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Cell Survival Computation via the Generalized Stochastic Microdosimetric Model (GSM2); Part I: The Theoretical Framework

Francesco G. Cordoni,[a,b] Marta Missiaggia,[b,c,1] Emanuele Scifoni[b] and Chiara La Tessa[b,c,2]

[a] *University of Verona, Department of Computer Science, 37134 Verona, Italy;* [b] *Trento Institute for Fundamental Physics and Applications (TIFPA), 38123 Povo, Trento, Italy; and* [c] *University of Trento, Department of Physics, 38123 Povo, Trento, Italy*

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The current article presents the first application of the Generalized Stochastic Microdosimetric Model (GSM2) for computing explicitly a cell survival curve. GSM2 is a general probabilistic model that predicts the kinetic evolution of DNA damages taking full advantage of a microdosimetric description of a radiation energy deposition. We show that, despite the high generality and flexibility of GSM2, an explicit form for the survival fraction curve predicted by the GSM2 is achievable. We illustrate how several correction terms typically added a posteriori in existing radiobiological models to improve the prediction accuracy, are naturally included into GSM2. Among the most relevant features of the survival curve derived from GSM2 and presented in this article, is the linear-quadratic behavior at low doses and a purely linear trend for high doses. The study also identifies and discusses the connections between GSM2 and existing cell survival models, such as the Microdosimetric Kinetic Model (MKM) and the Multi-hit model. Several approximations to predict cell survival in different irradiation regimes are also introduced to include intercellular non-Poissonian behaviors.

INTRODUCTION

In the last decades, there has been an increasing attention in the development of mathematical models for describing the biological damage induced by different types of radiation (1, 2). These predictive models have found their main application in two fields, particle therapy and space radioprotection. Currently, only two models are used in clinical treatments with both protons and carbon ions: the ''Microdosimetric Kinetic Model'' (MKM) (3, 4) and the ''Local Effect Model'' (LEM) (5, 6).

The MKM describes the temporal-evolution of the average number of DNA damages occurring in a single cell nucleus to obtain the survival probability of a cell population versus the macroscopic radiation dose delivered. Assuming a priori that the number of DNA lesions follows a Poisson distribution, the MKM predicts a linear-quadratic (LQ) cell survival curve. Although the linear-quadratic description of the survival curve is widely used in literature (7), experimental evidence have pointed out that in certain cases, such as for high-LET particles or in high-dose regimes, the cell survival deviates significantly from a LQ behavior.

The experimentally appearing linearization at high dose has been object of debate, including impact of prolonged irradiation (Dasu and Toma-Dasu, 2015), subpopulation sensitivities or different radibiological effects [see McMahon's Topical Review (7)] and even experimental bias due to the difficult operating conditions. It is however a largely observed effect, which typically challenges the radiobiological models.

Several models have been derived to overcome these limitations. For instance, the LEM model assumes a linear-quadratic-linear behavior for the cell survival, with a LQ curve at low doses, switching to a purely linear trend above a certain dose threshold. It is worth noticing that the newer version of LEM (LEM IV+) (6, 8), provides a RBE prediction based on explicit LQL parameterization and on a DSB-in-domain model, in a similar manner to what is done in the MKM and GSM2. As for the MKM, instead, *ad hoc* correction terms have been added to the main formulation, such as the overkilling effects and the inter-cellular damage interactions (4, 9–12). A comprehensive overview of the MKM original formulation along with all the generalizations can be found in the literature (2).

To date, several mechanistic models exist (3–6, 8–11, 13–19), to the best of our knowledge, there is no model to date that gives a rigorous probabilistic treatment of DNA damage formation and evolution to provide an accurate, mechanistic based, description of the resulting cell survival. In the data by Cordoni et al. (19), a new model has been introduced, the ''Generalized Stochastic Microdosimetric Model'' (GSM2), that describes the radiation-induced damages using differ-

[1] RRS Scholar in training.
[2] Corresponding author email: chiaral.latessa@unitn.it.

ential equations for the time evolution of the DNA damage probability distribution. It has been shown how the stochastic nature of energy deposition, based on microdosimetric arguments, and a probabilistic description of the damage kinetics can be combined in a *master equation*, expressing the spatio-temporal damage density function. In published article (19), it has been further investigated how different parameters, e.g., the initial DNA damage distribution or the radiation conditions, lead to different probability distributions that can significantly deviate from the Poissonian law which is typically assumed.

Using the findings reported by Cordoni et al. (19), the current work explores in addition the stochastic effects related to energy deposition and derive an explicit expression for the survival curve. We will demonstrate how the more general description provided by GSM2 naturally includes the description of several features typically added as correction terms to the existing models. Such corrections include for instance overkilling effects, dependence on the radiation LET or a linear behavior at high doses. To the best of our knowledge GSM2 is the first mechanistic model that naturally embeds all the above effects, typically referred to in literature as non-Poissonian effects.

From a more mathematical perspective, the pairwise DNA damage interaction term included into GSM2 implies that GSM2 does not fall into the class of so-called *birth and death processes* (20). This implies that the extensive literature on birth-death process cannot be directly used. Therefore, specific and advanced mathematical arguments must be used to derive an expression for the survival curves. We will first compute an explicit form for the solution of the master equation, prescribing thus the probability that the DNA damages repair. Notable enough, the resulting probability goes beyond the typical exponential repair of the MKM, showing a multi-exponential behavior as empirically predicted (21, 22). Thus, suitable mathematical arguments on the involved microdosimetric distribution using well-known properties of the Laplace transform, allow us to explicit the relation between the predicted survival probability and the imparted dose. The final survival curve exhibits a linear-quadratic behavior for low doses and gradually shifts towards a linear trend for higher doses. It is worth stressing that this behavior naturally emerges from the probabilistic description provided by the GSM2 and it is not assumed *a priori*.

Further we show how the GSM2 is strictly related to existing radiobiological models, such as the *multi-hit model* and the MKM, providing it also a suitable generalization. Given the importance of such an argument, investigation on the connection between GSM2 and existing models is currently under a deepening study.

At last, non-Poissonian corrections on the whole cell population are introduced averaging the single domain survival curve against the microdosimetric energy deposition distribution on the cell nucleus. Different approximations are treated to account for a wide variety of LET and doses regimes.

It must be noticed that, given the general probabilistic nature of GSM2, to estimate the model parameters requires both biological and physical data not available in the current literature. Therefore, an extensive data collection campaign is currently in progress within the experiment Microbe_IT, financed by *Istituto Nazionale di Fisica Nucleare* (INFN). Further, it must be highlighted that the current work has an important fallout in GSM2 parameter estimation. In fact, a close formula expression for the survival curve allows to directly estimate parameters with standard fitting procedure using survival data, which are easily obtainable in the literature.

In the companion paper, an extensive analysis of the survival curve derived in the present paper is treated. Simulating energy deposition by different particle beams using TOPAS (23), it is investigated how the survival curve changes for different ions and different energies. Particular attention is dedicated to higher LET particle for which the existing models fail to accurately predict the cell survival curve. Mixed radiation fields are also considered showing that GSM2 flexibility allows to model a wide variety of irradiation situations.

THEORY AND CALCULATIONS

The Generalized Stochastic Microdosimetric Model

GSM2 is a fully probabilistic model that aims at accurately describing the stochastic nature of energy deposition in volumes of interest for cellular systems. The final goal is to overcome existing models, which mostly assume a Poissonian distribution of energy deposition, to provide a better prediction of biological endpoints relevant for radiotherapy applications and to possibly link the related parameters to more mechanistically relevant quantitities. GSM2 was first introduced by Cordoni et al. (19), where a detailed description of its structure can be found. The model is based on the following funding assumptions:

- The cell nucleus can be divided into N_d independent domains d;
- radiation can create two different types of DNA damages, called lethal and sublethal lesions;
- lethal lesions represent a damage that cannot be repaired, while sublethal lesions can be either repaired or converted into a lethal lesion either by spontaneous death or by combination with another sublethal lesion;
- the average number of lethal and sublethal lesions in a single domain d is proportional to the specific energy z deposited by radiation on the site.

The further assumptions are then made to decide the cell fate:

- If a domain suffers a lethal lesion, then the domain is considered dead;
- if at least one domain is dead, then the whole cell is dead.

Using this description, lethal lesions represent clustered DNA damage that cannot be repaired whereas sublethal lesions are double-strand breaks that can be repaired; such assumption is in analogy with existing radiobiological models for cell survival computation (2, 3, 9–11).

For modelling the time evolution of the number of lethal and sublethal lesions, we will denote by $(Y(t), X(t))$ the state of the system at time t, where X and Y are two $\mathbb{N}-$valued random variables representing the number of sublethal and lethal lesions, respectively.

A sublethal lesion can evolves in three different ways: 1. it can become a lethal lesion at a rate a, 2. it can be be repaired at a rate r, or it can combine with another sublethal lesion to become a lethal lesion at a rate b. This scheme can be represented by the following equations:

$$\begin{aligned} \mathrm{X} &\xrightarrow{a} \mathrm{y} \\ \mathrm{X}+\mathrm{X} &\xrightarrow{\mathrm{b}} \mathrm{Y} \\ \mathrm{X} &\xrightarrow{r} \mathcal{A} \end{aligned} \tag{1}$$

where $\mathcal{A}$ represents the group of healthy cells.

