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A comprehensive stochastic model of irradiated cell populations in culture

Leonid Hanin[a,b,*], Ollivier Hyrien[a], Joel Bedford[c], Andrei Yakovlev[a]

[a]*Department of Biostatistics and Computational Biology, University of Rochester, 601 Elmwood Avenue, Box 630, Rochester, NY 14642, USA*
[b]*Department of Mathematics, Idaho State University, Pocatello, ID 83209-8085, USA*
[c]*Department of Environmental and Radiological Health Sciences, Colorado State University, Ft. Collins, CO 80523-1618, USA*

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Abstract

A comprehensive entirely mechanistic model of the kinetics of cell population in vitro exposed to continuous irradiation is formulated and analysed. The model provides a stochastic description of the processes of formation and repair of radiation-induced lesions, as well as of cell cycling, cell proliferation, and cell death. Unobservable kinetic parameters of the model are estimated from experimental data on the sizes of clones formed in synchronized cultures of S3 HeLa cells exposed to continuous irradiation by γ-rays at various dose rates. The effects of dose rate on cell cycle duration and damage repair kinetics are studied. Continuous and acute exposures with the same total dose are compared in terms of their impact on cell survival.

Keywords: Cell cycling; Continuous irradiation; Parameter estimation; Queueing system; Radiation damage repair; Simulation-based inference

0. Introduction

A remarkable progress in radiation biology since the 1920s has resulted in a prodigious amount of experimental data comprising all aspects of cell functioning, proliferation, survival, carcinogenesis, and mutagenesis. Most notably, thousands of assays have been conducted to describe quantitatively the behavior of various cell systems in vitro exposed to fractionated or continuously delivered ionizing radiation. These data represent an invaluable source of information for furthering our knowledge about intracellular processes in normal and irradiated cells. However, to a large extent, this "gold mine" of data amassed over years remains unclaimed.

The present work is an attempt to better understand and describe mathematically such processes of primary biological importance, that determine largely the response of cell populations to radiation exposure, as induction of primary lesions, kinetics of damage repair, cell cycling, cell proliferation, and cell death. All these basic components are incorporated into a single completely mechanistic mathematical model.

Notwithstanding the significant advances in understanding molecular mechanisms underlying the formation of radiation-induced primary lesions and their evolution, radiation damage repair, and proliferative reactions of irradiated cells (for a review, see Bedford and Dewey, 2002), many dynamical aspects of these phenomena remain elusive for methods of molecular biology. More importantly, quantitative relations between the characteristics of basic biological processes in irradiated cells and remote endpoints like cell survival can be studied only on the basis of mathematical models. This is the reason why mathematical modeling retains its role of an indispensable tool for describing, interpreting, and predicting biological effects of ionizing radiation.

The responses of cell populations to continuous irradiation depend critically on the dose rate. One of the most dramatic well-documented effects of this kind

*Corresponding author. Department of Mathematics, Idaho State University, Pocatello, ID 83209-8085, USA. Fax: +1 208 282 2636.
E-mail address: hanin@isu.edu (L. Hanin).

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is the prolongation of cell cycle phases (most notably, induction of G_2 blocks and mitotic blocks and delays, see e.g. Bedford and Dewey, 2002 and references therein; Mitchell and Bedford, 1977; Okada, 1970; Weichselbaum, 1986) which becomes more pronounced as the dose rate increases. This leads to the redistribution of irradiated cells among cell cycle phases and their progressive accumulation in the two most radiosensitive phases, G_2 and mitosis. The other two notorious dose rate effects are the change in damage repair capacity, that can be either enhanced or suppressed by radiation (Bedford and Dewey, 2002; Yakovlev and Zorin, 1988), and the change in radiosensitivities, that characterize the intensity of the induction of primary lesions, in various phases of the cell cycle. The latter two phenomena are very hard to observe directly and separately. As a result, every observed survival response of cell population to continuous irradiation can be attributed to and quantitatively explained by either mechanism. Furthermore, simultaneous incorporation of dose rate-dependent repair kinetics and cell cycle phase specific radiosensitivities into a single mathematical model may run a risk of model overparameterization and non-identifiability.

