MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **13**, Number **1**, February **2016**

doi:10.3934/mbe.2016.13.159

pp. **159–170**

THE CONSEQUENCE OF DAY-TO-DAY STOCHASTIC DOSE DEVIATION FROM THE PLANNED DOSE IN FRACTIONATED RADIATION THERAPY

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(Communicated by Yang Kuang)

Abstract. Radiation therapy is one of the important treatment procedures of cancer. The day-to-day delivered dose to the tissue in radiation therapy often deviates from the planned fixed dose per fraction. This day-to-day variation of radiation dose is stochastic. Here, we have developed the mathematical formulation to represent the day-to-day stochastic dose variation effect in radiation therapy. Our analysis shows that that the fixed dose delivery approximation under-estimates the biological effective dose, even if the average delivered dose per fraction is equal to the planned dose per fraction. The magnitude of the under-estimation effect relies upon the day-to-day stochastic dose variation level, the dose fraction size and the values of the radiobiological parameters of the tissue. We have further explored the application of our mathematical formulation for adaptive dose calculation. Our analysis implies that, compared to the premise of the Linear Quadratic Linear (LQL) framework, the Linear Quadratic framework based analytical formulation under-estimates the required dose per fraction necessary to produce the same biological effective dose as originally planned. Our study provides analytical formulation to calculate iso-effect in adaptive radiation therapy considering day-to-day stochastic dose deviation from planned dose and also indicates the potential utility of LQL framework in this context.

1. **Introduction.** Radiation therapy is one of the key treatment procedures of cancer. The delivery of radiation dose to the tissue usually involves administration of dose by daily fractions. In such fractionated radiation therapy, commonly constant magnitude of dose is planned to be delivered to the tissue in each daily fraction [12]. However, the magnitude of day-to-day delivered dose deviates from the planned dose. The deviations from the planned dose occur due to various underlying factors, e.g. errors regarding the positioning of the patients, beam placement and geometric variation of the organ [17]. It may be mentioned that the dose delivered in each fraction is a sample of stochastic (random) quantity [1].

The consequence of stochastic variation of a parameter on the response of the system had been often disregarded in the dynamical analysis of physical as well as biological systems [6] and such variation of the parameter is frequently considered

2010 *Mathematics Subject Classification.* Primary: 92B05.

Key words and phrases. Stochastic, Jensen's Inequality, daily dose, biological effect, radiation therapy.

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as nuisance [3]. As per deterministic viewpoint, it is often implied that the responses of systems are governed by the averaged value of the parameter undergoing stochastic variation [6]. However, due to the progress of the theory of stochastic processes, it is now known that the responses of diverse systems, with consideration of stochastic variation of parameter, are often markedly different from their responses when the parameter remains at the constant average value [6]. Such divergences of the responses under the influence of stochastic variation of photon flux have been demonstrated in various systems, ranging from chemical reaction [18], photo-chemical property of bio-molecules [7] to multi-cellular circadian system [16].

In adaptive radiation therapy (ART), the treatment plan is adapted during the course of the therapy utilizing the feedback information regarding the measurements in order to recompense or minimize the effect of variation of treatment plans [17]. Commonly, the intent of adaptation of the treatment plan is to curtail the error in the magnitude of the delivered dose from the planned dose during fractionated radiation therapy. However, in this context, the resultant biological effect may be different than that was originally planned, even though the total dose delivered during the fractionated dose delivery protocol is the same as the planned dose [15]. Therefore, the utilization of the notion of pertinent biological objective is generally preferred for dose adaptation compared to the above mentioned notion of dose error compensation [15]. The deterministic Linear-Quadratic (LQ) model is commonly utilized to elucidate the dose-response relation [2]. However, it is known that the above-mentioned LQ model is often unsuccessful to represent dose-response relationship when the magnitude of the administered dose is high [5]. On the other hand, the deterministic Linear-Quadratic-Linear (LQL) model is capable of portraying satisfactory dose-response relationships in the low dose and also in the high dose delivery conditions [5].

To the best of our knowledge, there is no available analytical formulation to represent the dose-response relation in the context of day-to-day stochastic dose deviation from the planned dose in fractionated radiation therapy. The primary objective of this article is to develop the above-mentioned mathematical formulation which we have pursued employing the frameworks of stochastic differential equation and Jensen's inequality for convex function, in order to explore the possible effect of day-to-day stochastic dose deviation in radiation therapy. Further, we have explored the applicability of our model in the context of dose adaptation strategy in fractionated radiation therapy and also contrasted the LQL and LQ framework based dose adaptation schemes considering day-to-day stochastic dose deviation.

2. **Theory.**

2.1. **Calculation of biological effective dose considering day-to-day stochastic dose variation.**

We consider a fractionated radiation delivery situation with planned constant daily dose d per fraction for n consecutive days. Considering complete repair involving two consecutive fractions in fractionated radiation therapy, the survival fraction after $n-$th day can be denoted under Linear Quadratic Liner (LQL) model [5] as:

$$S_n = exp\{n(-\alpha d - \beta G_{LQL} d^2)\} \tag{1}$$

where α, β are the radiation sensitivity parameters and

$$G_{LQL} = \{2/(\mu t + \delta D)\}[1 - \{1 - exp(-\mu t - \delta D)\}/(\mu t + \delta D)]$$

The parameter δ illustrates the bending of dose-response curves [5]. This parameter is also related to the yield of radiation induced lesion production and the probability of interaction of the newly formed lesion with the existing lesion [5]. μ represents the repair-rate of repairable DNA lesions.