On the bases of Eq. (1), we developed the Microdosimetric Master Equation (MME) (19)

$$\begin{aligned} \partial_t p(t,y,x) &= \left(E^{-1,2}-1\right)[x(x-1)bp(t,y,x)] \\ &\quad + \left(E^{-1,1}-1\right)[xap(t,y,x)] \\ &\quad + \left(E^{0,1}-1\right)[xrp(t,y,x)] \\ &= \mathcal{E}^{-1,2}[x(x-1)bp(t,y,x)] + \mathcal{E}^{-1,1}[xap(t,y,x)] \\ &\quad + \mathcal{E}^{0,1}[xrp(t,y,x)]\,, \end{aligned} \tag{2}$$

where the creation operator is defined as

$$\mathcal{E}^{i,j}[f(y,x)] := \left(E^{i,j}-1\right)[f(y,x)] := f(y+i,x+j)-f(y,x)\,.$$

The MME (2) governs the time evolution of the joint probability density function for lethal and sublethal lesions inside the cell nucleus. In particular, p(t,y,x) denotes the probability of having exactly x sublethal lesions and y lethal lesions at time t. The creation/annihilation operators instead model the increase/decrease of lesions, according to the a, b, r rates. A detailed derivation of the MME (2) can be found in the literature (19).

The MME is coupled with an initial damage distribution derived from microdosimetric spectra, which describe the radiation-field quality and allow as direct link with measurable quantities.

In fact, the single-event distribution of energy deposition on a domain d, referred to as $f_{1;d}(z)$ (24), can be either computed numerically with a Monte Carlo code or measured experimentally. Given a cell nucleus domain d, the probability of the domain being exposed to v events follow a Poisson distribution of mean $\lambda_n := \frac{z_n}{z_F}$, being z_n the mean energy deposition on the nucleus and z_F the first moment of the single event distribution $f_{1;d}$. Then, assuming a Poissonian probability that a domain could register v events, the energy deposition distribution is given by

$$f(z|z_n) := \sum_{v=0}^{\infty} \frac{e^{-\frac{z_n}{z_F}}}{v!}\left(\frac{z_n}{z_F}\right)^v f_{v;d}(z)\,, \tag{3}$$

where $f_{v;d}(z)$ is the energy deposition distribution resulting from v depositions.

In particular, the distribution resulting from v events can be computed convolving v times the single event distribution (24), Chapter II.2. Therefore, the distribution $f_{v;d}$ of the imparted energy z is computed iteratively as

$$\begin{aligned} f_{2;d}(z) &:= \int_0^\infty f_{1;d}(\bar{z}) f_{1;d}(z-\bar{z})\,d\bar{z}\,, \\ &\cdots\,, \\ f_{v;d}(z) &:= \int_0^\infty f_{1;d}(\bar{z}) f_{v-1;d}(z-\bar{z})\,d\bar{z}\,. \end{aligned}$$

Given an energy deposition z, the induced number of lesions is again a random variable. The standard assumption is that the distribution of sublethal lesions X or lethal lesions Y are Poisson random variables of mean value κz and λz, respectively.

We call $p_z^X(x|\kappa z)$ and $p_z^Y(y|\lambda z)$ the initial random distributions for the number of sublethal and lethal lesions, respectively, for a given energy deposition z. In the present work, we will assume that $p_z^X(x|\kappa z)$ and $p_z^Y(y|\lambda z)$ are Poisson random variables.

In this view, the MME (2) becomes

$$\begin{cases} \partial_t p(t,y,x) &= \mathcal{E}^{-1,2}[x(x-1)bp(t,y,x)] \\ &\quad +\mathcal{E}^{-1,1}[xap(t,y,x)] \\ &\quad +\mathcal{E}^{0,1}[xrp(t,y,x)]\,, \\ p(0,y,x) &= p_0^X(x)p_0^Y(y)\,, \end{cases} \tag{4}$$

where the initial distribution is obtained as

$$\begin{aligned} p_0^X(x) &= \int_0^\infty p_z^X(x|\kappa z) f(z|z_n)\,dz\,, \\ p_0^Y(y) &= \int_0^\infty p_z^Y(y|\lambda z) f(z|z_n)\,dz\,. \end{aligned} \tag{5}$$

The initial condition (5) represents a simple and yet important generalization of the standard assumptions. Both p_0^X and p_0^Y may not be Poisson distributed even if $p_z^X(x|\kappa z)$ and $p_z^Y(y|\lambda z)$ are Poisson random variables. Fig. 1 shows a schematic representation for survival assessment via GSM2.

Even if $p_z^X(x|\kappa z)$ is a Poisson random variable, the initial distribution $p_0^X(x)$ does not need to be Poissonian. For the

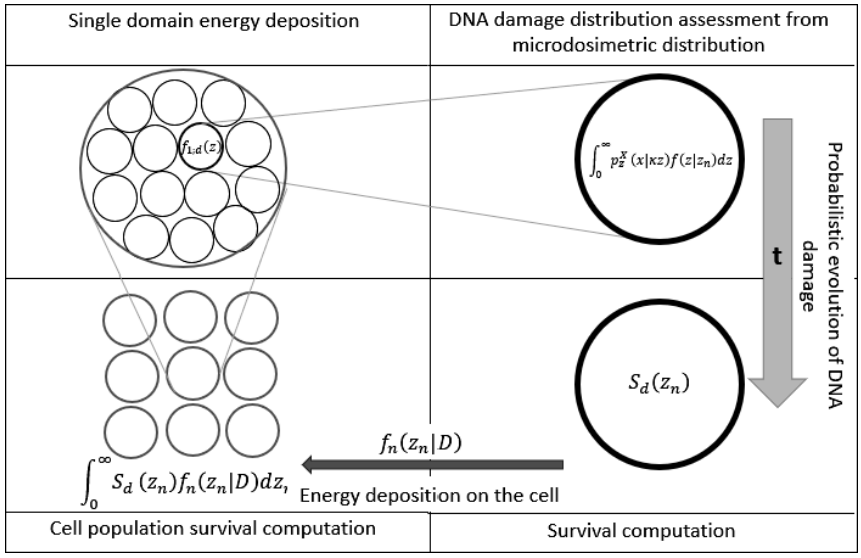

FIG. 1. Schematic representation of the procedure for cell survival fraction assessment implemented by means of GSM.

sake of brevity, we will only focus on $p_0^X(x)$, because an analogous argument holds for $p_0^Y(x)$.

Assuming $p_z^X(x|\kappa z)$ to be a Poisson random variable of mean κz, the first moment of the distribution $p_0^X(x)$ can be computed as

$$\begin{aligned}\sum_{x\geq 0} x p_0^X(x) &= \sum_{x\geq 0} x \int_0^\infty p_z^X(x|\kappa z) f(z|z_n) dz \\ &= \int_0^\infty f(z|z_n) \sum_{x\geq 0} x e^{-\kappa z} \frac{(\kappa z)^x}{x!} dz = \int_0^\infty \kappa z f(z|z_n) dz \\ &= \kappa z_n \,.\end{aligned}$$

It further follows that

$$\begin{aligned}\sum_{x\geq 0} x(x-1) p_0^X(x) &= \sum_{x\geq 0} x(x-1) \int_0^\infty p_z^X(x|\kappa z) f(z|z_n) dz \\ &= \int_0^\infty f(z|z_n) \sum_{x\geq 0} x(x-1) e^{-\kappa z} \frac{(\kappa z)^x}{x!} dz \\ &= \int_0^\infty \kappa z^2 \kappa^2 f(z|z_n) dz = \kappa^2 M_2 \,,\end{aligned}$$

being M_2 the second moment of the distribution $f(z|z_n)$. Using the Rossi and Zaider textbook (24), we have

$$M_2 = z_n(z_n + z_D), \quad z_D = \frac{m_2}{m_1} \,,$$

with m_n the nth moment of the single event distribution $f_{1;d}$. Here we have used that $m_1 = z_F$. Thus, the variance of $p_0^X(x)$ is given by

$$\begin{aligned}&\sum_{x\geq 0} x^2 p_0^X(x) - \left(\sum_{x\geq 0} x p_0^X(x)\right)^2 \\ &= \sum_{x\geq 0} x(x-1) p_0^X(x) + \sum_{x\geq 0} x p_0^X(x) - \left(\sum_{x\geq 0} x p_0^X(x)\right)^2 \\ &= \kappa^2 M_2 + \kappa z_n - \kappa^2 z_n^2 = \kappa^2 z_n z_D + \kappa z_n \,.\end{aligned}$$

The variable $p_0^X(x)$ is Poissonian distributed if the first two moments are equal, i.e., $\kappa z_n = \kappa^2 z_n z_D + \kappa z_n$. If $\kappa^2 z_n z_D << 1$, which is true for low-LET radiation or low doses, then $p_0^X(x)$ follows a Poisson distribution, but in general for high-LET radiation or high-dose regimes the distribution significantly deviates from a Poisson law. Therefore, a deviation from a Poissonian law emerges not only for high-LET radiation but also at high doses; so that, for the same radiation quality we might expect different probability distributions, not necessarily Poissonian, for lesions at different doses. This naturally incorporates the overkilling effect, often included in the existing radiobiological models with ad hoc correction.

It is worth stressing nonetheless that, even if $p_0^X(x)$ is Poisson, the long-time lethal lesion distribution might be different from a Poissonian distribution due to non-linear effects, such as the double lesions combination.

