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Mathematically Modeling Glioblastoma and Radiotherapy: Signaling and Differentiation
THESIS

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for the degree of

MASTERS OF SCIENCE
in Mathematical, Computational, and Systems Biology

by

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DEDICATION

I dedicate this to GC.

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ABSTRACT OF THE THESIS

Mathematically Modeling Glioblastoma and Radiotherapy: Signaling and Differentiation

By

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Glioblastoma is the most lethal and prevalent form of cancer to the central nervous system. Median life expectancy for patients is five years, and in that time the tumor evolves rapidly while modifying its microenvironment in the process. When targeted with radiotherapy it increases its fraction of cancer stem cell population, thereby increasing its resistance to radiation. Recent evidence suggests that the underlying process of de-differentiation, whereby more differentiated cells return to a stem-like state, also drives recurrence. By modeling proliferation, differentiation, de-differentiation and the response to radiotherapy, this model identifies the types of feedback consistent with an increase in CSC fraction and tumor size after radiotherapy, as well as a potential radiotherapy schedule by which treatment can improve upon conventional radiotherapy scheduling. The mechanisms identified are the application of treatment, the process of de-differentiation, and the existence of negative feedback on differentiated cell division rates or positive feedback on differentiated cell death is consistent with these outcomes.

Chapter 1

Introduction

1.1 Cancer Overview

Glioblastoma is the most lethal form of cancer of the central nervous system, with a median survival time of 12-14 months. After treatment, tumors tend to relapse, become more resistant, and progress to diffusive invasion due to treatment [1, 4, 2, 3]. A critical aspect of this process is the enrichment of stem-like cancer cells [5]. After treatment, CSC cells are known to increase in proportion [6]. There are a number of plausible mechanisms such as the promotion of hypoxia [7], changes in gene expression and gene repair [10, 7, 9, 8], increases in de-differentiation [11], and even changes in metabolism [12]. However, the contributions of each of these mechanisms combined have yet to be fully investigated for GBM.

De-differentiation is the process of differentiated cells gaining pluripotency and becoming stem-like. Treatment regimens like radiotherapy and chemotherapy can stimulate it in patients. This generally results in the tumor gaining resistance due to the increased amount of treatment-resistant stem cells. [11, 7] To illustrate how de-differentiation increases survivability of tumors, we will take survivin as an example. Survivin is an inhibitor of apoptosis

protein whose major functions include inhibiting cell death [13], promoting its own export via exosome surfaces under stress [14, 13], and promoting expression of genes associated with stemness. [13] Dahan et al 2014 has shown it does play a role in glioma tumor resistance – as exposure to radiation goes up, the fraction of stem cell goes up due to survivin. And as previously noted by Wang et al 2017, HIF-1 α contributes to dedifferentiation.

Tumors, especially glioblastoma, experiences positive and negative feedback on proliferation, invasion, and other processes TGF-beta pathway suppression results in inhibited growth of cancer stem cells (CSCs), indicating the existence of pathways that control GBM growth [15]. Major forms of negative feedback include miRNA upregulation that controls migration/proliferation in normal cells and may pose a potential pharmaceutical target [16]. Additionally, the PI3K/AKT pathway, which is constitutively expressed in many tumors and regulates the cell cycle and proliferation, is subject to negative feedback via S6K and IRS1 [17]. Manipulating musashi protein indicated the existence of a positive feedback loop that influences invasion, migration, and proliferation. [18] Survivin affects mitosis, stemness, and death. Expression of HIF-1alpha means upregulation of cell proliferation, dedifferentiation, and resistance to treatment. [8]. Studies like these indicate how feedback is an intrinsic part of the growth of glioblastoma and the process of de-differentiation, but the exact relationship remains unclear.

So far, resolving how tumor relapse occurs long after treatment has remained unclear. There have been many clinical studies that characterize cancers like glioblastoma as adapting to treatment, there is still a demand for treatments to improve and prolong the lives of patients [19, 20, 21]. To meet this goal, mathematical models can be used to test different hypotheses regarding tumor growth for long periods of time when it may not be feasible to do so experimentally. Though there has been some progress in understanding the role of CSCs, growth control, and signaling, assessing how each of these processes contribute to long-term relapse is not complete. [22, 23] Evidence shows that long-term increases cancer

stem cell fraction and reduction in patient viability strongly correlate with one another [24], suggesting that treatment forces the tumor to evolve into a more radioresistant state [4, 25]. Mathematical models can help us gain insight into the mechanisms connecting treatment, relapse, and cancer stem cell growth. And given that insight, alterations to conventional treatment scheduling can be done to take long-term increases in CSC fraction into account.