The biological effect of radiation (E_n) is defined as, $E_n = -lnS_n = n(\alpha d + \beta G_{LQL} d^2)$. Now we re-write this expression in the differential form as:

$$dE_n = \Phi(d)\Psi(E_n)dn \tag{2}$$

where $\Phi(d) = (\alpha d + \beta G_{LQL} d^2)$, $\Psi(E_n) = 1$. With the aim of elucidating the effect of day-to-day dose variation in fractionated radiation therapy, we replace d by $d_d + \xi_n$ in (2), where ξ_n represents the stochastic variation in day-to-day delivered dose and d_d is the mean delivered dose per fraction. Now from (2), considering day-to-day stochastic dose variation, the evolution of the biological effect over the days of fractionated radiation therapy can be denoted by the following generalized stochastic differential equation (SDE), $dE_n = \Phi(d_d + \xi_n)\Psi(E_n)dn$ where $\Phi(d_d + \xi_n) = (\alpha d_d + \beta G_{LQL} d_d^2) + (\alpha + 2\beta G_{LQL} d_d)\xi_n + \beta G_{LQL}\xi_n^2$. Initially, we represent ξ_n as coloured noise using the model of Ornstein-Uhlenbeck (OU) process with $E(\xi_n) = 0$ and the exponentially decreasing correlation function, $E(\xi_n \xi_m) = (t_c \sigma_d^2/2) exp(- \mid n - m \mid /t_c)$ [6]. Here, the correlation time is denoted by t_c and σ_d designates the standard deviation concerned with the day-to-day stochastic dose variation. Now, we represent the time evolution of E_n considering day-to-day stochastic dose variation using the SDEs of following forms:

$$dE_n = \lambda(d_d, \sigma_d)\Psi(E_n)dn + \tfrac{1}{\omega}\Psi(E_n)\eta_n dn$$

and

$$d\xi_n = -\tfrac{1}{t_c}\xi_n dn + \tfrac{\sigma_d}{\sqrt{t_c}} dW_n$$

where ω symbolizes the distance from the situation when $t_c \to 0$. W_n defines the standard Wiener process [6] and η_n is defined as,

$$\eta_n = \Phi(d_d + \xi_n) - E\{\Phi(d_d + \xi_n)\} = \Phi(d_d + \xi_n) - \lambda(d_d, \sigma_d) \text{ and}$$

$$\lambda(d_d, \sigma_d) = \int_{-\infty}^{+\infty} \Phi(\mathrm{d_d} + \mathrm{z})\mathrm{p(z)dz} \tag{3}$$

where $p(z) = \sqrt{\pi\sigma_d^2} exp(-z^2/\sigma_d^2)$ is the probability density corresponding to Ornstein-Uhlenbeck (OU) process. We re-write the expression of $\Phi(d_d + \xi_n)$ by substituting ξ_n by z as,

$$\Phi(d_d + z) = (\alpha d_d + \beta G_{LQL} d_d^2) + (\alpha + 2\beta G_{LQL} d_d)z + \beta G_{LQL} z^2 \tag{4}$$

Now, from (3), we obtain,

$$\lambda(d_d, \sigma_d) = \alpha d_d + \beta G_{LQL}(d_d^2 + \sigma_d^2/2) \tag{5}$$

At white noise limit ($t_c \to 0$), the time evolution of E_n can be denoted by the following form of Stratnovich SDE [6]:

$$dE_n = \lambda(d_d, \sigma_d)\Psi(E_n)dn + \tilde{\sigma_d}\Psi(E_n) \circ dW_n \tag{6}$$

where $\tilde{\sigma}_d$ is defined as

$$\tilde{\sigma}_d^2 = 2\int_{\mathcal{R}} \mathrm{d}z p(z)\{\Phi(d_d + z) - \lambda(d_d, \sigma_d)\}Y(d_d + z) \tag{7}$$

$Y(d_d + z)$ represents a particular solution of

$$F_1^+ Y = -\{\Phi(d_d + z) - \lambda(d_d, \sigma_d)\} \tag{8}$$

In (8), $F_1^+ = -z\partial_z + (\sigma_d^2/2)\partial_{zz}$ represents the OU process based Kolmogorov backward operator [6]. Now, we re-write (8) as,

$$\{-z\partial_z + (\sigma_d^2/2)\partial_{zz}\}Y = -\{\Phi(d_d + z) - \lambda(d_d, \sigma_d)\} \tag{9}$$