See Table 1, which contains a list of all free parameters of GSM2

Survival Curve Computation

An estimate of the survival probability after radiation exposure can be obtained with GSM2. We will describe the calculation process for a single domain, and then extend it to the entire cell population. The survival probability can be

TABLE 1
Full List of GSM2 Parameter

Parameter	Meaning
a	Rate at which a sublethal lesion becomes a lethal lesion
b	Rate at which two sublethal lesions combine to become a lethal lesion
r	Rate at which a sublethal lesion repairs
κ	Mean number of sublethal lesions per Gray
λ	Mean number of lethal lesions per Gray
r_d	Domain radius

calculated by solving the MME (2):

$$S_d(z_n) := \mathbb{P}\Big(\lim_{t\to\infty} Y(t) = 0\Big)\,, \tag{6}$$

where the dependence of S_d on the energy deposition z_n is explicitly reported.

Assuming that the domains are independent of each other, the survival of a single cell can be obtained as

$$S_n(z_n) := (S_d(z_n))^{N_d} = \Big(\mathbb{P}\Big(\lim_{t\to\infty} Y(t) = 0\Big)\Big)^{N_d}. \tag{7}$$

In the present work, the domains are considered independent, as it is typically assumed in similar studies. Nonetheless, as it has been demonstrated by Cordoni (19), this assumption can be dropped to allow for diffusive movements of the lesions within the entire cell nucleus.

Thus, a multi-event distribution on the whole cell population can be defined as

$$f_n(z_n|D) := \sum_{v=0}^{\infty} p_n(v|D) f_{v;c}(z_n)\,,$$

where $f_{v;c}(z_n)$ is the energy deposition distribution resulting from v deposition events in a single nucleus and $p_n(v|D)$ is the probability that v energy depositions occur in a nucleus. The $f_{v;c}(z_n)$ distribution can be obtained convolving the single event distribution $f_{1;c}(z_n)$, as described above.

As $D = \int_0^\infty z_n f_n(z_n|D) dz_n$, the cell survival probability for the whole cell population can be computed as

$$S(D) = \int_0^\infty S_n(z_n) f_n(z_n|D) dz_n\,. \tag{8}$$

Equation (8) provides the cell survival probability for a macroscopic dose D.

From a heuristic point of view, since the number of sublethal lesion can only decrease, the points $\{(y,0) : y \in \mathbb{N}_0\}$ are absorbing states. Furthermore, the system reaches an absorbing state in finite time with probability 1, converging towards a limiting stationary distribution. In particular, for any initial condition $\mathbf{x}$, it holds that,

$$\mathbb{P}\Big(\lim_{t\to\infty} X^{\mathbf{x}}(t) = 0\Big) = 1\,,$$

and we can infer that,

$$p_\infty(y,x) = \delta(x) * p_\infty(y) =: \bar{p}_\infty(y)\,. \tag{9}$$

By *absorbing state*, we mean that once the system reaches the point $(y,0)$ it cannot leave anymore that state and future evolutions are no longer of interest. A rigorous proof of this result can be found elsewhere (25, 26).

It is worth highlighting that, in explicitly deriving the above limiting distribution, the quadratic term in the MME (2) implies that the considered process does not fall into the broad category of *birth-death processes*, and thus we could not take advantage of the extensive literature available on such type of processes. In this direction, usually approximation of the general model enables to obtain an explicit form for the stationary distribution (25).

Despite these issues, in the present work we will illustrate a derivation of an explicit form for the survival curve.

For any y, x_0 and $t_0 < t$, we denote

$$\mathbb{P}_{t_0,x_0}(Y(t) = y) = \mathbb{P}(Y(t) = y | Y(t_0) = y, X(t_0) = x_0),$$

as the probability to have exactly y lethal lesions at time t, knowing that at a previous time t_0 there were y lethal lesions and x_0 sub-lethal lesions.

Knowing that at time $t_0 < t$ the system was in the state $(0,x_0)$, we define $S(t|x_0 1, t_0)$ as the survival probability at time t. Thus,

$$\begin{aligned} S(t|x_0,t_0) &:= \mathbb{P}(Y(t) = 0 | Y(t_0) = 0\,,\, X(t_0) = x_0) \\ &= \sum_{x=0}^{x_0} \mathbb{P}_{t_0,x_0}((Y(t),X(t)) = (0,x))\,. \end{aligned} \tag{10}$$

Differentiating with respect to time both sides of Eq. (10), we obtain

$$\begin{aligned} \partial_t S(t|x_0,t_0) &= \sum_{x=0}^{x_0} \partial_t \mathbb{P}_{t_0,x_0}((Y(t),X(t)) = (0,x)) \\ &= \sum_{x=0}^{x_0} \partial_t p_{t_0,x_0}(t,0,x)\,. \end{aligned} \tag{11}$$

Note that $p_{t_0,x_0}(t,0,x)$ is the solution to Eq. (2), considering its initial value,

$$p_{t_0,x_0}(t_0,x,y) = \delta(y)\delta(x - x_0)\,.$$

As discussed above, the solution for a general probabilistic initial datum $p(t_0,x,y) = p_0^X(x) p_0^Y(y)$ can be obtained using the total law of probability,

$$p(t,y,x) = \sum_{x_0,y_0} p_{t_0,y_0,x_0}(t,y,x) p(t_0,y_0,x_0)\,. \tag{12}$$

Therefore, merging Eqs. (11) and (12), we obtain that the survival probability must satisfy the following differential equation,

$$\partial_t S(t) = \sum_{x=0}^{x_0} \sum_{x_0 \geq 0} \partial_t p_{(t_0,x_0)}(t,0,x) p_0^X(x_0) p_0^Y(y_0). \tag{13}$$

To simplify the notation, we will drop the subscript (t_0,x_0), and instead use $p(t,x) = p_{t_0,x_0}(t,0,x)$. Furthermore, we will

describe the calculations for the specific case $t_0 = 0$, being the general case completely analogous.

The solution of Eq. (11) can be derived from Eq. (2), and then calculated iteratively. Using Eq. (2) we have that,

$$\partial_t p(t,x) = (x+1)rp(t,x+1) - ((a+r)x + bx(x-1))p(t,x)\,. \tag{14}$$

As the number of sublethal lesion (i.e., the x variable) can only decrease, we have that $p(t,x_0+1) = 0$ for $x = x_0$. Therefore, $p(t,x_0)$ satisfies,

$$\partial_t p(t,x_0) = -((a+r)x_0 + bx_0(x_0-1))p(t,x_0)\,,$$

whose explicit solution is given by,

$$p(t,x_0) = e^{-\gamma(x_0)t}\,,$$

$$\gamma(x_0) := ((a+r)x_0 + bx_0(x_0-1))\,. \tag{15}$$

For $x = x_0 - 1$, we obtain,

$$\partial_t p(t,x_0-1) = -\gamma(x_0-1)p(t,x_0-1) + \rho(x_0)p(t,x_0)\,,$$

With $\rho(x_0+1) := (x_0+1)r$. Using $p(t,x_0)$ from Eq. (15), it follows

$$p(t,x_0-1) = \int_0^t \rho(x_0)e^{-\gamma(x_0-1)(t-s)}p(s,x_0)ds = \frac{\rho(x_0)}{\gamma(x_0)-\gamma(x_0-1)}\left(e^{-\gamma(x_0-1)t} - e^{-\gamma(x_0)t}\right). \tag{16}$$

Iterating above reasoning for any x_0 we infer that the general solution $p(t,x)$ must be a sum of exponential functions

$$p(t,x) = \sum_{k=x}^{x_0} C(k,x,x_0)e^{-\gamma(k)t}\,, \tag{17}$$

for a given function $C(k,x,x_0)$.

Inserting Eq. (17) into Eq. (16), and comparing exponential functions of the same order, we conclude that the general solution is given by,

$$p(t,x) = \sum_{k=x+1}^{x_0} C(k,x,x_0)\left(e^{-\gamma(k)t} - e^{-\gamma(x)t}\right), \tag{18}$$

with

$$C(k,x,x_0) := \frac{\rho(x+1)\rho(x+2)\rho(x+3)\ldots\rho(x_0)}{C_1(k,x)C_2(k,x_0)}\,,$$

being

$$\begin{aligned} C_1(k,x) &:= (\gamma(x)-\gamma(k))(\gamma(x+1)-\gamma(k))\ldots\times \\ &\quad \times\ldots(\gamma(k-1)-\gamma(k))\,, \\ C_2(k,x_0) &:= (\gamma(k+1)-\gamma(k))\ldots(\gamma(x_0)-\gamma(k))\,. \end{aligned}$$

The calculation described above demonstrates that the repair probability follows a multi-exponential form, and thus deviates from the predictions of the existing theory, which assumes an exponential repair kinetics (21, 22).

For $x = 0$, we obtain,

$$\begin{aligned} p(t,0) &= \int_0^t rp(s,1)ds \\ &= r\sum_{k=2}^{x_0} C(k,1,x_0)\int_0^t \left(e^{-\gamma(k)s} - e^{-(a+r)s}\right)ds \\ &= \sum_{k=2}^{x_0} C(k,1,x_0)\left(\frac{1-e^{-\gamma(k)t}}{\gamma(k)} - \frac{1-e^{-(a+r)t}}{a+r}\right) \\ &= \sum_{k=0}^{x_0} C(k,0,x_0)e^{-\gamma(k)t}\,, \end{aligned} \tag{19}$$

which agrees with Eq. *(17)*.