In the present work, we explore a stochastic model of irradiated cell survival that focuses on kinetics of damage repair. According to a convention commonly accepted in radiation biology (see e.g. Hall, 1994) we define lethality as a loss of the capacity of a cell to proliferate indefinitely. The model is based on the results of a large body of experimental work on kinetics and survival of S3 HeLa human carcinoma cells exposed to continuous irradiation with various (low) dose rates (Bedford and Mitchell, 1973, 1977; Mitchell and Bedford, 1977; Mitchell et al., 1979a–d). Estimates of unobservable parameters of the model inferred from individual data contained in Mitchell (1978) serve as an important outcome of our analysis.

Since these earlier cellular experiments much has been learned about the nature of the molecular damage, its processing, and how its development leads to important biological effects of ionizing radiation, such as cell killing and perturbations in cell cycle progression. These advances have been reviewed on several occasions (see e.g. Bedford and Dewey, 2002). There seems to be little doubt that primary lesions are principally DNA double strand breaks (DSBs) whose failure to rejoin properly can result in cell killing. This occurs largely through the subsequent production of acentric chromosome fragments that results in massive genetic losses in the cell progeny. Other processes, such as apoptosis, can occur within a span of a few hours and contribute to cell killing to greater or lesser extents depending on the particular cells. For example, certain lymphoblastoid cells seem especially susceptible to this additional form of cell killing. In what follows, we refer to "primary lesions" as molecular damage produced immediately by the radiation that potentially can lead to the development of "lethal lesions" if they are not processed by the repair system into non-lethal products. Therefore, it is reasonable to postulate that (1) the primary lesion is a DNA DSB; (2) a DSB may be rejoined by an enzymatic "repair process" to form a non-lethal product; or (3) the DSB may either fail to rejoin or rejoin with another nearby DSB to form a secondary lesion that is lethal to the cell. However, our model of primary lesion formation and repair is general and flexible enough to accommodate other types of lesions. Some evidence for their existence comes from the fact that mutagenic and survival effects can be elicited in mammalian cells through irradiation of extranuclear compartments by tightly focused beams (Wu et al., 1999). Yet another evidence is provided by various bystander effects of radiation (Mothersill and Seymour, 2001) that either require gap-junction mediated signaling between neighboring cells (Azzam et al., 2001) or are independent of this mechanism (Mothersill and Seymour, 1998; Iyer and Lehnert, 2000).

A distinct advantage of cell culture assays, as opposed to in vivo studies, is that they allow for a much broader range of experiments, observations, and quantitative inference. The study of irradiated cell cultures was triggered by and has far-reaching implications for cancer radiotherapy. Over the last 50 years, bioassays involving irradiated cell cultures played an important role in formulating principles of radiation cancer treatment, developing physical methods for irradiation of tumors, and designing improved schedules of radiation dose delivery, see e.g. Hahn and Little (1972), Weichselbaum (1986), Weichselbaum and Little (1983), and Zaider and Minerbo (2000). While in vitro cell systems are not directly analogous to clinical settings and cannot be used for direct quantitative extrapolation, they do possess features that make them an experimental model of brachytherapy, that is, continuous irradiation of some human tumors (prostate cancer, cervical cancer, sarcomas, etc.) from interstitial or intercavitary placements of radioactive sources, and thus can serve as a proof of principle. Many radiotherapists believe strongly that "radioactive implant" modalities often give better results than multiple dose fractionation using an external beam (Joslin et al., 2001). When studying biological effects of fractionated radiation with sufficiently long interdose intervals (larger than a few minutes to hours, the time typically required for the completion of sub-lethal damage repair, Bentzen et al., 1999; Brenner and Hall, 1991), it can be assumed (Hanin et al., 1994; Yakovlev and Zorin, 1988) that the damage induced in a cell by an instantaneously delivered dose of radiation either leads to cell death or is completely repaired by the moment of the next exposure. This does not apply to the case of continuous irradiation where the