Following [6], we consider the following polynomial expression of Y,

$$Y = \kappa_1 z^3 + \kappa_2 z^2 + \kappa_3 z \tag{10}$$

At this point, using the expressions of $Y(10)$, $\Phi(d_d + z)$ (4) and $\lambda(d_d, \sigma_d)$ (5) and comparing the both sides of (9) we deduce: $\kappa_1 = 0$, $\kappa_2 = \beta G_{LQL}/2$ and $\kappa_3 = (\alpha + 2\beta G_{LQL} d_d)$. Further, using the expressions of κ_1, κ_2 and κ_3, we re-write (10) as,

$$Y(d_d + z) = \beta G_{LQL} z^2/2 + (\alpha + 2\beta G_{LQL} d_d)z \tag{11}$$

Now using the expressions of $Y(d_d + z)$ (11), $\lambda(d_d + \sigma_d)$ (5), $\Phi(d_d + z)$ (4) and $p(z)$, we deduce the following expression of $\tilde{\sigma_d}$ from (7):

$$\tilde{\sigma_d} = \sqrt{(\alpha + 2\beta G_{LQL} d_d)\sigma_d^2 + \beta^2 G_{LQL}^2 \sigma_d^4/2} \tag{12}$$

Now replacing the expressions of $\Psi(E_n)$, $\lambda(d_d + \sigma_d)$ (5), $\tilde{\sigma_d}$ (12), we re-write (6) as,

$$dE_n = \{\alpha d_d + \beta G_{LQL}(d_d^2 + \sigma_d^2/2)\}dn + \sqrt{(\alpha + 2\beta G_{LQL} d_d)\sigma_d^2 + \beta^2 G_{LQL}^2 \sigma_d^4/2} \circ dW_n \tag{13}$$

Further, we transform the Stratonovich SDE (13) to the corresponding Ito SDE [10]:

$$dE_n = \{\alpha d_d + \beta G_{LQL}(d_d^2 + \sigma_d^2/2)\}dn + \sqrt{(\alpha + 2\beta G_{LQL} d_d)\sigma_d^2 + \beta^2 G_{LQL}^2 \sigma_d^4/2} dW_n \tag{14}$$

Now we proceed to perform integration on the both sides of (14) utilizing the initial condition: at $n = 0$, $E_n = 0$. Using the Ito integral's zero expectation property [10], from (14), we deduce,

$$E_{sn} = n\{\alpha d_d + \beta G_{LQL}(d_d^2 + \sigma_d^2/2)\} \tag{15}$$

Here, we have substituted E_n by E_{sn}. E_{sn} represents the average biological effect on the $n-$th day under consideration of day-to-day stochastic dose variation. Now, the extended version of the LQL model under consideration of day-to-day stochastic variation of dose can be written as,

$$S_{sn} = exp(-E_{sn}) = \exp[n\{-\alpha d_d - \beta G_{LQL}(d_d^2 + \sigma_d^2/2)\}]$$

Further, following the definition of biological effective dose (BED) [2], the expression of the average biological effective dose under day-to-day stochastic variation of dose can be written as,

$$BED_{sn} = E_{sn}/\alpha = n\{d_d + (\beta/\alpha)G_{LQL}(d_d^2 + \sigma_d^2/2)\} \tag{16}$$

Note that, when $\sigma_d = 0$, replacing d_d with d, we obtain the expression of biological effective dose under day-to-day delivery of constant dose d,

$$BED_n = n\{d + (\beta/\alpha)G_{LQL} d^2\} \tag{17}$$

In order to compare BED under consideration of day-to-day stochastic variation of dose and constant dose delivery conditions, we introduce an augmentation measure, $\Delta BED_\sigma(\%) = \{(\Delta BED_{sn} - \Delta BED_n)/\Delta BED_n\} \times 100(\%)$. Now, using (16) and (17), we obtain

$$\Delta BED_\sigma(\%) = \frac{(d_d - d) + (\beta/\alpha)G_{LQL}(d_d^2 - d^2) + (\beta/\alpha)G_{LQL}\sigma_d^2/2}{(d + (\beta/\alpha)G_{LQL} d^2)} \times 100(\%)$$

The non-zero value of $\Delta BED_\sigma(\%)$ will be due to i) the contribution of the difference in the magnitudes of the average dose delivered per fraction (d_d) and the constant planned dose per fraction (d) and also due to ii) the day-to-day stochastic variation in the delivered dose. Therefore, in order to isolate the contribution of the day-to-day stochastic variation on $\Delta BED_\sigma(\%)$, throughout this article, we will consider that the average dose delivered per fraction under stochastic condition is equal to the planned constant dose per fraction ($d_d = d$). Note that the total delivered doses, during the fractionated therapy under the stochastic and the constant dose delivery conditions are also equal. Now, we use the condition, ($d_d = d$) in the above mentioned expression of $\Delta BED_\sigma(\%)$ and subsequently obtain the following expression,

$$\Delta BED_\sigma(\%) = \frac{G_{LQL}\sigma_d^2}{2\{(\alpha/\beta)d + G_{LQL}d^2\}} \times 100(\%) \tag{18}$$

When $\sigma_d > 0$, from (18) we observe, $\Delta BED_\sigma(\%) > 0$. Hence, when the day-to-day delivered dose varies stochastically, the positive value of $\Delta BED_\sigma(\%)$ will imply the under-estimation of biological effective dose under the approximation of constant dose delivery per fraction, even if the average dose delivered per fraction is same as the planned dose per fraction. It may be mentioned that at $\delta = 0$, the expression of G_{LQL} reduces to the expression of the Lea-Catcheside time factor, $G_{LQ} = (2/\mu t)[1 - \{1 - exp(-\mu t)\}/\mu t]$ and the dose-response relationship in (1) transforms to the standard LQ model [5]. Similarly, the mathematical expressions of the effect of stochastic day-to-day dose variation under LQ model can be obtained from the corresponding LQL model based formulations by replacing G_{LQL} with G_{LQ} or by substituting $\delta = 0$.