Integrating Eq. (11) with respect to time, we obtain from Eqs. (18) and (19),

$$\begin{aligned} S(t|x_0) - 1 &= \sum_{x=0}^{x_0}(p(t,x) - p(0,x)) = \sum_{x=0}^{x_0} p(t,x) - 1 \\ &= \sum_{x=1}^{x_0-1}\sum_{k=x+1}^{x_0} C(k,x,x_0)\left(e^{-\gamma(k)t} - e^{-\gamma(x)t}\right) \\ &\quad + e^{-\gamma(x_0)t} + \sum_{k=0}^{x_0} C(k,0,x_0)e^{-\gamma(k)t} - 1\,. \end{aligned}$$

For $t \to \infty$, we obtain,

$$e^{-\gamma(k)t} \to 0\,,$$

so that only the term with $k = 0$ does not converge to 0 and yields

$$S_{\infty;x_0} := \lim_{t\to\infty} S(t|x_0) = C(0,0,x_0)\,. \tag{20}$$

Equation (20) has a natural and intuitive meaning. Since the number of sublethal lesions can only decrease, it can reach 0 in a finite time with probability 1. Therefore, as $t \to \infty$, the only term that remains in Eq. (20) is the one coming from $p(t,0)$, that does not converge to 0.

Using the rule of total probability, we can obtain the solution for a probabilistic initial data from Eq. (12) as

$$\begin{aligned} p(t,0,x) &= \sum_{x_0=x}^{\infty} p_{x_0}(t,0,x)p(0,0,x_0) \\ &= \sum_{x_0=x}^{\infty} p_{x_0}(t,0,x)p_0^X(x_0)p_0^Y(0)\,, \end{aligned}$$

where $p_{x_0}(t,0,x)$ can be computed as in Eq. (18). In this case, the survival probability becomes

$$S(t) = \mathbb{P}(Y(t)=0) = \sum_{x=0}^{\infty} \mathbb{P}(Y(t)=0, X(t)=x)$$
$$= \sum_{x=0}^{\infty} p(t,0,x) = \sum_{x=0}^{\infty}\sum_{x_0=x}^{\infty} p_{x_0}(t,0,x) p_0^X(x_0) p_0^Y(0)\,. \tag{21}$$

The probability $p_{x_0}(t,0,x)$ can be calculated according to Eq. (18) only for $x_0 \geq 2$. We can also compute the values for $x_0 \geq 1$, considering that in such scenario no double interactions can occur. Thus, we obtain

$$\begin{cases} p_1(t,0,1) = e^{-(a+r)t}, \\ p_1(t,0,0) = r\frac{1-e^{-(a+r)t}}{a+r}, \\ p_1(t,0,x) = 0, x \geq 2, \\ p_0(t,0,0) = 1, \\ p_0(t,0,x) = 0, x \geq 1. \end{cases} \tag{22}$$

Combining a similar methodology as the one described above with Eqs. (18), (19), (21), (22), yields the following

$$\begin{aligned} S(t) &= \sum_{x=0}^{\infty}\sum_{x_0=x}^{\infty} p_{x_0}(t,0,x) p_0^X(x_0) p_0^Y(0) \\ &= \sum_{x_0=0}^{\infty} p_{x_0}(t,0,0) p_0^X(x_0) p_0^Y(0) \\ &\quad + \sum_{x=1}^{\infty}\sum_{x_0=x}^{\infty} p_{x_0}(t,0,x) p_0^X(x_0) p_0^Y(0) \\ &= p_0^X(0) p_0^Y(0) + \frac{r}{a+r} p_0^X(1) p_0^Y(0)\left(1 - e^{-(a+r)t}\right) \\ &\quad + \sum_{x_0=2}^{\infty}\sum_{k=0}^{x_0} p_0^X(x_0) p_0^Y(0) C(k,0,x_0) e^{-\gamma(k)t} \\ &\quad + \sum_{x=1}^{\infty} e^{-\gamma(x)t} p_0^X(x) p_0^Y(0) \\ &\quad + \sum_{x=1}^{\infty}\sum_{x_0=x+1}^{\infty}\sum_{k=x+1}^{x_0} p_0^X(x_0) p_0^Y(0) C(k,x,x_0) \\ &\quad \times \left(e^{-\gamma(k)t} - e^{-\gamma(x)t}\right). \end{aligned} \tag{23}$$

Considering Eq. (23) in the limit $t \to \infty$, and using that $e^{-\gamma(x)t} \to 0$ as $t \to \infty$, we obtain that only the terms with $k = 0$ do not converge to 0. Thus

$$\begin{aligned} S_d(z_n) &:= \lim_{t\to\infty} S(t) \\ &= p_0^X(0|z_n) p_0^Y(0|z_n) + \frac{r}{a+r} p_0^X(1|z_n) p_0^Y(0|z_n) \\ &\quad + \sum_{x_0=2}^{\infty} p_0^X(x_0|z_n) p_0^Y(0|z_n) C(x_0)\,, \end{aligned} \tag{24}$$

with $C(x_0) := C(0,0,x_0)$. Here we have employed the notation $p_0^X(x_0|z_n)$, $p_0^Y(0|z_n)$ and $S_\infty(z_n)$ to emphasize the dependence of the initial distributions on the average deposited energy on the cell nucleus z_n.

We can give a probabilistic interpretation of the terms appearing in Eq. (24): 1. $p_0^X(x_0|z_n)$ and $p_0^Y(0|z_n)$ represent the probability that the domain suffers x_0 sub-lesions and 0 lethal lesion, respectively; 2. $C(x_0)$ are weighting terms that represent the probability that x_0 sub-lethal lesions are repaired so that the domain survives.

The *survival probability* of the whole cell, when receiving an average energy deposition of z_n, is therefore evaluated as

$$\begin{aligned} S(z_n) &= \mathbb{P}\left(\lim_{t\to\infty}\left(\left\{Y^1(t)=0\right\} \cap \ldots \cap \left\{Y^{N_d}(t)=0\right\}\right)\right) \\ &= \prod_{i=1}^{N_d} \mathbb{P}\left(\lim_{t\to\infty} Y^i(t) = 0\right) = \prod_{i=1}^{N_d} S_\infty(z_n) \\ &= \prod_{i=1}^{N_d} p_0^X(0|z_n) p_0^Y(0|z_n) \\ &\quad + \prod_{i=1}^{N_d}\sum_{x_0=1}^{\infty} C(x_0) p_0^X(x_0|z_n) p_0^Y(0|z_n)\,. \end{aligned} \tag{25}$$

If we assume that all domains have the same probability distribution, we obtain

$$S(z_n) = \left(p_0^X(0|z_n) p_0^Y(0|z_n) + \sum_{x_0=1}^{\infty} C(x_0) p_0^X(x_0|z_n) p_0^Y(0|z_n)\right)^{N_d}. \tag{26}$$

The survival Eq. (26) calculated with GSM2 has a substantial difference from the standard Poisson-based models. As shown in Appendix B, the survival probability for a cell is generally computed by averaging the survival on a single domain, after it received an energy deposition z. On the contrary, we account for stochasticity deriving from energy deposition at the very beginning. In fact, the single domain survival probability is calculated taking into account all possible stochastic energy depositions z. Therefore, the cell survival probability is not the average over all possible energy depositions, but it is estimated as the probability that none of the domains suffers a lethal lesion.

Explicit Formulation of the Initial Conditions for the Survival Fraction Computation

The survival probability of Eq. (26) is expressed in terms of the initial damage distribution $p_0^X(x_0|z_n)$. We will derive a more explicit form for the survival equation by using the microdosimetric distribution $f_{1;d}$, so that the relation of the survival curve on the variable z_n appears explicitly. For the sake of readability, mathematical computations are reported in detail in Appendix A, whereas the current Section only reports main steps and results.

For $x>0$, using Eqs. (3)–(5), the following holds

$$p_0^X(x) = \sum_{v\geq 0} h(z_n, v, \kappa, x) \int_0^{\infty} e^{-\kappa z} z^x f_{v;d}(z) dz\,. \tag{27}$$

with

$$h(z_n, v, \kappa, x) := \frac{\kappa^x}{x!}\frac{z_n^v}{z_F^v v!}e^{-\frac{z_n}{z_F}}.$$

We will denote by $\mathcal{L}[g(z)]$ the *Laplace transform* of the function g, defined as

$$\mathcal{L}[g(z)](\kappa) := \int_0^\infty e^{-\kappa z} g(z) dz\,.$$

Taking advantage of the *Laplace transform* property, we have

$$\mathcal{L}[z^x g(z)](\kappa) = (-1)^x \frac{d^x}{d\kappa^x}\mathcal{L}[g(z)](\kappa), \quad x>0,$$

$$\mathcal{L}[g(z) * g(z)](\kappa) = \left(\mathcal{L}[g(z)](\kappa)\right)^2. \tag{28}$$

Substituting Eq. (28) into Eq. (27), we find

$$p_0^X(x) = (-1)^x \frac{\kappa^x}{x!} e^{-\frac{z_n}{z_F}} \times \frac{d^x}{d\kappa^x}\exp\left[\frac{z_n}{z_F}\int_0^\infty e^{-\kappa z} f_{1;d}(z) dz\right]. \tag{29}$$

$M(\kappa)$ and $M_x(\kappa)$ represent the *moment generating function* and the $x-$translated *moment generating function*, respectively, of the single-event distribution f_1 defined as

$$M(\kappa) := \int_0^\infty e^{-\kappa z} f_1(z) dz = \sum_{n\geq 0}\frac{(-1)^n}{n!}\kappa^n m_n,$$

$$M_x(\kappa) := \int_0^\infty z^x e^{-\kappa z} f_1(z) dz = \sum_{n\geq 0}\frac{(-1)^n}{n!}\kappa^n m_{n+x},$$

where m_n is the nth moment of single-event distribution $f_{1;d}(z)$.

