Multiscale modelling of 5-fluorouracil antitumour activity

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5-fluorouracil (5FU) is a key anticancer drug for the treatment of many types of solid tumours, including colorectal cancer liver metastases.

This work is aimed at building a pharmacokinetic/pharmacodynamic model of 5FU. As a first step, we developed a multiscale mathematical model of 5FU activity on tumour growth which allows to i) simulate the effect of 5FU on liver metastastic colorectal cancer and ii) test hypotheses to help improve the clinical results observed in patients with this tumour.

Based on a review of 5FU mechanism of action, we modelled 5FU efficacy by taking into account two different observation levels. At the cell level, we focused on 5FU effect on DNA synthesis through two identified ways, a blockade of thymidylate synthase (TS) enzyme, resulting in an inhibition of DNA synthesis, and an incorrect incorporation of FdUTP to DNA leading to abnormal DNA production. At the tissue level, the model integrates the impact of normal and abnormal DNAs on tumour growth through cell cycle regulation. We studied the effect of continuous infusion 5FU, commonly used in advanced colorectal cancer, and tested the role of the TS level on the efficacy results as it is reported as a potential prognostic factor.

Simulation results may help comparing different 5FU-based protocols in terms of efficacy. This model may also provide relevant information about the optimal combination with other anticancer drugs such as oxaliplatin to improve clinical outcomes.