Hyperthermia is a cancer treatment that has a synergistic effect when combined with radio- or chemotherapy. The radiosensitization has different origins – one of which is the temporary impedance of the repair of the radiation-induced DNA damage.

Mathias Weyland

In contrast to radiotherapy, no satisfactory dose concept is established for hyperthermia. Such a dosimetric concept, however, would offer the possibility of optimizing hyperthermia treatments, thus resulting in more bearable and successful treatments for human and animal patients. Similar to the exiting principles in radiation therapy, the aim is to ground such a dose concept for hyperthermia in biophysical models. When implemented in this manner, model-based data-analysis is not only able to predict the result of a particular treatment, but also a tool to find optimal treatments, to perform sensitivity analyses, to investigate alternative treatments, to explore the modeled system with simulations and much more.

In order to be used in this way, however, these models must be calibrated: During the calibration procedure, numerical values are assigned to the various model parameters such that the model can (in a first step) reproduce experimentally observed findings, e.g. from assays performed in the lab. This work addresses calibration of a model suitable for the simulation of combined hyperthermia and radiotherapy – the Multi-Hit-Repair (MHR) Model.

One focus of this work is on the assessment of the usability of various assays that serve as inputs for model calibration. This work demonstrates that a combination of the clonogenic assay (a test to evaluate the clonogenicity of cells), as well as the comet assay (a method to quantify DNA damage in individual cells) is particularly suitable. In addition, it is shown that at least these two assays are needed for calibration and that the omission of one assay has a negative impact on the calibration result.

A second focus of this work is – after the above-mentioned determination of suitable assays – the implementation of the actual model calibration. First, a mapping of the results from comet assay onto the model structure is developed. Second, the power of Approximate Bayesian Computation (ABC) as a calibration method is demonstrated. This includes the simplicity of analyses of the calibration results, as well as the possibility to combine the results of different calibration passes easily, even if they originate from data from different assays.

Regarding both, mapping of results from the comet assay to the model structure and calculations for the model calibration, this work proposes a paradigm shift in which available data are not aggregated to their mean or median, but the entire distribution of the data is considered instead. This work showcases the advantages of such a distribution-based approach which can also be applied in many other fields.

With an improved calibration of the MHR model, it will be possible to perform improved hyperthermia dose calculations for cell cultures at first, and later for patients, in order to achieve a better overall treatment.

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