For $x = 0$, we find the particular case

$$p_0^X(0) = \exp\left[-\frac{z_n}{z_F}\int_0^\infty (1 - e^{-\kappa z}) f_{1;d}(z) dz\right], \tag{30}$$

and analogously for $p_0^Y(0)$

$$p_0^Y(0) = \exp\left[-\frac{z_n}{z_F}\int_0^\infty \left(1 - e^{-\lambda z}\right) f_{1;d}(z) dz\right]. \tag{31}$$

From Eq. (29), some mathematical computations (see Appendix A) yield the following

$$p_0^X(x_0|z_n)p_0^Y(0|z_n) = \exp\left[-\frac{z_n}{z_F}\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \frac{(-\kappa)^x}{x!} H(z_n, x, M),$$

with

$$H(z_n, x, M) := \sum_{i=1}^{x}\sum_{j=1}^{i}\sum_{l=1}^{j}\frac{(-1)^i(-1)^j}{(i-j)!(j-l)!}\left(\frac{z_n}{z_F}\right)^j \times M^{i-l}B_{x,l}(M_1, \ldots, M_{x-l+1}).$$

Above we have defined by $B_{x,l}(M_1, \ldots, M_{x-l+1})$ is the *Bell's polynomial* defined as

$$B_{x,l}(M_1, \ldots, M_{x-l+1}) := \sum \frac{x!}{j_1! \ldots j_{x-l+1}!}(M_1)^{j_1} \ldots (M_{x-l+1})^{j_{x-l+1}},$$

and the summation ranges over multi-indexes such that

$$j_1 + j_2 + \ldots + j_{x-l+1} = l,$$

$$j_1 + 2j_2 + \ldots + (x - l + 1)j_{x-l+1} = x.$$

The survival Eq. (24) becomes

$$S_d(z_n) = \exp\left[-\frac{z_n}{z_F}\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \left[1 + \sum_{x_0=1}^{\infty}\frac{(-\kappa)^{x_0}}{x_0!}H(z_n, x_0, M)C(x_0)\right]. \tag{32}$$

Thus, the survival for the whole cell nucleus is calculated as

$$S(z_n) = \exp\left[-N_d\frac{z_n}{z_F}\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \left[1 + \sum_{x_0=1}^{\infty}\frac{(-\kappa)^{x_0}}{x_0!}H(z_n, x_0, M)C(x_0)\right]^{N_d}. \tag{33}$$

To emphasize the dependence of Eq. (33) on z_n, the terms of $H(z_n, x, M)$ contained in Eq. (33) can be rearranged to obtain

$$S(z_n) = \exp\left[-N_d\frac{z_n}{z_F}\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \left(1 + \sum_{k=1}^{\infty}\left(\frac{z_n}{z_F}\right)^k G_k(M)\right)^{N_d}, \tag{34}$$

with

$$G_k(M) := \sum_{x_0=k}^{\infty}\sum_{i=1}^{x_0}\sum_{j=1}^{i}\frac{(-1)^i(-1)^j}{(i-j)!(j-k)!}\frac{(-\kappa)^{x_0}}{x_0!}C(x_0) \times M^{i-k}B_{x_0,k}(M_1, \ldots, M_{x_0-k+1}). \tag{35}$$

Remark 1: In the very particular case of low-LET radiation, as showed above since $\kappa^2 z_n z_D << 1$, we infer that p_0^X follows a Poisson distribution.

Therefore, using the fact that the initial damage distribution is Poisson distributed, Eq. (34) simplifies to

$$S(z_n) = e^{-N_d z_n(\kappa+\lambda)}\left(1+\sum_{x_0=1}^{\infty} z_n^{x_0}\frac{\kappa^{x_0}}{x_0!}C(x_0)\right)^{N_d}. \quad (35)$$

Comparison with Existing Radiobiological Models for Predicting Survival Fraction

Equation (34) depends on the biological parameters a, b, r, κ and λ, as well as on the physical parameters related to energy deposition, mainly described by the single-event specific energy spectra $f_{1;d}(z)$. In particular, the survival Eq. (34) is the product of a linear exponential function

$$\exp\left[-N_d\frac{z_n}{z_F}\int_0^{\infty}\left(2-e^{-\kappa z}-e^{-\lambda z}\right)f_{1;d}(z)dz\right],$$

and a polynomial function of general order on z_n

$$\left(1+\sum_{k=1}^{\infty}\left(\frac{z_n}{z_F}\right)^k G_k(M)\right)^{N_d}.$$

The linear exponential function describes the initial damage formation inside the cell. This term depends on the biological parameters κ and λ, describing the number of initial lethal and sublethal lesions for a given energy event z, and on the radiation quality via the single-event spectra $f_{1;d}(z)$. It is worth stressing that, differently from most existing models, the whole microdosimetric distribution is considered rather than solely mean values, preserving the largest part of information achievable by physics measurements or simulation of a given radiation field.

The polynomial function, instead, accounts for the time evolution of the DNA damages. Each term G depends on the full energy spectrum $f_{1;d}(z)$ through the moment generating function M; this is a relevant difference with the majority of existing models, which are mainly based on the first two moments of the microdosimetric distribution. The probabilistic description of the G terms is that the ith term accounts for the damage caused by i events. Each term is weighted by the probability that such event occurs and that the induced DNA damage is repaired.

The survival curve in Eq. (24), written in compact form as,

$$S_d(z_n) := \sum_{x_0\geq 0} p_0^X(x_0|z_n)p_0^Y(0|z_n)C(x_0), \quad (36)$$

can be seen as a generalization of a *multihit* (MH) model (24, 28). We recall in fact that the MH model assumes that cell killing is due to several events that might happens in a target. Therefore, the survival probability at a given dose D can be expressed as

$$S(D) = \sum_{j=0}^{N} p(j|D),$$

where N is the maximum number of events that can occur, and p(j|D) is the probability of registering exactly events at a prescribed dose D. Unlike the standard MH model, we do not assume *a priori* any a priori upper limit for the number of hits. In fact, GSM2 suitably weighs the number of observed damages by the probability that a certain number of damages results from a specific microdosimetric and further consider the probability that damages are repaired.

Another difference between the MH and the proposed model, is that the number of lesions generated by an event is derived exploiting microdosimetry. In particular, the probability that a certain number of damages results from energy deposition is not assumed to Poissonian but it is derived from a mechanistic dynamical Eq. (2) allowing for repair and damage interaction. As shown in the literature (19), the resulting probability can be Poissonian under specific irradiation conditions, but can also differ significantly from a Poisson distribution, e.g., in high-dose regimes.

Several possible choices for p(j|D) have been shown in the literature; for instance, the standard assumptions is to consider p(j|D) to be a Poisson distribution [(24) see Chapter VI, ''Applications of Microdosimetry in Biology'']. More recently an advanced version of the MH modal has been proposed in Vassiliev (28) assuming a more general probability distribution. Notable enough, the generalized MH model derived in Vassiliev (28) can be seen as a particular case of the GSM2.

If we approximate the multi-event microdosimetric distribution as

$$f_{v;d}(z) = \delta(z - vz_F), \quad (37)$$

with $\delta(z-vz_F)$ the Dirac delta centered in vz_F, we obtain from Eq. (27),

$$\begin{aligned} p_0^X(x) &= \int_0^{\infty} e^{-\kappa z}\frac{(\kappa z)^x}{x!}f(z|z_n)dz \\ &= \sum_{v\geq 0}\int_0^{\infty} e^{-\kappa z}\frac{(\kappa z)^x}{x!}\frac{z_n^v}{z_F^v v!}e^{-\frac{z_n}{z_F}}\delta(z-vz_F)dz \\ &= \sum_{v\geq 0} e^{-\kappa v z_F}\frac{(\kappa v z_F)^x}{x!}\frac{z_n^v}{z_F^v v!}e^{-\frac{z_n}{z_F}} \\ &= e^{-\frac{z_n}{z_F}(1-e^{-\kappa z_F})}B_x\left(e^{-\frac{z_n}{z_F}e^{-\kappa z_F}}\right), \end{aligned} \quad (38)$$

with B_x the Bell polynomial. Equation (38) is equal to the main equation derived in Vassiliev (28). Therefore, inserting Eq. (38) into Eq. (26) we obtain a generalization of the non-Poissonian multi-hit model proposed in Vassiliev (28).

Although a distribution $f_{v;d}(z)$ of the type described by Eq. (37) is reasonable, it is nonetheless an approximation because it completely neglects the variance in the microdosimetric energy deposition event. To overcome this limitation, in this work we have exploited the full microdosimetric information coming from the entire spectrum.

After taking the logarithm, Eq. (34) becomes

$$\log S(z_n) = \left[-N_d \frac{z_n}{z_F} \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \right] + N_d \log\left(1 + \sum_{k=1}^{\infty} \left(\frac{z_n}{z_F}\right)^k G_k(M) \right). \quad (39)$$

For low doses, we have that $z_n << 1$, and expanding up to the second term in z_n in Eq. (39), we obtain

$$\begin{aligned} \log S(z_n) &\underset{0}{\sim} -\frac{z_n}{z_F} N_d \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \\ &+ \frac{z_n}{z_F} N_d G_1(M) - N_d \left(\frac{z_n}{z_F}\right)^2 \left(\frac{G_1(M)^2}{2} - G_2(M)\right) \\ &= -\alpha_0(M) z_n - \beta_0(M) z_n^2, \end{aligned} \quad (40)$$

with

$$\begin{cases} \alpha_0(M) & = \frac{N_d}{z_F} \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \\ & \quad - \frac{N_d}{z_F} G_1(M), \\ \beta_0(M) & = \frac{N_d}{z_F^2} \left(\frac{G_1(M)^2}{2} - G_2(M)\right). \end{cases} \quad (41)$$

In Eq. (40), we are neglecting higher order polynomials in z_n coming from Eq. (34). Additionally, the linear and quadratic terms depend on all the moments of the single event microdosimetric distribution $f_{1;d}$, rather than just on the first two moments z_F and z_D as in all classical models. By dropping all moments greater than the second, GSM2 provides the similar results as the existing models (2).

