Yu model

Victoria Yu's model is as follows:

$$\frac{\mathrm{d}\hat{U}}{\mathrm{d}t} = (2p-1)k(\hat{W})r_1\hat{U}$$
$$\frac{\mathrm{d}\hat{V}}{\mathrm{d}t} = 2(1-p)k(\hat{W})r_1\hat{U} + (r_2k(W)-d)\hat{V},$$

where $\hat{W} = \hat{U} + \hat{V}$, $k(\hat{W}) = 1 - \hat{W}^4$, and $\hat{U}$ and $\hat{V}$ are volume fractions of the tumor volume LQ model:

$$\hat{U}_s = \hat{U} \cdot e^{-\alpha_{\hat{\mathrm{U}}}d_i - \beta_{\hat{\mathrm{U}}}{d_i}^2} + c \cdot d_i \cdot \hat{V}$$
$$\hat{V}_s = \hat{V} \cdot e^{-\alpha_{\hat{\mathrm{V}}}d_i - \beta_{\hat{\mathrm{V}}}{d_i}^2} - c \cdot d_i \cdot \hat{V}$$

Kim model

Nayeon Kim's model is as follows:

$$\frac{\mathrm{d}U}{\mathrm{d}t} = (2p-1) \cdot r_1 \cdot U$$
$$\frac{\mathrm{d}V}{\mathrm{d}t} = 2\,(1-p) \cdot r_1 \cdot U + (r_2 - d)V,$$

where $U = \left(\frac{1}{\rho}N\right)\hat{U}$, $V = \left(\frac{1}{\rho}N\right)\hat{V}$, $p \leftarrow \frac{\bar{p}}{1+lV^n}, r_1 \leftarrow \frac{\bar{r_1}}{1+hV^z}, r_2 \leftarrow \frac{\bar{r_2}}{1+hV^z}$ This rescaling allows us to translate results between models, which only differ in how rate parameters are controlled. In Yu's model, a logistic type of growth controls the division rates. Meanwhile, Kim's model uses negative feedback from differentiated cells on division rate and on probability of proliferation, and we assume the same feedback takes place on both division rates.

The LQ model followed exactly from that of Yu up to that factor of conversion between volume and cell number:

$$U_s = U \cdot e^{-\alpha_{\mathrm{U}}d_i - \beta_{\mathrm{U}}{d_i}^2} + c \cdot d_i \cdot V$$
$$V_s = V \cdot e^{-\alpha_{\mathrm{V}}d_i - \beta_{\mathrm{V}}{d_i}^2} - c \cdot d_i \cdot V$$

Moving to a new model

- In order to study the effect of survivin and chemotherapy on tumor survival after therapeutic interventions take place, we have apoptosis of differentiated cells be subject to negative feedback from itself as a proxy for survivin in the interim.

- An additional extension to Kim's model is that survivin has a rate equation and that the reprogramming term of the LQ model is restricted to having a maximum value of 1, as we should not allow the model to get more differentiated cells than is physically possible.
- A further modification is to have only differentiated cells which survive radiotherapy to reprogram.
- Extracellular survivin amounts produced from the cell are not negligible during normal tumor growth; in fact, survivin is constitutively secreted in normal and cancer cells. However, for now we ignore it to study the effects of radiotherapy on survivin alone. We expect results to indicate less pronounced recurrence of tumor.
- Effects of survivin on apoptosis will be only temporarily ignored, as we want to study the effects of survivin on radiotherapy alone. We expect results to possess a further reduced rate of growth in the tumor. Specifically, there will be fewer stem cells and fewer differentiated cells than expected. Either by measurement or by literature search can parameters relevant to this limitation or the one before be used to relax them.

Survivin model 1

Tumor Growth

$$\begin{aligned}\frac{\mathrm{d}U}{\mathrm{d}t} &= (2p-1)\cdot r_1 \cdot U \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= 2\,(1-p)\cdot r_1 \cdot U + (r_2 - d)V \\ \frac{\mathrm{d}S}{\mathrm{d}t} &= -\sigma S,\end{aligned}$$

$$p \leftarrow \frac{\bar{p}}{1+l\,V^n}, r_! \leftarrow \frac{\bar{r_1}}{1+h\,V^z}, r_2 \leftarrow \frac{\bar{r_2}}{1+h\,V^z}, d \leftarrow \frac{\bar{d}}{1+h\,V^z}$$