2.2. **Investigation of the effect of day-to-day stochastic dose variation using the Jensen's inequality.** In the preceding sub-section, we have explored the effect of day-to-day stochastic (random) dose variation using stochastic calculus. In this sub-section, we will investigate the same using the Jensen's inequality [8, 13]. Now, differentiating twice both sides of (17) with respect to d, we obtain, $\partial^2 BED_n/\partial d^2 = 2n(\beta/\alpha)G_{LQL} > 0$. This implies that BED_n (17) is a convex function of d. Let us consider that $f(x)$ is a real convex function of the random variable x (x_i, $i = 1, 2, .. n$). As per the Jensen's inequality for the strictly convex function [8, 13],

$$f(\sum x_i/n) < \{\sum f(x_i)\}/n$$

Similarly, in the context of biologically effective dose under consideration of day-to-day random variable doses d_i ($i = 1, 2, .. n$), we write

$$BED_n(\sum d_i/n) < \{\sum BED_n(d_i)\}/n$$

When the average delivered dose per fraction under consideration of day-to-day dose variation is equal to the planned constant dose per fraction (i.e. $\sum d_i/n = d$), we re-write the inequality as $BED_n(d) < \{\sum BED_n(d_i)\}/n$. Now, the term on the left hand side of the inequality corresponds to the BED under the consideration of daily constant dose d. On the other hand, the term on the right hand side of the inequality represents the average BED under consideration of day-to-day random dose variation. Therefore, even if the average delivered dose per fraction under stochastic condition is equal to the planned constant dose per fraction, the value of biological effective dose under consideration of day-to-day dose variation is higher than that under the approximation of daily delivery of constant dose. Therefore,

constant dose delivery approximation under-estimates BED. Note that we deduced the same inference using SDE based approach in the previous sub-section.

2.3. **Dose adaptation in fractionated radiation therapy.** Previously, we mentioned a fractionated radiation therapy which continues for n successive days with daily planned constant radiation dose d. However, the delivered dose per day was different from the planned dose during the initial n_b ($n_b < n$) days of the fractionated protocol. Let us consider that the daily average dose was d and σ_d represents the corresponding standard deviation of the day-to-day stochastic dose variation during those initial days. Under the premise of the LQL model, we are interested to find out the amount of daily dose (d_r^{LQL}) that is required to deliver for the remaining $n - n_b$ days in order to produce the same biological effective dose as was originally planned. Now, using the iso-BED criteria for the considered dose adaptation scheme, from (16) and (17), we write,

$$BED_n(n,d) = BED_{sn}(n_b,d,\sigma_d) + BED_n(n-n_b,d_r^{LQL})$$

$$\text{i.e. } n\{d+(\beta/\alpha)G_{LQL}d^2\} = n_b\{d+(\beta/\alpha)G_{LQL}(d^2+\sigma_d^2/2)\} + (n-n_b)\{d_r^{LQL}+(\beta/\alpha)G_{LQL}(d_r^{LQL})^2\}$$

Subsequently we obtain,

$$d_r^{LQL} = -\frac{\alpha/\beta}{2G_{LQL}} + \frac{\alpha/\beta}{2G_{LQL}}\sqrt{1-\frac{4G_{LQL}}{(\alpha/\beta)}\left\{\frac{n_bG_{LQL}\sigma_d^2}{2(n-n_b)(\alpha/\beta)} - \left(d+\frac{G_{LQL}d^2}{(\alpha/\beta)}\right)\right\}} \tag{19}$$

Now we compute,

$$\Delta d(\%) = \{(d-d_r^{LQL})/d\}\times 100(\%) \tag{20}$$

where, $\Delta d(\%)$ denotes the percentage difference of the required dose per fraction from the planned constant dose per fraction during the remaining days of the therapeutic protocol in order to produce the same biological effective dose as was originally planned. Similarly, using iso-BED criteria under the context of the LQ model, the expression of d_r^{LQ} can be obtained after replacing G_{LQL} by G_{LQ} in (19). Now we compare the daily doses required to deliver for the remaining $n - n_b$ days in order to produce the same biological effective dose as was originally planned under the LQL and the LQ models using the following expression:

$$\Delta d_{LQL-LQ}(\%) = \{(d_r^{LQL}-d_r^{LQ})/d_r^{LQ}\}\times 100(\%) \tag{21}$$

Positive value of $\Delta d_{LQL-LQ}(\%)$ will imply the under-estimation of required daily dose under the premise of the LQ model than that under the premise of LQL model.