For high doses, i.e., $z_n >> 1$, the linear term in Eq. (39) dominates the logarithm, so that

$$\log S(z_n) \underset{\infty}{\sim} -\frac{z_n}{z_F} N_d \left(\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \right). \quad (42)$$

Above low and high dose approximation emphasize how the proposed model naturally incorporates the linear-quadratic-linear (LQL) behavior of the survival curves experimentally observed, especially in low-LET regime (29).

Furthermore, GSM2 satisfies the *Hugh-Kellerer theorem* (13, 24). In fact, assuming that no bystander effects (30) can occur, cells that experience no event must survive. As shown above, the event frequency for a given absorbed dose D is D/z_F. As the events are statistically independents, the Poisson statistics implies that there is a natural lower bound to the survival, that is

$$S_d(D) \geq e^{-\frac{D}{z_F}}. \quad (43)$$

The standard linear-quadratic model violates the lower bound in the high-dose region.

If each cell has received the same dose, i.e., $z_n = D$, Eq. (42) shows that in the high-dose regime, the derived survival follows a linear exponential function

$$S_d(D) = e^{-\frac{D}{z_F}\left(\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \right)} \geq e^{-\frac{D}{z_F}},$$

where the inequality follows from the fact that

$$\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz \leq 1.$$

The bound is clearly satisfied under the low-dose regimes, proving that GSM2 does not violate the *Hugh-Kellerer theorem*.

Non-Poissonian Inter-Cellular Corrections

Given a dose D, the energy deposition distribution can be computed as described above for $f(z|z_n)$. We therefore have that

$$f_n(z_n|D) := \sum_{v=0}^{\infty} p_n(v|D) f_{v;c}(z_n),$$

where $f_{v;n}(z_n)$ is the distribution resulting from v energy depositions in a single cell nucleus and $p_n(v|D)$ is the probability that a v energy deposition occurs in a cell nucleus. The distribution $f_{v;n}(z_n)$ can be obtained convolving the single event distribution $f_{1;n}(z_n)$.

Therefore, the total *cell survival probability* can be obtained as described in Rossi and Zaider (24).

Equation (8) contains all the overkilling corrections typically added to the survival curve formulations to account for the stochastic nature of energy deposition.

Given the survival curve $S_n(z_n)$ explicitly computed in Eq. (34) the survival curve $S(D)$ can efficiently calculated using standard numerical integration techniques. Nonetheless, using some physical considerations concerning the stochasticity of energy deposition some useful simplifications can be derived. In the companion paper, a detailed comparison of the survival curve $S(D)$ and the approximations derived in subsequent sections are investigated into details.

It is worth stressing that, as highlighted in Appendix B, in the original MKM formulation (3), it has been assumed that no stochasticity in energy deposition among cell domains happens, so that $S(D)$ can be obtained via the approximation

$$f_n(z_n|D) \approx \delta(z_n - D),$$

yielding using Eq. (8) the survival curve

$$S(D) = S_d(D) = \exp\left[-N_d \frac{D}{z_F}\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z)dz\right] \times \left(1 + \sum_{k=1}^{\infty}\left(\frac{D}{z_F}\right)^k G_k(M)\right)^{N_d},$$

with $G_k(M)$ as in Eq. (35).

In the following, suitable approximation of the microdosimetric spectrum $f_n(z_n|D)$ will be introduced and considered under different LET and doses regimes. Thus, the resulting survival curve will be computed highlighting its main aspects.

The Low-Dose Regime

For low doses, and in particular in the case

$$\alpha_0(M)z_n + \beta_0(M)z_n^2 << 1\,,$$

with α_0 and β_0 given as in Eq. (41), Eq. (40) yields

$$S(D) \approx 1 - \int_0^\infty \left(\alpha_0(M)z_n + \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right)z_n^2\right) f_n(z_n|D)dz_n = 1 - \alpha_0(M)m_1^c - \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right)m_2^c, \tag{44}$$

with m_1^c and m_2^c the first and second moment, respectively, of the multi-event distribution $f_n(z_n|D)$. Using the explicit forms for the moments m_1^c and m_2^c (24), we can conclude using Eq. (44) that

$$S(D) \approx 1 - \left(\alpha_0(M) + \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right)z_D\right)D - \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right)D^2 \approx e^{-\alpha(M)D - \beta(M)D^2}, \tag{45}$$

with

$$\begin{cases} \alpha(M) &= \alpha_0(M) + \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right)z_{D;n}\,, \\ \beta(M) &= \left(\beta_0(M) - \frac{\alpha_0^2(M)}{2}\right), \end{cases} \tag{46}$$

where $z_{D;n}$ is the dose average of the specific energy in multi events. Equations (45) and (46) emphasize the connection of the current models with the classical MKM. In fact, as shown in Cordoni (19), in the low-dose regimes the GSM2 predicts a Poissonian behaviour of lethal damages so that the standing assumption of the MKM is recovered. Nonetheless, it is worth stressing that, differently from the MKM, the α and β coefficients in Eq. (46) depends on the radiation quality via M.

The Medium-/Low-Dose and High-LET Regime

For high-LET regimes and medium/low doses, more precisely in regimes for which $\frac{D}{z_F} << 1$, the probability of more than one event is negligible. In such a situation, either 0 or 1 event is registered, so that the multi-event energy distribution can be approximated as

$$f_n(z_n|D) := \sum_{\nu=0}^{\infty}\frac{e^{-\frac{D}{z_F}}}{\nu!}\left(\frac{D}{z_F}\right)^n f_{\nu;c}(z) \approx e^{-\frac{D}{z_F}}\left(\delta(z_n) + \frac{D}{z_F}f_{1;c}(z_n)\right). \tag{47}$$

Calculating Eq. (8) with the approximated multi-event distribution Eq. (47), we obtain

$$S(D) = \int_0^\infty S_d(z_n)f_n(z_n|D)dz_n \approx e^{-\frac{D}{z_F}} + e^{-\frac{D}{z_F}}\frac{D}{z_F}\int_0^\infty S_d(z_n)f_{1;c}(z_n)dz_n. \tag{48}$$

A further approximation can be included into Eq. (48); in fact, Eq. (40) demonstrated that the survival at low doses is linear-quadratic, and thus, combining Eq. *(40)* with Eq. (48) we obtain

$$S(D) \approx e^{-\frac{D}{z_F}} + e^{-\frac{D}{z_F}}\frac{D}{z_F}\int_0^\infty e^{-\alpha_0 z_n - \beta_0 z_n^2}f_{1;c}(z_n)dz_n, \tag{49}$$

with α_0 and β_0 as in Eq. (41).

From Eq. (49) we find further

$$S(D) \approx \exp\left[-\frac{D}{z_F}\int_0^\infty \left(1 - e^{-\alpha_0 z_n - \beta_0 z_n^2}\right)f_{1;c}(z_n)dz_n\right]. \tag{50}$$

It is worth stressing that Eq. (50) highlights an insightful connection to the DNA-lesion theory of radiation action (24). In fact, Eq. (50) recover the main equation of DNA-lesion theory of radiation action (24).

The High-Dose Regime

For a high-dose regime, more rigorously in regimes for which it holds that $\frac{D}{z_F} >> 1$, the multi-event distribution becomes Gaussian distributed (13). We therefore have that

$$f(z|z_n) := \sum_{\nu=0}^{\infty}\frac{e^{-\frac{z_n}{z_F}}}{\nu!}\left(\frac{z_n}{z_F}\right)^n f_{\nu;d}(z) \approx \frac{1}{\sqrt{2\pi z_D D}}e^{-\frac{1}{2}\frac{(z_n - D)^2}{z_D D}}, \tag{51}$$

where z_D is the dose average of the specific energy in single events.

Assessing Eq. (8) with the approximated multi-event distribution Eq. (51), we obtain using the purely linear behavior for the survival curve $S_d(z_n)$ showed in Eq. (42),

$$S(D) = \int_0^\infty S_d(z_n) f_n(z_n|D) dz_n$$

$$\approx \frac{1}{\sqrt{2\pi z_D D}} \int_0^\infty e^{-\alpha_{HL} z_n} e^{-\frac{1}{2}\frac{(z_n - D)^2}{z_D D}} dz_n, \quad (52)$$

where z_D is the dose average of the specific energy in single events on the cell-nucleuous and

$$\alpha_{HL} := N_d \left(\int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;c}(z) dz \right).$$

Solving Eq. (52), we find

$$S(D) = e^{-\alpha_{HL}\left(1 - \frac{\alpha_{HL} z_D}{2}\right) D}. \quad (53)$$

As mentioned above, Eq. (53) accounts for overkilling effects. In fact, a cell irradiated with a higher LET will have a lower probability of surviving, resulting in a greater value for α_{HL}. According to Eq. (53), the corresponding survival curve will be corrected and shifted upward by a greater term $\frac{\alpha_{HL}^2 z_D}{2}$, yielding in fact the typical effect of overkilling corrections.