1.2 Model Overview

To address these biological issues, many models have been developed to attempt to give insight into the underlying processes. They range from ODE models [27, 26] to PDE models [28] to agent-based models [29] to neural network-based models, incorporating processes related to proliferation, differentiation, and treatment as well as the proliferate/migrate characterization, otherwise known as the go and grow model [30, 32, 31], hyperthermia [33], and immunotherapy. Many models look at total tumor volume for the purposes of data fitting and simpler dynamics, but this usually requires neglecting the effect of regulation or cell-cell processing [34, 35, 36, 37]. These models focus on phenomena occurring over the span of weeks at most, sometimes due to working closely with data for parametric estimation.

Many models do not look at CSC growth in the long-term since they are more concerned with clinical application and thus restrict themselves to a more conservative time window for extrapolation [36, 30, 26], and it is difficult to directly measure CSC percentage experimentally. Other papers like [38], which focused on diffusion through white and gray matter and using brain atlases, are more concerned with fitting for insight at the time of radiotherapy rather than after radiotherapy, as with [35, 27]. However, there are some models that try to characterize stem cell populations explicitly and model their dynamics [41, 39, 42, 40]. Even among these however, those which explicitly include de-differentiation are less common. [30, 43] Similarly, not many models explicitly approach dynamics at least a half year out, which

could be due to computational constraints or because data on cell growth is difficult to gather that far into the future. [44, 45, 46] We'll highlight a few papers closely related to the work in this document.

Rhodes and Hillen [43] designed and analyzed a model that incorporated survivin and anti-survivin drugs into the dynamics. After fitting their model to experimental results produced by Iwasa et al[47], they found that even hypofractionated radiotherapy alone could not drive down CSC numbers. Only through a combination of anti-survivin chemotherapy and radiotherapy was this possible. However, there was no consideration of feedback on division or differentiation, which could change this outcome through controlling long-term CSC population levels. Furthermore, overfitting the model to the data is a concern expressed by the authors since the model has so many parameters, so the results may be too optimistic.

Wodarz and Rodriguez-Brenes et al [39] developed a model of cancer growth that incorporated feedback, wound-healing, and chemotherapy. They showed permanent long-term growth in cases with weak feedback on division by reducing its inhibition of rate of growth, though they have also shown that chemotherapy alone would result in bigger tumors, so for their model wound-healing amplified the effect of chemotherapy. The model predictions also don't necessarily concern themselves with growth after a significant relapse and are focused on an increased proportion of CSC after treatment. Additionally, it is unclear if there are any parameter regimes wherein CSC regrowth is permanently changed due to treatment and wound-healing since the simulations largely focus on the duration of treatment and do not look far after treatment.

Yu et al's work [44, 45, 46] directly precedes the work done here. To model the cancer dynamics, they used a two-state system that considered a cell lineage of CSCs and DCCs only in tandem with the linear-quadratic model of radiotherapy and de-differentiation. The general framework of growth dynamics and simplified radiotherapy dynamics allowed them to find new optimal schedules that predict prolonging the life of patients while being below

the threshold of toxicity in her 2021 paper [46]. The dynamics also showed increase in CSC fraction and tumor size after treatment. However, the dynamical equations she used did not incorporate feedback a la signaling pathways, and her description of de-differentiation is flawed due to the potential for the process to de-differentiate more DCCs than there actually are in the system, especially at higher doses. This could result in negative DCC counts and exaggerate the elevation of CSC fraction.

Sottoriva et al [41] developed an agent-based model that incorporates a PDE for the oxygen concentration, an agent-based model of stem cells and non-stem cells, and treatment of an unspecified modality. They do convincingly show that CSC fraction increase and tumor regrowth happens after treatment takes place while taking the sensitivity of stem and non-stem cells into account. A possible extension would be to specify the kind of treatment used, i.e. using the LQ model for radiotherapy, and including feedback and de-differentiation to see how it would affect the response to radiotherapy.

These models have partially addressed the effects of treatment on tumor relapse and CSC enrichment. While the models discussed above did indicate CSC fraction increases after treatment, none have attempted to characterize the lifespan of this change. The question remains if this change indicates a transient change or a long-term shift in homeostasis. And mathematical models are well-positioned to test out various hypotheses regarding tumor growth after treatment. It is particularly rare to find models that have feedback, dedifferentiation, and treatment while studying long-term relapse and CSC dynamics. The highlighted models overlook at least one of these components and focus on processes related to cancer, like angiogenesis. Thus, it remains unclear how each component contributes to relapse. The model in this paper will make attempts to clarify the contributions of signaling and differentiation to relapse and CSC growth, as well as offer potential improvements over conventional therapy.