3. Results.

3.1. **Effect of day-to-day stochastic dose variation on the biological effective dose.** In order to compute $\Delta BED_\sigma(\%)$ (18), we have considered a fractionated radiation therapy protocol with $n = 35$ days, $d = 2$ Gy, dose-rate = 1.0 Gy/minute [12]. We have considered the following ranges of variations of the radiobiological parameters: α/β (0.4-16 /Gy) [9], μ (0.003-0.14 /minute) [9], δ (0.053-0.452 /Gy) [5]. However, we will vary the value of the parameter δ from 0 to 0.452/ Gy, as $\delta = 0$ represents the situation concerned with the LQ model. We have varied the level of dose variation (σ_d) up to 30% [4]. The positive values of $\Delta BED_\sigma(\%)$ implies the under-estimation of biological effective dose under constant dose delivery approximation in fractionated radiation therapy (Fig 1 (a-c)). When the day-to-day delivered dose varies stochastically, the magnitude of under-estimation of biological

effective dose ($\Delta BED_\sigma(\%)$) increases as the daily variation of radiation dose (σ_d) increases (Fig 1 (a-c)). The under-estimation effect is higher in the tissues with lower values of α/β ratio (Fig 1a). However, there was no substantial change in the magnitude of this under-estimation effect as the repair rate (μ) increases (Fig 1b). We have previously mentioned that at $\delta = 0$, the LQL model reduces to the LQ model. The positive value of the δ parameter implies the departure from the premise of the LQ model. As the magnitude of the δ parameter increases from 0, the above mentioned under-estimation effect decreases (Fig 1c). The magnitude of under-estimation of the biological effective dose is the most sensitive to the change in the magnitude of the α/β ratio of the tissue and the least sensitive to the change in the value of the tissue's repair-rate parameter (Fig 1d).

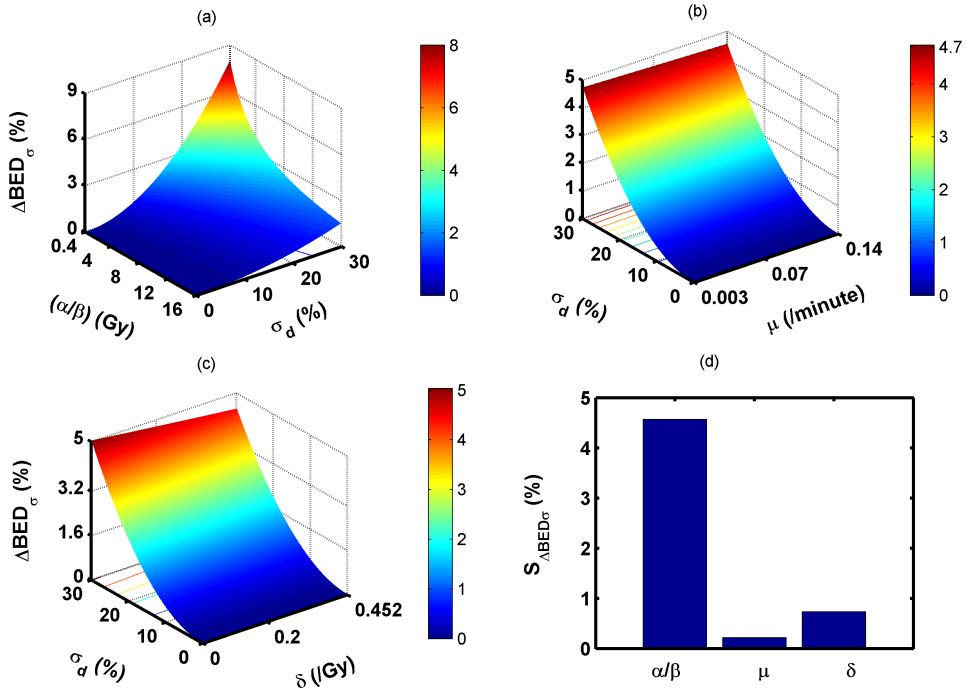

FIGURE 1. The 3D surface plots of $\Delta BED_\sigma(\%)$ (18) as the function of the magnitude of day-to-day stochastic variation of delivered dose (σ_d) and the magnitudes of the radiobiological parameters α/β ratio, μ and δ are displayed in (a), (b) and (c) respectively. The colorbars display the values of $\Delta BED_\sigma(\%)$. The percentage decreases in the magnitude of ΔBED_σ at $\sigma_d = 10\%$ due to the 10% increase in the value of the α/β ratio, μ and δ from their respective fixed values (α/β= 3.0 Gy, μ =0.07 /minute, δ= 0.253 /Gy) has been shown in (d). Here, $S_{\Delta BED_\sigma}(\%)$ denotes the corresponding percentage decrease in the value of ΔBED_σ.

