purposes. We are in favour of the second approach, agreeing completely that collaboration between mathematicians and biologists or medical doctors can enhance both areas of science. As Prof. Cohen said "Mathematics is biology's next microscope, only better. Biology is mathematics' next physics, only better" [2].

Mathematical models of gliomas - future perspectives

In the case of gliomas, mathematical models presented so far have been usually based on a vast number of parameters and intracellular quantities, some of which are very difficult (if possible) to measure or even estimate, e.g. [6]. However, up to now only on the basis of the simplest models it has been possible to extract conclusions useful for clinicians, as in e.g. [5]. Therefore, in this project we aim to build parametric models of tumour growth that would be accurate enough to reflect clinical observations and simple enough so that they can be analysed mathematically.

We will construct new or modify existing mathematical models describing the growth of gliomas and their response to therapies on the basis of discussions with collaborating biologists and medical doctors as well as the literature on these kind of tumours. We will focus on the development of mathematical models for LGGs, which have been studied only scarcely from the mathematical point of view, but have a simpler biological phenomenology (no angiogenesis, good oxygenation, less phenotype heterogeneity). We would like to verify different possible terms for motility term in model of tumour growth, e.g.one as in porous medium. In that case we will try to derive analytical

estimates of total tumour mass and velocity of its growth. We will consider mainly radio- and chemotherapy, but we would like to investigate also a joint effect of both as well as some non-standard therapies.

In such kind of research, mathematical analysis of models is a task necessary, among others, to understand better the system' dynamics and to revise results obtained numerically. We will check whether constructed systems are well-posed and study asymptotic behaviour of the systems as well as try to prove system dynamics that could be important from the point of view of applications. We will possibly study which parameters have greater influence on behaviour of model's solutions, thus indicating parameters responsible mostly for tumour growth or response to therapy. If interesting and scientifically justified, we will also

perform mathematical analysis of models constructed
by other scientists. We will also validate developed models using data from our cooperating institutions or available in medical literature.
The ultimate goal is to use proposed mathematical models and results of mathematical analysis of them to improve the current treatment of cancer patients and to raise hypothesis that can be later tested by clinicians and biologists. Based on models which reproduce characteristics of tumour and its response to therapy, we will be able to optimise current treatment protocols or help in designing new ones. In particular, we opt to derive proper formulas which could help clinicians in assessing tumours aggressiveness and selecting best therapies. We intend to formulate clinically relevant hypotheses and study mathematically if different therapeutical approaches may lead to a better patients' outcome. In order to do so, we will use different kinds of mathematical tools (mathematical analysis, optimization
tools, sensitivity analysis, numerical simulations, etc.). Our research up to now gives us a promising perspective for realisation of all purposes described here.

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