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Predictive Relay Control in Constrained Minimum-Time Delivery of Therapeutic Dose

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The effectiveness of many treatments depends on the therapeutic dose delivered to the patient. The dose can be delivered systemically, or targeted to the specific organ or a spatially distributed region of the patient. Chemotherapy, radiation and thermal treatments are examples of clinical modalities, the effectiveness of which is characterized by the systemic or targeted delivery of the therapeutic dose. The therapeutic dose expresses the relationship between the evolution of the treatment and its outcome. By its very nature, the therapeutic dose is an integral expression, which correlates the instantaneous treatment progression (e.g. radiation rate, temperature elevation or the instantaneous drug concentration at the target site, respectively for radiation, thermal and chemotherapies) to the treatment outcome. From a clinical perspective, the dose delivered to the target should not cause unacceptable damage to the surrounding normal tissue in the case of the targeted treatments, or exceed the maximum allowable levels in the vulnerable regions during systemic treatment administration. Therefore, the problem of the therapeutic dose delivery is the problem of controlling the treatment progression to achieve the desired final dose without violating the trajectory or the endpoint constraints in normal tissue. In this paper, the therapeutic dose delivery problem is formally stated as the problem of controlling nonlinear integrators with saturation constraints on actuation and the state constraints to prevent damage to the normal tissue. We analyze and discuss unique features of the dose control problem, and establish the necessary condition for the time optimality of the control for nonlinear integrating systems is also derived. The result states that the time-optimal policy is achieved when the controller operates at the actuation or the state constraints. The availability of the general optimality result allows us to eliminate the need for solving the optimization program in real time. The role of the predictive controller in the proposed approach is to calculate control inputs leading to the treatment progression at one of the imposed constraints. The feedback of the predictive controller is used to update the predictive model. The main dose controller is the switching controller, which selects the actuation corresponding to the boundary of the allowable set in the space of states and inputs. The problem formulation is motivated by the examples of the chemotherapeutic, radiation and thermal dose delivery. The problem of the thermal dose delivery is used to supplement the general discussion with computational and experimental results.

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