3.2. **Effect of dose fraction size on $\Delta BED_\sigma(\%)$.** In this sub-section, we have compared the magnitudes of the term $\Delta BED_\sigma(\%)$ (18) between the radiation therapy protocols with total durations of $n = 2$ to 35 successive days. We have considered the following values of the radiobiological parameters: $\alpha/\beta = 3.0$ Gy, $\mu = 0.07$ /minute, $\delta = 0.253$ /Gy. Total dose delivered through each fractionated protocol was the same (70 Gy) and dose-rate was 1.0 Gy/minute. When the value of n is small, the dose delivered per fraction (i.e. fraction size) is high (e.g., $n = 2$ involves the delivery of 35 Gy per fraction). Such high magnitude of dose delivery per fraction has been considered only in the spirit of generality. The magnitude of the under-estimation of biological effective dose under constant dose delivery approximation ($\Delta BED_\sigma(\%)$) (18) increases as the total radiation dose in the fractionated radiation therapy is delivered within shorter total duration of the fractionated protocol (Fig 2). In other words, the aforesaid under-estimation effect is more prominent when the fraction size is larger. We have also observed that the magnitude of concerned under-estimation enhances as the magnitude of the day-to-day variation of the delivered dose (σ_d) increases in all the fractionated protocols with the durations of 2 to 35 days (Fig 2).

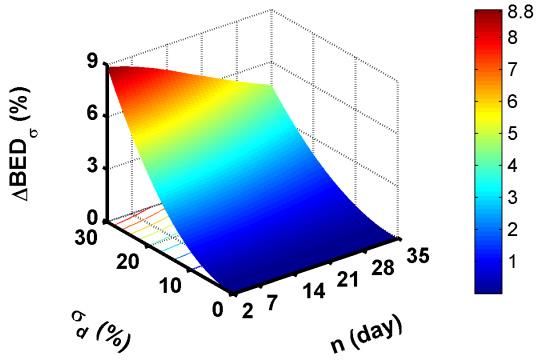

FIGURE 2. The 3D surface plot of $\Delta BED_\sigma(\%)$ (18) as the function of the magnitude of day-to-day stochastic variation of delivered dose (σ_d) and the total duration of the fractionated radiation therapy (n) has been shown in this figure. The colorbar displays the values of $\Delta BED_\sigma(\%)$.

3.3. **Application for dose adaptation.** Now we proceed to compute $\Delta d(\%)$ (20), which denotes the percentage difference of the required dose per fraction from the planned constant dose per fraction during the remaining days of the therapeutic protocol in order to produce the same biological effective dose as was originally planned. We have computed $\Delta d(\%)$ (20), considering $\alpha/\beta = 3.0$ Gy, $\mu = 0.07$ /minute, $\delta = 0.253$/Gy, $d = 2$ Gy, $n = 35$ days, dose-rate = 1.0 Gy/minute. In the considered dose adaptation scheme, smaller value of n_b implies that the dose adaptation has been started earlier in the fractionated therapeutic protocol. When dose adaptation starts late in the fractionated protocol, the magnitude of $\Delta d(\%)$ increases (Fig 3a). The level of $\Delta d(\%)$ also increases with the increase in the level of σ_d (Fig 3a-d) and with the decreases in the magnitudes of α/β (Fig 3b). We have observed no appreciable change in the level of $\Delta d(\%)$ with the increase in the

magnitude of repair rate (Fig 3c). Further, the magnitude of $\Delta d(\%)$ decreases as the value of δ parameter increases from 0 (Fig 3d).

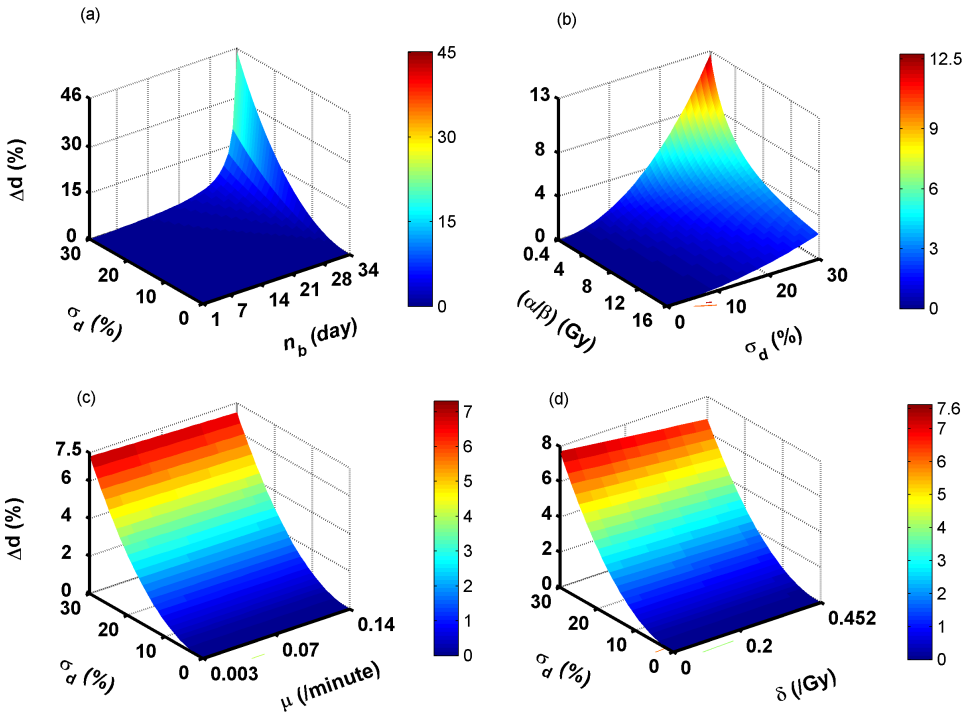

FIGURE 3. The 3D surface plot of $\Delta d(\%)$ (20) as the function of the magnitude of day-to-day stochastic variation of delivered dose (σ_d) and n_b has been displayed in (a). Figure 3 b-d illustrate the 3D surface plots of $\Delta d(\%)$ as the function of σ_d and the radiobiological parameters. The colorbars display the values of $\Delta d(\%)$.