Chapter 2

Model Overview

2.1 Cell Lineage Model

We characterize glioblastoma by considering a well-mixed system of ordinary differential equations to describe cell lineages. This is based on the work done by Lander et al (2009) [48] to describe dynamics of hierarchical tissues and extends them to allow for treatment and dedifferentiation. These models typically involve pluripotent stem cells, transient-amplifying cells, and post-mitotic differentiated cells. The stem cells act as an eternally dividing and immortal pool of progenitors which means that they do not die. Below is the general form of the two stage cell lineage model that we'll be using:

$$\begin{aligned}\frac{dU}{dt} &= (2p - 1)r_U U \\ \frac{dV}{dt} &= 2(1 - p)r_U U + (r_V - d)V\end{aligned}$$

Here, U represents the number of pluripotent stem cells and V represents the number of post-mitotic cells. In this model, instead of transient-amplifying cells replicating, the V

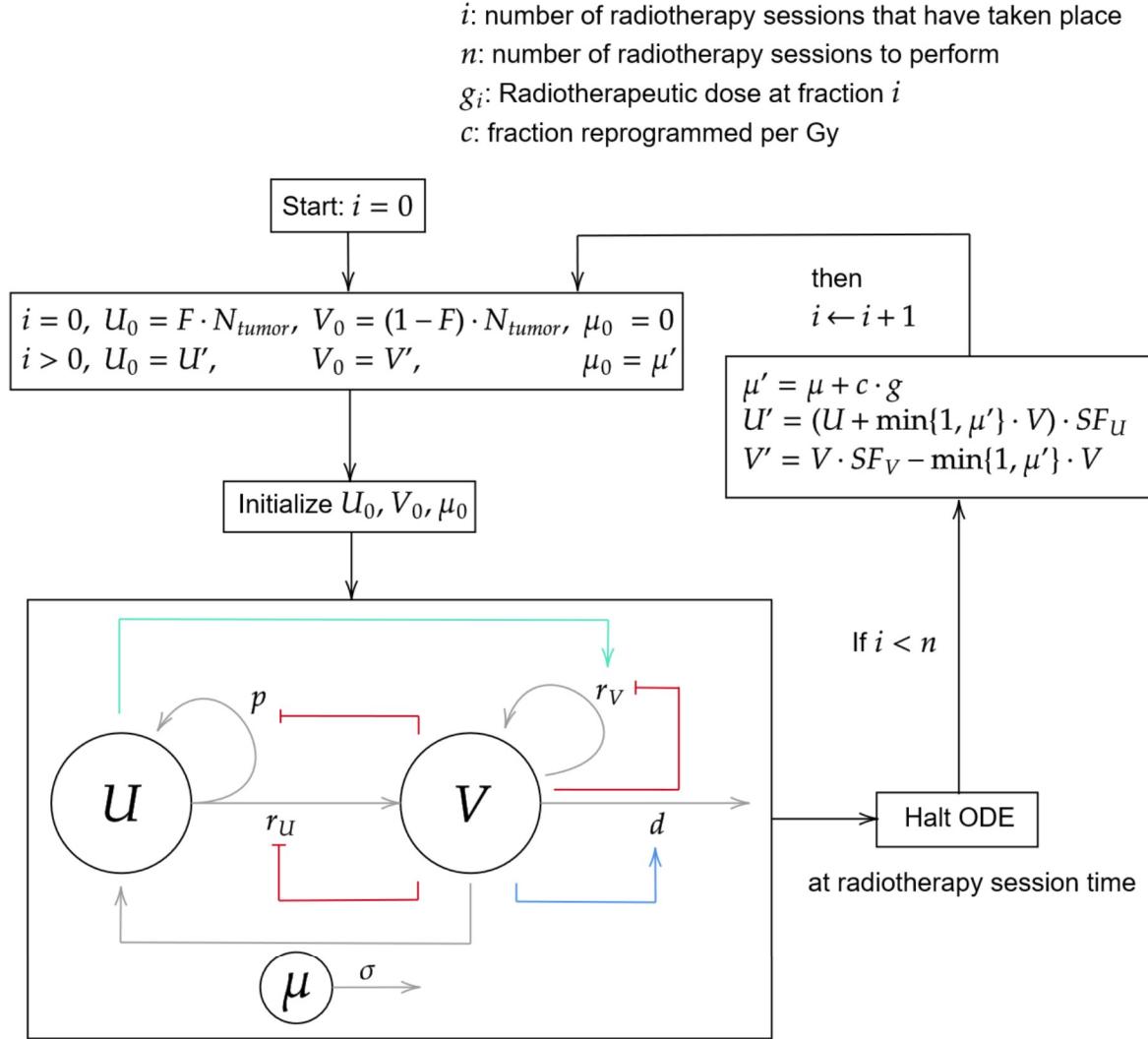


Figure 2.1: The entire simulation is a sequence of initial value problems (IVPs). The first IVP uses empirical proportions of stem cells to determine the initial conditions, which are multiplied with $N_{tumor} = \frac{0.0005}{64} \cdot \frac{4}{3}\pi \cdot 10^9$ cells. After a brief period of time, 100 days in this paper, radiotherapy takes place and the new CSC and DCC populations are determined by damage and reprogramming. Then tumor dynamics resume with the reshuffled populations as the new initial values. Then this repeats until the number of radiotherapy fractions have been reached. After the final fraction, tumor dynamics resume for an arbitrary number of days, in this case a few years' worth of days (1000 days).

population replicates. r_U and r_V are the rates of division for U and V , respectively, d is the death rate of DCC, and p is the probability of self-renewal of stem cell from existing stem cells. The exact form is modified from the one used by Bachman and Hillen 2013 and Hillen et al 2013 [50, 49]. The major difference between their equations and this one is that their model focused on volume fractions directly. This required the usage of fractional values of U and V and much model exploration did not involve fractional values, so they were dropped in favor of preventing CSC-independent growth and unrestricted growth via feedback mechanisms based on population sizes.

What form will the feedback functions take?

- The more V there is, the lower p is. Mathematically, $0 \leq p \leq 1$. In glioblastoma, there is an inverse relationship between proliferation and migration, with some suggesting that one cell type is more stem-like than the others due to the motility associated with them.[53, 51, 52] One way to interpret this mathematically is to have p decrease as V increases.
