Using an automaton model for the cell cycle to probe temporal patterns of drug administration in cancer chronotherapy

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Abstract- Determining optimal patterns of drug administration represents a central issue in chronopharmacology. Given that circadian rhythm profoundly affect the response to a variety of anticancer drugs, circadian chronotherapy is used clinically in cancer treatment. Assessing the relative cytotoxicity of various temporal patterns of administration of anticancer drugs requires a model for the cell cycle, since these drugs often target specific phases of this cycle. Here we use an automaton model to describe the transitions through the successive phases of the cell cycle. The model accounts for progressive desynchronization of cells due to the variability in duration of the cell cycle phases, and for entrainment of the cell cycle by the circadian clock. Focusing on the cytotoxic effect of 5-fluorouracil (5-FU), which kills cells exposed to this drug in S phase, we compare the effect of continuous infusion of 5-FU with various circadian patterns of 5-FU administration. The model indicates that the cytotoxic effect of 5-FU is minimum for a circadian delivery peaking at 4 a.m. —which is the profile used clinically for 5-FU— and maximum for the continuous infusion or a circadian pattern peaking at 4 p.m. These results are explained in terms of the relative temporal profiles of 5-FU and of the fraction of cells in S phase. The model further indicates that the optimal pattern of drug delivery depends on the characteristics of the cell cycle, such as its duration, variability, or entrainment by the circadian clock. Extension of this modeling approach to the case of another anticancer drug, oxaliplatin, will be discussed. The results throw light on possible mechanisms for the simultaneous improvement of chronoefficacy and chronotolerance in cancer chronotherapy.

References:

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