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Bystander effects and their implications for clinical radiation therapy: Insights from multiscale *in silico* experiments

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HIGHLIGHTS

- Multiscale spatio-temporal model to study radiation-induced bystander effects.
- Improved model to study the cellular response to radiation.
- Results highlight the role of bystander effects at low-doses of radiotherapy.
- Model predicts the role of bystander signals in low-dose hypersensitivity.

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ABSTRACT

Radiotherapy is a commonly used treatment for cancer and is usually given in varying doses. At low radiation doses relatively few cells die as a direct response to radiation but secondary radiation effects, such as DNA mutation or bystander phenomena, may affect many cells. Consequently it is at low radiation levels where an understanding of bystander effects is essential in designing novel therapies with superior clinical outcomes. In this paper, we use a hybrid multiscale mathematical model to study the direct effects of radiation as well as radiation-induced bystander effects on both tumour cells and normal cells. We show that bystander responses play a major role in mediating radiation damage to cells at low-doses of radiotherapy, doing more damage than that due to direct radiation. The survival curves derived from our computational simulations showed an area of hyper-radiosensitivity at low-doses that are not obtained using a traditional radiobiological model.

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1. Introduction

Radiotherapy is used in the treatment of 50% of patients with cancer. The classic view of the action of ionising radiation is that it inactivates cells by causing the DNA damage which leads to cell death (Prise et al., 2005). However, depending upon circumstances, a greater or lesser proportion of the DNA damage may be repaired, and so the consequences, at the level of the individual cell, can vary from damage with complete repair, through damage with incomplete or inaccurate repair, to lethal damage (Prise and O'Sullivan, 2009). Cells vary in their intrinsic radiosensitivity (Steel, 1991) and other factors also influence the cellular response to radiation: the oxygen level in the environment; the phase of the cell cycle; the repair capacity of individual cells. At the tissue level, the response will depend not just upon these cellular factors, but also on the ability of the cells that are critical for maintenance to repopulate the organ or tissue. The doses and fractionation schemes used in clinical radiotherapy represent a compromise between the desire to eliminate as many cancer cells as possible and the need to minimise the damage to normal cells and tissues.

Advances in radiobiology have expanded this classical view and it is now realised that signals produced by irradiated cells can influence the behaviour of non-irradiated cells – a range of phenomena known as the "bystander effect" (Blyth and Sykes, 2011; Prise and O'Sullivan, 2009; Mothersill and Seymour, 2004; Morgan, 2003a, 2003b). New technologies such as intensity-modulated radiotherapy (IMRT) allow irregularly shaped target volumes to be irradiated to high-dose whilst minimising the dose to vulnerable normal structures immediately adjacent to the tumour. The penalty paid however is an increase in the volume of normal tissue that is treated to a low-dose of irradiation (Hall et al., 2003).

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Since direct cell-kill is relatively low at low radiation doses, bystander effects play a major role in determining the fate of cells and may be particularly relevant to radiation-induced carcinogenesis. Therefore, it is important to understand how novel therapeutic techniques might influence the occurrence and clinical consequences of bystander effects (Mothersill and Seymour 2004; Munro 2009; Prise and O'Sullivan 2009).

Clinically, this is not an easy problem to investigate, it may be many years before the consequences are expressed. Nor is it easy to separate direct effects from bystander effects (Prise and O'Sullivan, 2009; Munro, 2009). Recently, however, several techniques have been developed which enable discrimination between direct effects and bystander phenomena: trans-generational studies in fish (Smith et al., 2016); microbeam techniques (Fernandez-Palomo et al., 2015); modelling track structure in medium transfer experiments (Fernandez-Palomo et al., 2015). Mathematical and computational models offer the potential, at least in part, to circumvent these difficulties. By providing mechanistic insights into bystander phenomena these approaches will help to identify the key factors that are involved. However, one should note that, in general, model predictions are very much dependent on the initial assumptions and hence any predictions are biologically relevant only when these assumptions are based on biological/clinical evidence and further, the results are validated with experimental data. Traditionally the linear quadratic model has been used as a useful tool for assessing radiotherapeutic treatments (Powathil et al., 2007, 2012, 2013; Thames et al., 1982). Furthermore, several mathematical models have been proposed to incorporate and study the effects of bystander phenomena (Brenner et al., 2001; Little., 2004; Khvostunov and Nikjoo, 2002; Nikjoo and Khvostunov, 2003; Little et al., 2005; Shuryak et al., 2007; Richard et al., 2009; McMahon et al., 2012, 2013). Since the effects of radiation on tissue can manifest themselves in many ways at the cell, tissue and organ levels, we need systems-based multiscale models to better understand the impact of bystander signals on clinical outcomes. Multiscale approaches have the ability to incorporate several critical interactions that occur on different spatio-temporal scales to study how they affect a particular cell's radiation sensitivity, whilst simultaneously analysing the effects of radiation at the larger (tissue) scale (Powathil et al., 2013; Richard et al., 2009; Ribba et al., 2006).

In this paper, we develop the hybrid multiscale mathematical and computational model to study multiple effects of radiation and radiation-induced bystander effects on a tumour growing within a host tissue. We use the new multiscale model to predict the effects of bystander signals on tissue treated with different radiation dosage protocols and analyse the implications for radiation protection, radiotherapy and diagnostic radiology.

