

### **C. DESCRIPTION FOR THE GENERAL PUBLIC**

Cancer is a leading cause of death worldwide, accounting for over 8 million deaths every year. Developed countries have been hence allocating a substantial portion of their resources in order to find new means of conquering this disease. Although the progress which has been made over the past few decades is unquestionable, tumours are still capable of evading even the most sophisticated sorts of treatment. Cancer has therefore been attracting scientists representing various scientific fields – not only biologists, medics and biochemists, but also mathematicians.

Experimental oncologists nowadays are swamped with data. The refinement of measurement techniques in recent decades made it possible to gather more and more information about the cancer-related processes. Given the amount of data, it seems natural that oncologists could greatly benefit from the help of quantitative, mathematical methods. Somehow surprisingly, however, medical papers seldom feature equations and oncology is yet to fully capitalise the full potential of mathematics. The main purpose of our project is therefore to construct a suitable framework with a potential to be used in a clinical context.

Mathematicians are capable of formulating models, which usually take a form of systems of differential equations. Differential equations relate functions, which typically represent some physical quantities, to their derivatives. These equations are meant to represent the actual biochemical and physical processes occurring in the tumour, such as cell proliferation, mutations or diffusion and effects of an administered drug.

Equipped with a suitable model, an oncologist could theoretically conduct a computer simulation to predict the tumour behaviour (e.g. growth rate, likelihood of metastasis) and plan the treatment accordingly. Mathematical models could also be used to test hypotheses concerning the growth of tumours and preliminarily assess the effectiveness of different types of treatments.

In our project we are planning to focus on investigating mathematical models which provide insight into two major obstacles which arise in cancer treatment planning – acquired drug resistance and the interactions between the chemotherapy combined with the antiangiogenic treatment (so called joint therapy).

Acquired drug resistance is a process during which the cancer cells develop immunity to the chemotherapeutic drug over the course of treatment. The emergence of drug resistance is usually attributed to the high mutation and proliferation rates exhibited by cancer cells. Our preliminary results, however, suggest that this process is heavily influenced by cell competition.

Cancer cells, just like macroscopic organisms, exist in an environment with limited resources (e.g. oxygen and nutrients) and hence need to compete with each other in order to survive. As the malignant cells are being heavily altered by mutations, the principles of Darwinian natural selection apply. In the absence of a cytotoxic agent, the chemotherapy-sensitive cells are able to outcompete the resistant ones and the resulting tumour responds well to the therapy. When a selective force (a drug) is applied, the resistant cells win the competition, as they are better suited to exist in the new, hostile conditions. Mathematical modelling may contribute to a better understanding of these processes and suggest chemotherapeutic schemes which minimise the drug resistance.

The other issues regard a very promising treatment strategy – the joint therapy. Antiangiogenic drugs are agents which block a formation of new blood vessels (a process known as angiogenesis), which are necessary for cancer to acquire oxygen and nutrients. Much hope was associated with the antiangiogenic agents, but their effectiveness in extending the patients' survival time proved to be at most mediocre when applied on their own. Much better results were obtained when antiangiogenic treatment was applied together with chemotherapy. This seems counter-intuitive at first – inhibition of the tumour's vasculature should decrease the efficacy of chemotherapy, as less of a cytotoxic agent can reach tumour with bloodstream.

It was therefore postulated that although antiangiogenic treatment decreases the number of blood vessels, it increases the quality of the remaining ones (so called vessel normalisation). This kind of treatment may therefore result in a refinement of tumour vasculature and hence chemotherapy efficacy. To fully capitalise on this fact, however, a careful timing and dosage is necessary, which suggests the use of mathematical methods.

Defeating cancer is the greatest challenge facing contemporary medicine, yet oncologists and biologists seem to be reluctant to fully exhaust the potential of mathematical modelling. This can be potentially changed by formulating models with strong links to experimental studies and clinical data. After all, the fight against cancer should be played with no holds barred.