We have also computed $\Delta d_{LQL-LQ}(\%)$ (21) using $\delta = 0$ - 0.452 /Gy, $\sigma_d = 25\%$ and also using the magnitudes of the other parameters mentioned earlier in this sub-section. Corresponding 3D plot of $\Delta d_{LQL-LQ}(\%)$ as a function of δ and n_b has been shown in Fig 4a. Further, we have also computed $\Delta d_{LQL-LQ}(\%)$ using $\delta = 0.252$ /Gy and the magnitudes of other parameters as mentioned earlier in this sub-section. Corresponding 3D plot of $\Delta d_{LQL-LQ}(\%)$ as a function of σ_d and n_b has been displayed in Fig 4b. Let us recapitulate that the positive magnitude of $\Delta d_{LQL-LQ}(\%)$ entails the under-estimation of required daily dose under the context of LQ model than that under the framework of LQL model. We observe that the LQ model under-estimates the required daily dose compared to that under the LQL model (Fig 4a-b). This under-estimation effect increases when the magnitude of the radiobiological parameter δ increases and the dose adaptation scheme starts late in the fractionated radiation therapy (Fig 4 a, b). Fig 4b shows that the aforesaid under-estimation effect ($\Delta d_{LQL-LQ}(\%)$) also becomes prominent when the magnitude of dose variation (σ_d) increases (Fig 4b).

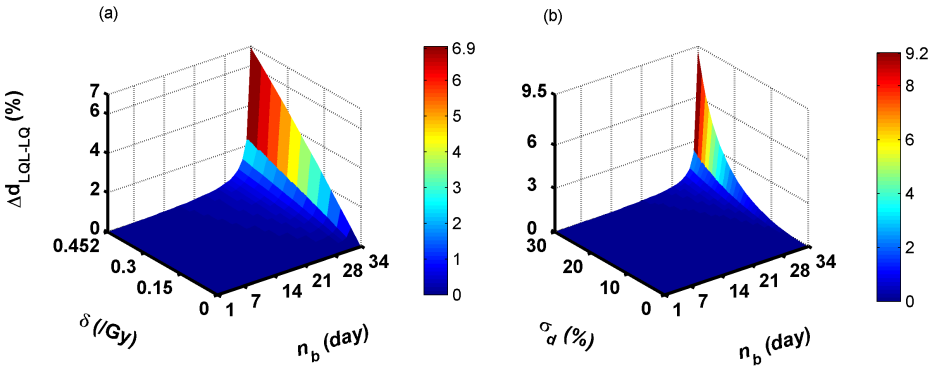

FIGURE 4. The 3D surface plot of $\Delta d_{LQL-LQ}(\%)$ (21) as the function of the magnitudes of n_b and δ parameter has been displayed in a. Figure 4b shows the 3D surface plot of $\Delta d_{LQL-LQ}(\%)$ as the function of the magnitudes of n_b and σ_d parameter. The colorbars display the values of $\Delta d_{LQL-LQ}(\%)$.

4. **Discussion and conclusions.** In this article, we have developed the analytical formulation to represent the effect of day-to-day stochastic dose deviation from the planned dose in the context of fractionated radiation therapy. We have developed the formulation using the framework of stochastic differential equation which provides an essential scaffold to explore the effect of random variation of the parameters on the response of a system.

On the other hand, the mathematical formulation of Jensen's inequality also furnishes a valuable quantitative framework to probe the effect of variation in the parameters on the response of a system [14]. It is well known that many biological functions display non-linear signatures. In the biological context, the conceptual formulation of Jensen's inequality has important implication when the system portrays non-linear parametric response [14]. We have shown in this article that our aforesaid outcome of day-to-day stochastic dose variation on biological effective dose as obtained using stochastic calculus can also be corroborated using the Jensen's inequality for the convex function.

When the day-to-day delivered dose undergoes stochastic deviation from the planned constant dose, the constant dose delivery approximation under-estimates the biological effective dose. The magnitude of this under-estimation is more prominent in the tissues characterized with high α/β ratio, low value of radio-biological parameter δ. Also, the level of afore-mentioned under-estimation is higher in the therapeutic protocols where total dose has been delivered within smaller duration and dose deviation level is high. The analytical formulation was formulated under the premise of the LQL framework instead of the LQ framework, because the LQ framework often fails to sufficiently illustrate the dose-response relationship in the high dose delivery situation [5]. In this circumstance, when the day-to-day delivered dose varies stochastically, our model elucidates that the LQ framework based analytical formulation under-estimates the required dose per fraction in the considered dose adaptation procedure, compared to that under the premise of the LQL framework. Our analysis also shows that this under-estimation effect is more prominent when dose adaptation scheme starts late in the fractionated radiation

therapy. Moreover, the magnitude of this under-estimation effect is reliant upon the value of day-to-day stochastic dose variation level and the value of the radiobiological parameter δ. Note that when $\delta = 0$, the LQL framework based analytical formulation developed in this study also renders applicability in the context of the LQ framework. Additionally, when $\sigma_d = 0$, our formulation transforms to the standard analytical representation of dose-response relationship concerned with the fixed magnitude of dose delivery per fraction.

