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Computational Model of Targeted Drug Delivery via Low-Temperature Sensitive Liposomes and image-guided focused ultrasound

The chemotherapeutic agent doxorubicin (DOX) is commonly used in cancer treatment, but causes dose limiting side effects. Various liposomal drug carriers were developed to overcome short plasma half-life and negative side effects of chemotherapeutic agents. Low temperature sensitive liposomes (LTSL) release their content only if exposed to a temperature above approximately 40 C and in contrast release a relatively small amount of drug at normal body temperature. The combination of LTSL with local heat generated by image-guided focused ultrasound enables non-invasively targeted drug delivery. We developed an axial symmetric computational model to simulate temperature, blood perfusion, and drug concentrations in different compartments of the model. The model describes the release of drug from the liposomes, transport mechanisms of the drug between different compartments and spatio-temporal drug and liposome concentrations. We compared two cases: Tissue heated to hyperthermic temperatures with a target temperature of 43C, and hyperthermia followed by a short high temperature exposure with a target temperature of 68 C of the same region. Blood perfusion was reduced of 7% of the baseline value within the heated area after hyperthermia, whereas it was completely eliminated inside the target region in case of the high-temperature exposure. Due to the eliminated blood flow drug is facilitated to remain trapped within the tissue. The plasma concentration of DOX reached a peak value of 12.1 g/g at t=3 min in both cases. The intracellular concentration of DOX during hyperthermia followed by short high temperature exposure was almost two times higher than hyperthermia alone with peak values of 18 g/g and 10 g/g, respectively. The complex interaction between thermal cancer treatments and locally induced chemotherapy agents, require a mathematical model to identify the relationship between heat exposure and pharmacokinetics in order to optimize drug delivery.