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Optimising chemo- and radiotherapeutic treatment protocols using synergy and tumour synchronisation

We present an agent-based approach to the modelling of cellular dynamics within tumour spheroids under the effect of combined chemotherapy and radiation treatment. Within our agent-based approach cells are represented as instances of a C++ cell-class which advance through a realistic cell cycle in response to external and internal stimuli such as the concentration of nutrients and the pressure upon the cell by neighbouring cells. The model makes use of a dynamic Delaunay triangulation in order to derive the cell neighbourhood topology while its dual, a Voronoi tessellation, is employed in order to calculate the contact surfaces between adjacent cells. Our model employs the well-known linear quadratic model for irradiation damage in combination with a stochastic model for the cell's dynamic reaction to damage.

We can study the growth of tumour spheroids up to a volume of about $1mm^3$ which show a high degree of complexity and can thus be used as a model system for larger amounts of tumour tissue as they possess all properties which are present in large-scale tumours (hypoxic regions, necrosis, concentration gradients). As a results of irradiation treatment a dynamic reaction is triggered in the tumour system which can be studied in detail. Reoxygenation of the tumour volume and a decrease in pressure due to cell necrosis lead to excessive regrowth after irradiation as previously quiescent cells are reactivated. A distinct resynchronisation of the cell cycle is observed which can be exploited within fractionated irradiation treatment or the timed delivery of drugs.

Using measured survival curves for single cell cycle phases we can show that the amount of tumour killing will strongly depend on the activation status of the tumour. A radiation- or drug-induced synchronisation of the cell cycle can be exploited to target the tumour in an optimal state where the sensitivity to the planed treatment is maximal. Thus we can calculate treatment protocols which will result in a greatly enhanced amount of tumour killing for the same dose of radiation or drug.

Combining medication and radiation treatment in our simulation we can show that the tumour can be optimally prepared to increase the radiosensitivity during following treatments. Vice versa there are optimal points to employ chemotherapy after irradiation sessions.

References

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