The mathematical framework for calculation of required dose per fraction under the context of the considered dose adaptation scheme as presented in this article requires the information regarding the average dose delivered per fraction and the standard deviation of the doses delivered over different fractions. These parameters can be estimated utilizing the previously delineated methodology [1]. In this article, we have provided analytical framework for calculation of required dose per fraction in the context of adaptive radiation dose delivery considering day-to-day stochastic deviation of radiation dose and also indicated the possible utility of the LQL framework for the same.

Acknowledgments. The work of SP and PKR were supported by Govt. of India's Dept. of Biotechnology (DBT, Glue Grant scheme), Defense Research & Development Organization, and Dept. of Electronics & Information Technology (Spatiotemporal dynamics project). Support for the logistics of the work of PKR is from Tata Innovation Program, DBT, and Office of Principal Science Adviser, National Knowledge Network, Govt. of India.

REFERENCES

[1] E. Budiarto, M. Keijzer, P. R. M. Storchi, A. W. Heemink, S. Breedveld and B. J. M. Heijmen, Computation of mean and variance of the radiotherapy dose for PCA-modeled random shape and position variations of the target, *Phys. Med. Biol.*, **59** (2014), 289–310.

[2] J. F. Fowler, The linear-quadratic formula and progress in fractionated radiotherapy, *Br. J. Radiol.,* **62** (1989), 679–694.

[3] L. Gammaitoni, P. Hänggi, P. Jung and F. Marchesoni, Stochastic Resonance: A remarkable idea that changed our perception of noise, *Eur. Phys. J. B,* **69** (2009), 1–3.

[4] A. Godley, E. Ahunbay, C. Peng and X. A. Li, Accumulating daily-varied dose distributions of prostate radiation therapy with soft-tissue–based kV CT guidance, *J. Appl. Clin. Med. Phys.,* **13** (2012), 1–3.

[5] M. Guerrero and M. Carlone, Mechanistic formulation of a lineal-quadratic-linear (LQL) model: Split-dose experiments and exponentially decaying sources, *Med. Phys.*, **37** (2010), 4173–4181.

[6] W. Horsthemke and R. Lefever, *Noise-Induced Transitions in Physics, Chemistry, and Biology*, 2^{nd} edition, Springer, Berlin, 2006.

[7] B. Huang, W. Wang, M. Bates and X. Zhuang, Three-dimensional super-resolution imaging by stochastic optical reconstruction microscopy, *Science*, **319** (2008), 810–813.

[8] J. L. W. V. Jensen, Sur les fonctions convexes et les inégalités entre les valeurs moyennes, *Acta Math.,* **30** (1906), 175–193.

[9] M. C. Joiner and A. Kogel, *Basic Clinical Radiobiology*, 4^{th} edition, CRC Press, Boca Raton, 2009.

[10] P. E. Kloeden and E. Platen, *Numerical Solution of Stochastic Differential Equations*, 1^{st} edition, Springer, London, 1992.

[11] D. E. Lea, *Actions of Radiations on Living Cells*, 2^{nd} edition, Cambridge University Press, New York, 1962.

[12] G. Murphy, W. Lawrence and R. Lenard, *ACS Textbook of Clinical Oncology*, 2^{nd} edition, The American Cancer Society, Inc., Atlanta, 1995.

[13] T. Needham, A visual explanation of Jensen's inequality, *Amer. Math. Monthly*, **100** (1993), 768–771.

[14] J. J. Ruel and M. P. Ayres, Jensen's inequality predicts effects of environmental variation, *Trends Ecol. Evol.,* **14** (1999), 361–366.
[15] F. C. Su, C. Shi, P. Mavroidis, P. R. Szegedi and N. Papanikolaou, Evaluation on lung cancer patients' adaptive planning of TomoTherapy utilising radiobiological measures and planned adaptive module, *J. Radiother. Pract.,* **8** (2009), 185–194.
[16] E. Ullner, J. Buceta, A. Díez-Noguera and J. García-Ojalvo, Noise-induced coherence in multicellular circadian clocks, *Biophys. J.*, **96** (2009), 3573–3581.
[17] D. Yan, F. Vicini, J. Wong and A. Martinez, Adaptive radiation therapy, *Phys. Med. Biol.*, **42** (1997), 123–132.
[18] E. C. Zimmermann and J. Ross, Light induced bistability in $S_20_6F_2 \rightleftharpoons 2S0_3F$: Theory and experiment, *J. Chem. Phys.*, **80** (1984), 720–729.

Received March 16, 2015; Accepted June 12, 2015.

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