CONCLUSIONS

In the present work, we used the new GSM2 model (19) to obtain an equation for cell survival. GSM2 takes into account the effects of stochasticity in different aspects of radiation-induced damage, e.g., in the initial damage distribution as well as in the damage evolution, and for this reason the derivation of an explicit and consistent form for the survival curve is not trivial. The pairwise interaction of damages implies that the resulting *Microdosimetric Master Equation* does not fall into the class of the standard *birth-death processes*, thus preventing the use of the extensive literature already available and requiring the development of ad hoc mathematical techniques methods. Furthermore, the general form of the initial damage distribution takes advanced physical and mathematical arguments to derive an explicit form for the survival curve predicted by GSM2.

From the comparison of GSM2 calculations with the typical shape of measured survival cell curves, two important aspects emerge: 1. The model predicts a *linear-quadratic-linear* behavior of the survival as a function of the dose, i.e. a linear-quadratic behavior at low doses and a purely linear at high doses; and 2. Describing the radiation field quality with the whole microdosimetric spectrum can include a more detailed description of the radiation quality than considering only average values, as most of the existing models do. These aspects make GSM2 a very promising model for providing a general description of cell survival for ions of different LET, with specific reference to high-LET regimes.

In addition, we illustrated a rigorous generalization to consider inter-cellular non-Poissonian effects. Using suitable approximations for the microdosimetric spectra at high and low doses, we showed how the stochasticity of energy deposition among different cells can be taken into account.

This article also described the connection between GSM2 and different existing radiobological models for cell survival computation. Besides a close connection with the MKM already discussed in Cordoni (19), analogies with predictions from the *Multi-Hit Model* and the *DNA-lesion theory of radiation action* (28, 31), emerged in the current work. Further links between the GSM2 and existing survival models, such as the *Multi-Hit Model* and the *Repair-Misrepair Model*, are currently under investigation.

A detailed analysis of the survival curves, whose calculation method has been reported here will be reported in a companion paper. The study will focus on the dependence of the survival curves on the ion type and LET.

APPENDIX A

Explicit Formulation of the Initial Conditions for the Survival Fraction Computation: Detailed Mathematical Derivation

The current section expands ''Explicit Formulation of the Initial Conditions for the Survival fraction Computation'' reporting detailed mathematical derivation of the Survival curve. Recall that, the following holds

$$p_0^X(x) = \int_0^\infty e^{-\kappa z} \frac{(\kappa z)^x}{x!} f(z|z_n) dz = \sum_{v \geq 0} \int_0^\infty e^{-\kappa z} \frac{(\kappa z)^x}{x!} \frac{z_n^v}{z_F^v v!} e^{-\frac{z_n}{z_F}} f_{v;d}(z) dz$$

$$= \sum_{v \geq 0} h(z_n, v, \kappa, x) \int_0^\infty e^{-\kappa z} z^x f_{v;d}(z) dz. \quad (A1)$$

with

$$h(z_n, v, \kappa, x) := \frac{\kappa^x}{x!} \frac{z_n^v}{z_F^v v!} e^{-\frac{z_n}{z_F}}.$$

We will denote by $\mathcal{L}[g(z)]$ the *Laplace transform* of the function g, defined as

$$\mathcal{L}[g(z)](\kappa) := \int_0^\infty e^{-\kappa z} g(z) dz.$$

Taking advantage of the *Laplace transform* property, we have

$$\mathcal{L}[z^x g(z)](\kappa) = (-1)^x \frac{d^x}{d\kappa^x} \mathcal{L}[g(z)](\kappa), \quad x > 0$$

$$\mathcal{L}[g(z) * g(z)](\kappa) = (\mathcal{L}[g(z)](\kappa))^2. \quad (A2)$$

Substituting Eq. (A2) into Eq. (A1), we find

$$p_0^X(x) = \sum_{v\geq 0} h(z_n, v, \kappa, x) \int_0^\infty e^{-\kappa z} z^x f_{v;d}(z) dz$$
$$= \sum_{v\geq 0} h(z_n, v, \kappa, x)(-1)^x \frac{d^x}{d\kappa^x}\left(\mathcal{L}\left[f_{1;d}(z)\right]^v(\kappa)\right)$$
$$= (-1)^x \frac{\kappa^x}{x!} e^{-\frac{z_n}{z_F}} \times \frac{d^x}{d\kappa^x} \sum_{v\geq 0} \frac{z_n^v}{z_F^v v!} \left(\int_0^\infty e^{-\kappa z} f_{1;d}(z) dz\right)^v$$
$$= (-1)^x \frac{\kappa^x}{x!} e^{-\frac{z_n}{z_F}} \times \frac{d^x}{d\kappa^x} \exp\left[\frac{z_n}{z_F} \int_0^\infty e^{-\kappa z} f_{1;d}(z) dz\right]. \quad \text{(A3)}$$

$M(\kappa)$ and $M_x(\kappa)$ represent the *moment generating function* and the $x-$translated *moment generating function*, respectively, of the single-event distribution f_1 defined as

$$M(\kappa) := \int_0^\infty e^{-\kappa z} f_1(z) dz = \sum_{n\geq 0} \frac{(-1)^n}{n!} \kappa^n m_n,$$

$$M_x(\kappa) := \int_0^\infty z^x e^{-\kappa z} f_1(z) dz = \sum_{n\geq 0} \frac{(-1)^n}{n!} \kappa^n m_{n+x},$$

where m_n is the nth moment of single-event distribution $f_{1;d}(z)$.

Defining for short

$$g(\kappa) = \frac{z_n}{z_F} \int_0^\infty e^{-\kappa z} f_{1;d}(z) dz = \frac{z_n}{z_F} M(\kappa),$$

the following equalities hold true (27)

$$\frac{d^x}{d\kappa^x} e^{g(\kappa)} = e^{g(\kappa)} \sum_{i=1}^x \frac{(-1)^i}{i!} \sum_{j=1}^i (-1)^j \binom{i}{j} \frac{d^x}{d\kappa^x} g^j(\kappa) g(\kappa)^{i-j},$$

$$\frac{d^x}{d\kappa^x} g^j(\kappa) = \sum_{l=1}^j \left(\frac{z_n}{z_F}\right)^l \frac{j!}{(j-l)!} g^{j-l}(\kappa) B_{x,l}(M_1, \ldots, M_{x-l+1}), \quad \text{(A4)}$$

where $B_{x,l}(M_1, \ldots, M_{x-l+1})$ is the *Bell's polynomial* defined as

$$B_{x,l}(M_1, \ldots, M_{x-l+1}) := \sum \frac{x!}{j_1! \ldots j_{x-l+1}!} (M_1)^{j_1} \ldots (M_{x-l+1})^{j_{x-l+1}},$$

and the summation ranges over multi-indexes such that

$$j_1 + j_2 + \ldots + j_{x-l+1} = l,$$

$$j_1 + 2j_2 + \ldots + (x-l+1) j_{x-l+1} = x.$$

Using Eq. (A4), we thus get

$$\frac{d^x}{d\kappa^x} e^{g(\kappa)} = e^{g(\kappa)} \sum_{i=1}^x \sum_{j=1}^i \sum_{l=1}^j \frac{(-1)^i (-1)^j}{(i-j)!(j-l)!} \left(\frac{z_n}{z_F}\right)^j \times M^{i-l} B_{x,l}(M_1, \ldots, M_{x-l+1}). \quad \text{(A5)}$$

Inserting Eq. (A5) into Eq. (A3) we finally obtain

$$p_0^X(x) = \frac{(-\kappa)^x}{x!} \exp\left[-\frac{z_n}{z_F} \int_0^\infty (1 - e^{-\kappa z}) f_{1;d}(z) dz\right] \times \sum_{i=1}^x \sum_{j=1}^i \sum_{l=1}^j \frac{(-1)^i (-1)^j}{(i-j)!(l-2)!} \left(\frac{z_n}{z_F}\right)^j \times M^{i-l} B_{x,l}(M_1, \ldots, M_{x-l+1})$$
$$= \exp\left[-\frac{z_n}{z_F} \int_0^\infty (1 - e^{-\kappa z}) f_{1;d}(z) dz\right] \times \frac{(-\kappa)^x}{x!} H(z_n, x, M), \quad \text{(A6)}$$

with

$$H(z_n, x, M) := \sum_{i=1}^x \sum_{j=1}^i \sum_{l=1}^j \frac{(-1)^i (-1)^j}{(i-j)!(j-l)!} \left(\frac{z_n}{z_F}\right)^j \times M^{i-l} B_{x,l}(M_1, \ldots, M_{x-l+1}). \quad \text{(A7)}$$

For $x = 0$, we find the particular case

$$p_0^X(0) = \exp\left[-\frac{z_n}{z_F} \int_0^\infty (1 - e^{-\kappa z}) f_{1;d}(z) dz\right], \quad \text{(A8)}$$

and analogously for $p_0^Y(0)$

$$p_0^Y(0) = \exp\left[-\frac{z_n}{z_F} \int_0^\infty (1 - e^{-\lambda z}) f_{1;d}(z) dz\right]. \quad \text{(A9)}$$

From Eqs. (A6), (A8) and (A9), and exploiting the fact that

$$p_0^X(x_0|z_n) p_0^Y(0|z_n) = \exp\left[-\frac{z_n}{z_F} \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \frac{(-\kappa)^x}{x!} H(z_n, x, M),$$

the survival Eq. (24) becomes

$$S_d(z_n) = \exp\left[-\frac{z_n}{z_F} \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \left[1 + \sum_{x_0=1}^\infty \frac{(-\kappa)^{x_0}}{x_0!} H(z_n, x_0, M) C(x_0)\right]. \quad \text{(A10)}$$

Thus, the survival for the whole cell nucleus is calculated as

$$S(z_n) = \exp\left[-N_d \frac{z_n}{z_F} \int_0^\infty \left(2 - e^{-\kappa z} - e^{-\lambda z}\right) f_{1;d}(z) dz\right] \times \left[1 + \sum_{x_0=1}^\infty \frac{(-\kappa)^{x_0}}{x_0!} H(z_n, x_0, M) C(x_0)\right]^{N_d}. \quad \text{(A11)}$$

APPENDIX B

The Microdosimetric Kinetic Model (MKM) and its Connection to the GSM2

The *Microdosimetric Kinetic Model* (MKM) is one of the most used radiobiological model that, starting from microdosimetric spectra, aims at quantifying the cell survival, for a given radiation field.

