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A biophysical model of cell evolution after cytotoxic treatments: Damage, repair and cell response

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HIGHLIGHTS

- Agent-based model of cell population damage by radio- and chemotherapy.
- Includes cell damage, repair, healthy and tumoral cells, chemical diffusion, cell motility, and more.
- Simulation of experimental cell survival curves and of bystander effect in radiotherapy.

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ABSTRACT

We present a theoretical agent-based model of cell evolution under the action of cytotoxic treatments, such as radiotherapy or chemotherapy. The major features of cell cycle and proliferation, cell damage and repair, and chemical diffusion are included. Cell evolution is based on a discrete Markov chain, with cells stepping along a sequence of discrete internal states from 'normal' to 'inactive'. Probabilistic laws are introduced for each type of event a cell can undergo during its life: duplication, arrest, senescence, damage, reparation, or death. We adjust the model parameters on a series of cell irradiation experiments, carried out in a clinical LINAC, in which the damage and repair kinetics of single- and double-strand breaks are followed. Two showcase applications of the model are then presented. In the first one, we reconstruct the cell survival curves from a number of published low- and high-dose irradiation experiments. We reobtain a very good description of the data without assuming the well-known linear-quadratic model, but instead including a variable DSB repair probability. The repair capability of the model spontaneously saturates to an exponential decay at increasingly high doses. As a second test, we attempt to simulate the two extreme possibilities of the so-called 'bystander' effect in radiotherapy: the 'local' effect versus a 'global' effect, respectively activated by the short-range or long-range diffusion of some factor, presumably secreted by the irradiated cells. Even with an oversimplified simulation, we could demonstrate a sizeable difference in the proliferation rate of non-irradiated cells, the proliferation acceleration being much larger for the global than the local effect, for relatively small fractions of irradiated cells in the colony.

1. Introduction

The development of cancer in a living organism follows complex paths, not without seemingly contradictory features. From the broad point of view of systems theory, the emergence of cancer cells may be seen as a stochastic process, in which a few cells, or even just one, change their nature without a traceable cause-effect mechanism, and start proliferating abnormally. On the other hand, the rapid and uncontrolled development of tumoral tissues is unlikely to be described as a purely stochastic phenomenon, and metastatic propagation is drastically distinct from a simple diffusion-like flow: these features rather have the character of self-organising, non-equilibrium dynamical systems, susceptible of taking on a chaotic or avalanche pattern under the effect of a small perturbation (see, e.g., Hart et al., 2015; Greaves, 2015)).

Introducing such a language from theoretical physics in the domain of cancer may seem unusual. However, physical-

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Table 1
List of the principal model variables. Unless differently indicated, all the variables are adimensional.

Symbol	Variable	Units	Role	Values
N	Lattice size		Linear size of the square lattice	–
i	Site index		Label of lattice site	$[1,N^2]$
N_c	Number of cells		Running size of the cell population	–
$u(i)$	Cell index		Label of cell u on a lattice site	$[1,N_c]$
Δ	Dose		Amount of energy supplied over a given time interval	$[0,\infty]$
$\mathbf{n}$	Cell state vector		vector containing all local cell parameters	–
t	Global time	Seconds	Universal 'laboratory' time of the simulation	$[-\infty,\infty]$
Δt	Time step	Seconds, minutes	Discrete simulation time increment	[0.001–0.1]
t_d	Cell time	Minutes	Time clock local to each cell	[0,1440]
t_0	Duplication time	Minutes	Time since last duplication for each cell	$[0,\infty]$
τ	Duplication time constant	Minutes	See Eq. (1)	30
ϕ	Cell phase index		Defines the cell phase (G0,G1,S,G2,M)	[0,4]
T	Cell type index		Epithelial, fibroblast, nerve, muscle, hematopoietic	[1,5]
λ	Cell state index		Normal, senescent, quiescent, arrested, neoplastic, stem, dead	[1,7]
ν	Damage type		Double- or single-strand breaks (DSB, SSB)	[1,2]
z_ν	Damage counter		Counts accumulated number of defects of type ν	$[0,\infty]$
p_ν	Damage probability		Probability of generating a defect of type ν	$[0,1]$
r_ν	Repair probability		Probability of healing a defect of type ν	$[0,1]$
N_{crit}	Critical damage		Number of lethal damage (DSBs) above which a cell is considered dead	[5,100]
D	Number of duplications		Number of duplications undergone by each cell	$[0,\infty]$
S	Senescence factor		Describe the senescence of each cell	[1,0]
D_0	Number of duplications		Number of duplications at which senescence starts	30
D_s	Number of duplications		Number of duplications at which senescence is complete	60
P_n	Cell state probability		Probability that cell is in state $\mathbf{n}$ at a given time	[0,1]
P_{dupl}	Duplication probability		Controls probability of duplication for each cell	[0,1]
P_{arr}	Arrest probability		Controls probability of arresting a cell for DSB accumulation or senescence	[0,1]
P_{death}	Death probability		Controls probability of cell death when DSBs in a cell approach N_{crit}	[0,1]
α	Retarding parameter		Slows cell killing by DSB accumulation	>1
$P_{restart}$	Restart probability		Controls probability of restarting cell cycle from an arrested state	[0,1]
β	Accelerating parameter		Accelerates cell repair capability to promote restarting	[0.5–2.]
$c^\mu_{u(i)}$	Chemical concentration		Instantaneous concentration of species μ in cell $u(i)$	$[0,\infty]$
$s^\mu_{u(i)}$	Source concentration		Constant source of species μ in cell $u(i)$	$[0,\infty]$
θ^μ	Diffusion time	Minutes	Inverse diffusion coefficient for species μ	$[0,\infty]$
c^B	B-factor concentration		Instantaneous concentration of 'bystander' pro-mitogenic factor	$[0,\infty]$
s^B	B-factor source		Constant source of 'bystander' pro-mitogenic factor	$[0,1]$
D^B	B-factor diffusion coefficient		Reciprocal of θ^B, the diffusion time of the 'bystander' pro-mitogenic factor across the cell membrane	$[0,1]$
γ	Coupling parameter		Couples concentration of B-factor to cell duplication time	[0.1–2.]

