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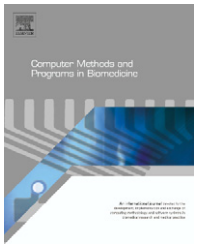

A coupled drug kinetics-cell cycle model to analyse the response of human cells to intervention by topotecan

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ABSTRACT

A model describing the response of the growth of single human cells in the absence and presence of the anti-cancer agent topotecan (TPT) is presented. The model includes a novel coupling of both the kinetics of TPT and cell cycle responses to the agent. By linking the models in this way, rather than using separate (disjoint) approaches, it is possible to illustrate how the drug perturbs the cell cycle. The model is compared to experimental *in vitro* cell cycle response data (comprising single cell descriptors for molecular and behavioural events), showing good qualitative agreement for a range of TPT dose levels.

1. Introduction

In this paper, an approach is described in which a coupled mathematical model has been developed that is capable of describing the *in vitro* drug kinetics of the anti-cancer agent topotecan (TPT) for single human osteosarcoma cells linked to primary biological (cell cycle) responses. The model offers the possibility of demonstrating both the dynamic and temporal interactions of active drug delivered to its DNA-associated molecular target and the downstream impact on cell growth and death. Live-cell data generated from new experimental procedures have been used and these procedures were developed to meet the demands of model comparison/validation [1]. In order to do this a series of robust quantitative laboratory assays have been designed to track and measure time-integrated events at the single cell level. Acquired data are used for parameter estimation and model simulation to further investigate the interactions of the drug with its target and possible routes for cellular evasion of drug action (i.e. drug resistance). The aim of this study was to assess the possibility of linking an existing drug kinetic model (for TPT) with a basic model for cell cycle dynamics [2]. Ultimately, a robust and validated version of such a generic model could be used to design and predict the consequences and potential failure of drug treatment regimens.

In Section 2 an outline of coupled drug kinetic-cell cycle response modelling and the underlying biochemistry for TPT is provided. The mathematical model developed is described

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in Section 3 and the methods for data collection and database generation are given in Section 4. The parameter estimation approach is presented in Section 5. Results from the parameter estimation using the experimental data are provided in Section 6.

2. Background

2.1. *Coupled drug kinetics/cell cycle response modelling*

In general the relationships between drug kinetics and the drug's effect on the cell cycle are extremely complicated, especially when the perturbed biological system being modelled expresses discrete events within a heterogeneous cellular population. The linking of drug kinetics and cell cycle models to describe the kinetics for heterogeneous cell populations is relatively new. A recent model, developed independently by Alarcón et al. [3] considers an approach that uses the cell cycle as a descriptor of the biological response. A current drawback is the difficulty in obtaining model validation or comparison with experimental data.

Critical to the modelling of the cell cycle responses to the action of topotecan is the ability to undertake high temporal resolution monitoring of cell cycle progression enabling the tracking of a single cell in a non-invasive manner even within

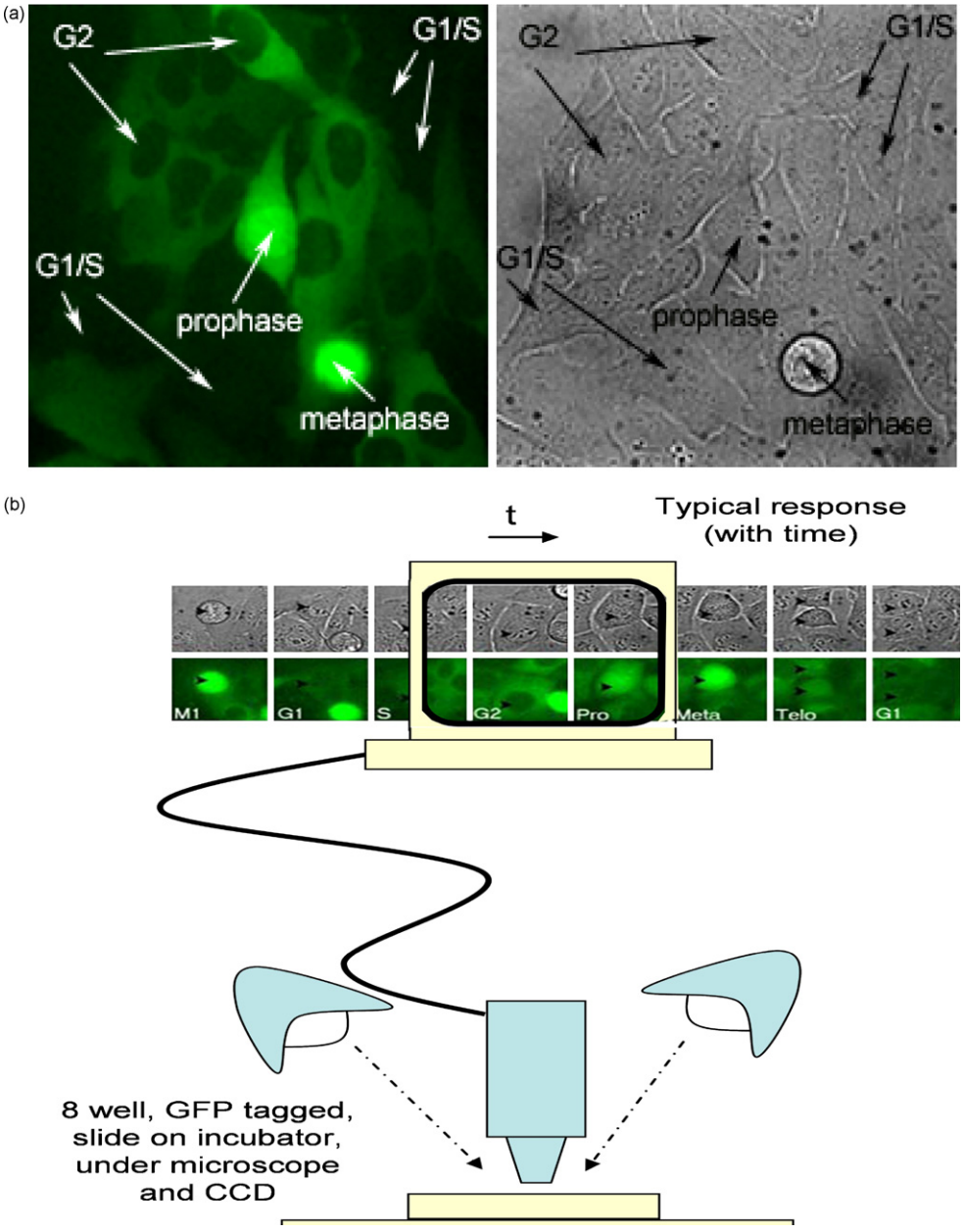

Fig. 1 – (a) Human osteosarcoma cells (U-2 OS cells) expressing a cyclin B1-GFP stealth reporter (left panel) and a corresponding transmission image (right panel) to identify all the cells in the field of view. The cells are expressing different levels of cyclin B1-GFP and are hence at all different stages of the cell cycle. (b) Capturing an image every 20 min enables single cell tracking, providing a means of continuous cell cycle monitoring for every cell. This provides the experimental data for building and validating the cell cycle model.