The MKM starting point is the same as the GSM2 but, instead of the full probability distribution for lethal and sublethal lesions, the corresponding average values are considered. Using assumptions introduced in section ''*The Generalized Stochastic Microdosimetric Model,*'' denoting by $\bar{x}_{g,z}$ and $\bar{y}_{g,z}$ the number of type *II* and type *I* lesion for domain d and dose z, respectively, it is assumed that they satisfy the following set of coupled ODE

$$\begin{cases} \frac{d}{dt}\bar{y}_{d,z}(t) = a\bar{x}_{d,z} + b\bar{x}_{d,z}^2, \\ \frac{d}{dt}\bar{x}_{d,z}(t) = -(a+r)\bar{x}_{d,z} - 2b\bar{x}_{d,z}^2. \end{cases} \quad \text{(B1)}$$

Assuming further that $(a+r) \gg 2b$ above equation is reduced to

$$\begin{cases} \frac{d}{dt}\bar{y}_{d,z}(t) = a\bar{x}_{d,z} + b\bar{x}_{d,z}^2, \\ \frac{d}{dt}\bar{x}_{d,z}(t) = -(a+r)\bar{x}_{d,z}. \end{cases} \quad \text{(B2)}$$

In the following, for ease of notation, we will omit the subscript (d,z) denoting for short $\bar{x} := \bar{x}_{d,z}$, resp. $\bar{y} := \bar{y}_{d,z}$.

One of the final goals of the MKM model, starting from microdosimetric measurements, is to predict the survival probability of cell nuclei when exposed to ionizing radiation. In order to achieve the goal one more assumption is made.

The lethal lesion distribution follows a Poissonian distribution.

Under Poissonian distribution assumptions above, the probability that domain d survives as $t \to \infty$ when exposed to the specific energy z, denoted by S_{d,z_d} can be computed as the probability that the random outcome of a Poisson random variable is null. Therefore S_{d,z_d} is given by,

$$S_{d,z_d} = e^{\lim_{t\to\infty} \bar{y}_{d,z}(t)}. \tag{B3}$$

Explicit computation (3, 32), shows that the number of lethal lesions as $t \to \infty$ can be computed as

$$\lim_{t\to\infty} \bar{y}_{d,z}(t) = \left(\lambda + \frac{a\kappa}{a+r}\right) z + \frac{b\kappa^2}{2(a+r)} z^2,$$

so that we obtain from Eq. (B3)

$$S_{d,z_d} = e^{Az+Bz^2},$$

with A and B some suitable constants independent of the domain d and specific energy z_d of the domain d.

The survival log probability Eq. (B3) cab be extended to the whole cell nucleus, denoted by $\log S_n$ as

$$\begin{aligned} \log S_{n,z_n} &:= \sum_{i=1}^{N_d} \log S_{d,z_d} \\ &= -N_d A \int_0^\infty z_d f_d(z_d; z_n) dz_d - N_d B \int_0^\infty z_d^2 f_d(z_d; z_n) dz_d, \end{aligned} \tag{B4}$$

where $f_d(z_d, z_n)$ denotes the probability density of z_d for a cell nucleus specific energy z_n. In particular, the following holds

$$z_n = \int_0^\infty z_d f_d(z_d; z_n) dz_d \,.$$

The log survival in Eq. (B4) can be thus written as

$$\log S_{n,z_n} = -(\alpha + \bar{z}_d \beta) z_n - \beta z_n^2 \,,$$

being $\bar{z}_d$ the dose mean z_d per event defined as

$$\bar{z}_d := \frac{\int_0^\infty z_d^2 f_{d,1}(z_d) dz_d}{\int_0^\infty z_d f_{d,1}(z_d) dz_d} \,,$$

where $f_{d,1}(z_d)$ is the single-event probability density of z_d in the domain d.

The total survival log probability $\log S$ for a population of irradiated cells is then given by,

$$\log S = \log \left(\int_0^\infty S_{n,z_n} f_n(z_n; D) dz_n \right), \tag{B5}$$

where similar to above we have denoted by $f_n(z_n; D)$ the probability density of z_n for an absorbed dose D, i.e.,

$$D = \int_0^\infty z_n f_n(z_d; D) dz_n \,.$$

Assuming that Eq. (B5) can be approximated as

$$\begin{aligned} \log S = \log \left(\int_0^\infty S_{n,z_n} f_n(z_n; D) dz_n \right) &\approx \int_0^\infty \log\left(S_{n,z_n}\right) f_n(z_n; D) dz_n \\ &= -(\alpha + (\bar{z}_d - \bar{z}_n)\beta) D - \beta D^2, \end{aligned} \tag{B6}$$

with $\bar{z}_n$ the dose mean z_n per event.

The first line of Eq. (B6) is an approximation that is not valid in.

Several generalizations (4, 9–12, 32, 33), have been proposed in order to take into account effects due to a non-Poissonian distribution of lethal lesions. To the best of our knowledge, most of these models try to correct the log survival Eq. (B6) introducing some correction term based on overkilling effects. For instance, in Sato and Furusawa (11) the following correction has been proposed

$$\log S = -(\alpha + (\bar{z}_d - \bar{z}_n)\beta) f(\bar{z}_d, \bar{z}_n) D - \beta D^2 \,,$$

where $f(\bar{z}_d, \bar{z}_n)$ is a suitable correction term that depends on both $\bar{z}_d$ and $\bar{z}_n$. Another form is given in Kase (12) as

$$\log S = -\left(\alpha + \bar{z}_d^* \beta\right) D - \beta D^2 \,,$$

where $\bar{z}_d^*$ is a term that accounts for overkilling effects.

Connection between the MKM and the GSM2

The present section aims at showing that the mean value of the master equation does satisfy, under certain assumptions, the kinetic Eq. (B1). In what follows, $\mathbb{E}$ denotes the mean value of a random variable defined as

$$\bar{x}(t) := \mathbb{E}[X(t)] = \sum_{x,y\geq 0} x p(t, y, x),$$

$$\bar{y}(t) := \mathbb{E}[Y(t)] = \sum_{x,y\geq 0} y p(t, y, x).$$

Note that the following holds true,

$$\sum_{x,y\geq 0} x \mathcal{E}^{i,j}[f(y,x)p(t,y,x)] = -\mathbb{E}if(Y,X),$$

$$\sum_{x,y\geq 0} y \mathcal{E}^{i,j}[f(y,x)p(t,y,x)] = -\mathbb{E}if(Y,X). \tag{B7}$$

Therefore, multiplying the MME (2) by x and y, we obtain using (B7)

$$\begin{cases} \frac{d}{dt}\mathbb{E}[Y(t)] &= b\mathbb{E}[X(t)(X(t)-1)] + a\mathbb{E}[X(t)], \\ \frac{d}{dt}\mathbb{E}[X(t)] &= -2b\mathbb{E}[X(t)(X(t)-1)] - (a+r)\mathbb{E}[X(t)]. \end{cases} \tag{B8}$$

Equation (B8) are still not of the form of Eq. (B1); in particular they depend on a second order moment $\mathbb{E}[X(t)(X(t)-1)]$. Nonetheless, explicit computation will show that, if we try to compute a kinetic equation for the second order moment $\mathbb{E}[X(t)(X(t)-1)]$, we would obtain a dependence on higher moments, and so to obtain an infinite set on coupled ODE. To solve the impasse, we shall make what is called a *mean-field* assumptions, that is, we assume that,

$$\mathbb{E}[X(t)(X(t)-1)] \sim \mathbb{E}[X(t)]^2 \,,$$

so that under the *mean-field assumption* Eq. (13) become,

$$\begin{cases} \frac{d}{dt}\bar{y}(t) &= b\bar{x}^2(t) + a\bar{x}(t) \,, \\ \frac{d}{dt}\bar{x}(t) &= -2\bar{x}^2(t) - (a+r)\bar{x}(t) \,, \end{cases} \tag{B9}$$

and the original kinetic equations are in turn recovered.

A quick remark on the *mean-field assumption* is needed. In the case of x being large enough, we have that the following approximation holds true $\mathbb{E}[X(t)(X(t)-1)] \sim \mathbb{E}[X(t)]^2$; therefore, the *mean-field assumption* means that $\mathbb{E}[X(t)(X(t)-1)] - \mathbb{E}[X(t)]^2 \sim 0$. Noticing that the last term is nothing but the variance, and recalling that the variance for a random variable is null if and only if the random variable is in fact deterministic, if the *mean-field assumption* is realistic than the realized number of lesions does not differ much from the mean value so that everything we need to know is the mean value. On the contrary if there are evidence that the mean value is not a realistic approximation for the realized number of lesions, the *mean-field assumption* must be considered unrealistic so that the knowledge of the full probability distribution is essential to have a complete understanding of the system.

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