Radiotherapy

$$\begin{aligned}U_s &= U\cdot e^{-\alpha_{\mathrm{U}} d_i - \beta_{\mathrm{U}} {d_i}^2} + \min(1, c\cdot d_i)\cdot V \cdot e^{-\alpha_{\mathrm{V}} {d_i}^2 - \beta_{\mathrm{V}} {d_i}^2} \\ V_s &= (V - \min(1, c\cdot d_i)\cdot V)\cdot e^{-\alpha_{\mathrm{V}} d_i - \beta_{\mathrm{V}} {d_i}^2} \\ S_s &= S + \zeta_U U_{\text{killed}} + \zeta_V V_{\text{killed}},\end{aligned}$$

where

$$\alpha_U \leftarrow \frac{\bar{\alpha}_U}{1+\gamma_{\alpha_U} S}, \beta_U \leftarrow \frac{\bar{\beta}_U}{1+\gamma_{\beta_U} S}, U_{\text{killed}} = U\cdot e^{-\alpha_{\mathrm{U}} d_i - \beta_{\mathrm{U}} {d_i}^2}, V_{\text{killed}} = \min(1, c\cdot d_i)\cdot V\cdot e^{-\alpha_{\mathrm{V}} d_i - \beta_{\mathrm{V}} {d_i}^2}$$

and similarly defined for α_{V} and β_{V}.

Use of prior results for survivin

We suspect that, if we take survivin to be a fraction of sorts, then the alphas and betas gleaned from Yu's thesis can be used as our baseline $\bar{\alpha}$ and $\bar{\beta}$:

$$\alpha_U \leftarrow \frac{\bar{\alpha}_U}{1+\gamma_{\alpha_U}(S-S_d)}$$
$$\beta_U \leftarrow \frac{\bar{\beta}_U}{1+\gamma_{\beta_U}(S-S_d)},$$

which takes into account a level of baseline survivin (S_d) which comes from a single round of therapy. This baseline survivin amount will be smaller than what S can be, as values of S_d are based on only one round of radiotherapy as opposed to the multiple rounds of radiotherapy which tend to occur; i.e.

$$S_d = \zeta_S \frac{U_{\text{killed}}}{N^*}$$

This has the effect of putting N^* In order to see the effect of the control parameter on radiotherapy dynamics, we note that the relative values of α and β in each compartment are known to influence the outcome of radiotherapy. With that in mind, we consider an asymptotic argument to show how we will vary parameters:

$$\lim_{S\to\infty}\frac{\alpha_U}{\beta_U} = \frac{\bar{\alpha}_U}{\bar{\beta}_U}\frac{\gamma_{\beta_U}}{\gamma_{\alpha_U}}, \lim_{S\to\infty}\frac{\alpha_U}{\beta_U} = \frac{\bar{\alpha}_U}{\bar{\beta}_U}\frac{\gamma_{\beta_U}}{\gamma_{\alpha_U}} = \frac{\bar{\alpha}_U}{\bar{\beta}_U}\frac{\zeta_U\gamma_{\beta_V}}{\gamma_{\alpha_V}}$$

We thus need only control the three parameters γ_{α_V}, γ_{β_V}, and ζ_U. Since we know that stem cells are very hardy under radiation under normal circumstances, $\zeta_U > 1$. It is unknown exactly how survivin can alter the balances of α and β.

Numerical simulations

Adding de-differentiation terms

Numerical simulations indicate a need to add this. It may cause a convex shape on the dose curve, as we'd expect, but we don't know.

Hence we will add a de-differentiation term in the form of

$$\mu(s) = \frac{\bar{\mu}s}{\frac{1}{\chi}+s},$$

where $\bar{\mu}$ is the maximum rate of de=differentiation and χ is the positive feedback term. The

equations now have the form:

$$\begin{aligned}\frac{\mathrm{d}U}{\mathrm{d}t} &= (2p-1)\cdot r_1 \cdot U + \mu(s)\\ \frac{\mathrm{d}V}{\mathrm{d}t} &= 2\,(1-p)\cdot r_1 \cdot U + (r_2 - d)V - \mu(s)\\ \frac{\mathrm{d}S}{\mathrm{d}t} &= -\sigma S,\end{aligned}$$

$$p \leftarrow \frac{\bar{p}}{1+l\,V^n}, r_! \leftarrow \frac{\bar{r_1}}{1+h\,V^z}, r_2 \leftarrow \frac{\bar{r_2}}{1+h\,V^z}, d \leftarrow \frac{\bar{d}}{1+h\,V^z}, \mu(s) \leftarrow \frac{\bar{\mu} s}{\frac{1}{\chi}+s}$$