2. Mathematical model

The multiscale mathematical model is developed by incorporating intracellular cell-cycle dynamics, an external oxygen concentration

Cell-cycle dynamics

$$\frac{d[\mathrm{CycB}]}{dt} = k_1 - (k_2^{'} + k_2^{''}[\mathrm{Cdh1}] + [\mathrm{p27/p21}][HIF])[\mathrm{CycB}],$$

$$\frac{d[\mathrm{Cdh1}]}{dt} = \frac{(k_3^{'} + k_3^{''}\ [\mathrm{p55cdc_A}])(1-[\mathrm{Cdh1}])}{J_3 + 1 - [\mathrm{Cdh1}]} - \frac{k_4[\mathrm{mass}][\mathrm{CycB}][\mathrm{Cdh1}]}{J_4 + [\mathrm{Cdh1}]},$$

$$\frac{d\ [\mathrm{p55cdc_T}]}{dt} = k_5^{'} + k_5^{''}\frac{([\mathrm{CycB}][\mathrm{mass}])^n}{J_5^n + ([\mathrm{CycB}][\mathrm{mass}])^n} - k_6\ [\mathrm{p55cdc_T}],$$

$$\frac{d\ [\mathrm{p55cdc_A}]}{dt} = \frac{k_7[\mathrm{Plk1}](\ [\mathrm{p55cdc_T}] - \ [\mathrm{p55cdc_A}])}{J_7 + \ [\mathrm{p55cdc_T}] - \ [\mathrm{p55cdc_A}]} - \frac{k_8[Mad]\ [\mathrm{p55cdc_A}]}{J_8 + \ [\mathrm{p55cdc_A}]} - k_6\ [\mathrm{p55cdc_A}],$$

$$\frac{d[\mathrm{Plk1}]}{dt} = k_9[\mathrm{mass}][\mathrm{CycB}](1\text{-}[\mathrm{Plk1}]) - k_{10}[\mathrm{Plk1}],$$

$$\frac{d[\mathrm{mass}]}{dt} = \mu[\mathrm{mass}]\left(1 - \frac{[\mathrm{mass}]}{m_*}\right),$$

Oxygen dynamics

$$\frac{\partial K(x,t)}{\partial t} = \nabla.(D_K(x)\nabla K(x,t)) + r(x)m(x) - \phi K(x,t)\mathrm{cell}(x,t)$$

Drug dynamics

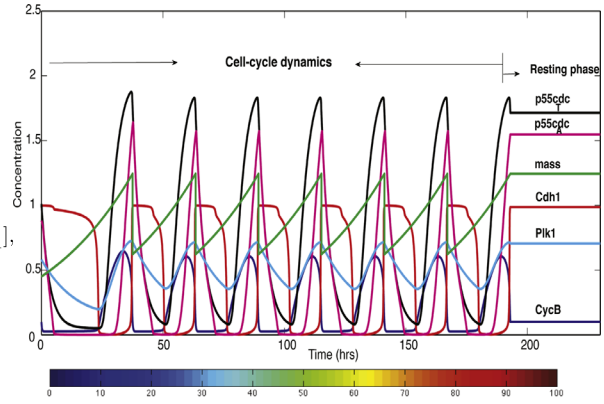
$$\frac{\partial C_i(x,t)}{\partial t} = \nabla.(D_{ci}(x)\nabla C_i(x,t)) + r_{ci}(x)m(x) - \phi_{ci}C_i(x,t)\mathrm{cell}(x,t) - \eta_{ci}C_i(x,t)$$

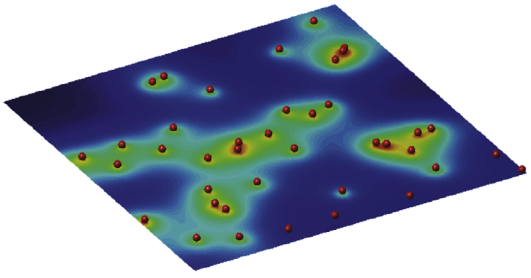
Radiation effects

$$S(d) = \exp\left[\gamma\left(-\alpha.\mathrm{OMF}.d - \beta(\mathrm{OMF}.d)^2\right)\right]$$

where

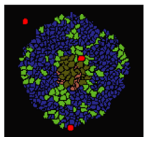
$$\mathrm{OMF} = \frac{\mathrm{OER}(pO_2)}{\mathrm{OER}_m} = \frac{1}{\mathrm{OER}_m}\frac{\mathrm{OER}_m.pO_2(x) + K_m}{pO_2(x) + K_m}$$





Hybrid multiscale modelling techniques

Hybrid cellular potts model (Compucell3D)



Hybrid CA model

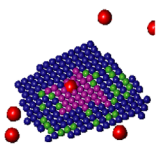


Fig. 1. Figure showing various processes involved in the simulation. Plot of the concentration profiles of the various intracellular proteins and the cell-mass over a period of 200 h for one automaton cell in the model. This is obtained by solving the system of equations governing the cell-cycle dynamics with the relevant parameter values from Powathil et al. (2012b) and the plot below shows a representative realisation of the spatial distribution of oxygen (K) or drugs (C_i), obtained by solving the corresponding equations. Adapted from Powathil et al. (2015).

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