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Mathematical investigation into the effects of the anti-cancer compound RHPS4 on cell-cycle dynamics

The pentacyclic acridinium salt RHPS4 displays anti-tumour properties *in vitro* as well as *in vivo* and is potentially cell-cycle specific. We have collected experimental data and formulated a compartmental model using ordinary differential equations to investigate how the compound affects cells in each stage of the cell cycle. The eukaryotic cell cycle primarily consists of five phases, namely a resting state, G_0, and four cycling phases: G_1, S, G_2 and M phase with cells progressing in this order and then dividing into two cells back in G_1. Understanding how a drug affects the cell cycle could give insight into the drug's mechanism of action and may assist research into potential treatment strategies.

We treated colorectal cancer cells with three different concentrations of the drug and fitted simulations from our models to experimental observations. We found that RHPS4 caused a concentration-dependent, marked cell death in treated cells, which is best modelled by allowing rate parameters in the cell cycle to be time-dependent functions. Our compartmental models fit data from control cells and cells treated with lower concentrations of RHPS4 particularly well. We have also shown that the model is "identifiable", meaning that, at least in principle, the parameter values can be determined from observable quantities. Our fitting procedure generates information on the sensitivity of parameters in the model.

We find that at low concentrations RHPS4 primarily affects the cells' behaviour in the G_2/M phase, and that the drug has a delayed effect with the delay decreasing at larger doses. Since the drug diffuses into the nucleus, the observed delayed effect of the compound is unexpected and is a novel finding of our research into this compound. We propose that secondary effects lead to the induction of observed cell death and that changes in the molecular structure of the non-coding DNA sequences at chromosome ends, called telomeres, might be a precursor of delayed cell death.