mathematical models have already accumulated a considerable tradition in cancer studies. Early analytical models based on coupled partial differential equations (see, e.g., Brunton and Wheldon, 1980; Sachs et al., 2001) have been accompanied in recent years, and often superseded by complex numerical simulations models (Edelman et al., 2010; Deisboeck et al., 2011; Lowengrub et al., 2010; Tracqui, 2009), which attempt at following the space- and time-dependent dynamics of cancer growth, by adding an increasing wealth of details and phenomenological correlations coming from biochemical and clinical studies.

Despite the considerable efforts in modelling, cancer treatments are still relying on a substantially empirical knowledge. Radiotherapy employs ionising radiation to eradicate cancer cells, mainly through the generation of DNA double-strand breaks (DSB), although the detailed mechanisms by which DSB and other sub-cellular lesions are generated are still quite far from clear. Empirical descriptions, such as the so-called linear-quadratic model (Dale, 1985) are still extensively used in radiotherapy, to describe cell damage upon the delivery of ionising radiation, together with extensions, such as the 'Tumor Control Probability' model (Kutcher, 1996), aimed at predicting the clinical efficacy of radiotherapeutic protocols. However, a detailed correlation between the radiation dose and its microscopic outcomes, both at the cell and tissue level, is still missing.

In this work we develop, implement, calibrate, and apply a discrete-cell model with internal degrees of freedom, capable of describing both normal and cancer cell evolution, and accounting for localised damage and repair mechanisms, with the aim of studying the long-term evolution of a cell population subject to cytotoxic therapeutic treatments. Our main interest and application concerns the immediate and delayed action of radiotherapy treatments. However, the formalism developed here is enough general to be easily applicable to other cytotoxic agents, such as chemotherapy, oxidative poisoning, environmental (UV) radiation damage.

The virtual cell population is represented by a large assembly (up to several millions) of individual stochastic agents (see, e.g., Byrne and Drasdo, 2009; Wang et al., 2015; Cilfone et al., 2015), endowed with a number of probabilistic properties (phenotypes), which allow us to follow the evolution of individual cells through their daily cycle over very long time scales (days, months, up to years). Each cell has a local clock which goes through the G1, S, G2 and M phases, typically (but not necessarily) following a 24 h cycle. Cell duplication with inheritance is allowed, with individual probability laws depending on the cell state at any given time. Normal, stem, or tumor cells of various kinds can be included, though in this work only normal cells will be considered. In the simplest implementation, adapted to mimicking in vitro experiments on cell colonies, simulated cells live on a two-dimensional fixed square grid and can migrate by vicinal displacements. Diffusion of, e.g., oxygen, nutrients, or other chemical species is allowed on the same grid.

These model cells can absorb a number of different damaging events, described by a Markov chain which changes the state of each cell from healthy, to progressively damaged, to arrested and finally dead. In this first paper we model only radiation-induced