- The less U there is, the less r_v there is. Without having enough stem cells, the population would collapse. And with additional V , there is more U .
- The more V there is, the lower r_u or r_v gets and/or the higher d gets. The system is resource-limited, so the overall growth of the system will inevitably slow down, either through having more cells die off or from fewer cells divide.

The conditions can be conveniently written via Hill equations (Eqs 2.1-2.4). While there exist alternative formulations, a number of publications have commented on how varying the particular functional form does not impact the qualitative nature of the dynamics greatly.

$$p \leftarrow \frac{\bar{p}}{1 + lV} \quad (2.1)$$

$$r_U \leftarrow \frac{\bar{r}_U}{1 + h_U V} \quad (2.2)$$

$$r_V \leftarrow \frac{\bar{r}_V}{1 + h_V V} \cdot \frac{h_4 U}{1 + h_4 U} \sim \frac{\bar{r}_V}{1 + h_U V} \quad (2.3)$$

$$d \leftarrow \bar{d} + \frac{(1.1\bar{r}_V - \bar{d})h_d V}{1 + h_d V}. \quad (2.4)$$

In Figure 2.1, red lines indicate negative feedback, the teal line indicates feedforward regulation of r_V via U , and the blue line indicates positive feedback of V onto its death rate. Plausible mechanism driving feedforward regulation of U on r_V would be those related to differentiation and transient-amplifying cells. While there are a variety of ways to mathematically describe negative or positive feedback, empirical fit of growth and response curves indicate that feedback is of the Hill equation type [30, 54, 55]. Thus their utilization in 2.1-2.4.

In Equation (2.3), there is negative feedback from V onto its own rate of growth, as well as a positive feedforward circuit from U to V indicating a dependency of division of V on the level of U in the system. Equation (2.4) indicates the usage of positive feedback of V onto its own death rate due to constraints in the system, i.e. the V cells incurs growth similar to logistic growth, but the carrying capacity depends on the volume of V . Parameters l , h_U , h_V , h_d , and h_4 are feedback gains controlling self-renewal, rate of CSC division, rate of DCC division, rate of DCC death, and feedforward regulation, respectively. We explicitly model the fraction of the DCC population that will de-differentiate back into CSC and label it as μ .

The work Bachman et al 2013 and Fowler et al 2010 indicate using $\frac{\ln(2)}{T_p}$ (where T_p is the doubling time of malignant brain tumors) for determining the rate of mitosis for CSCs and

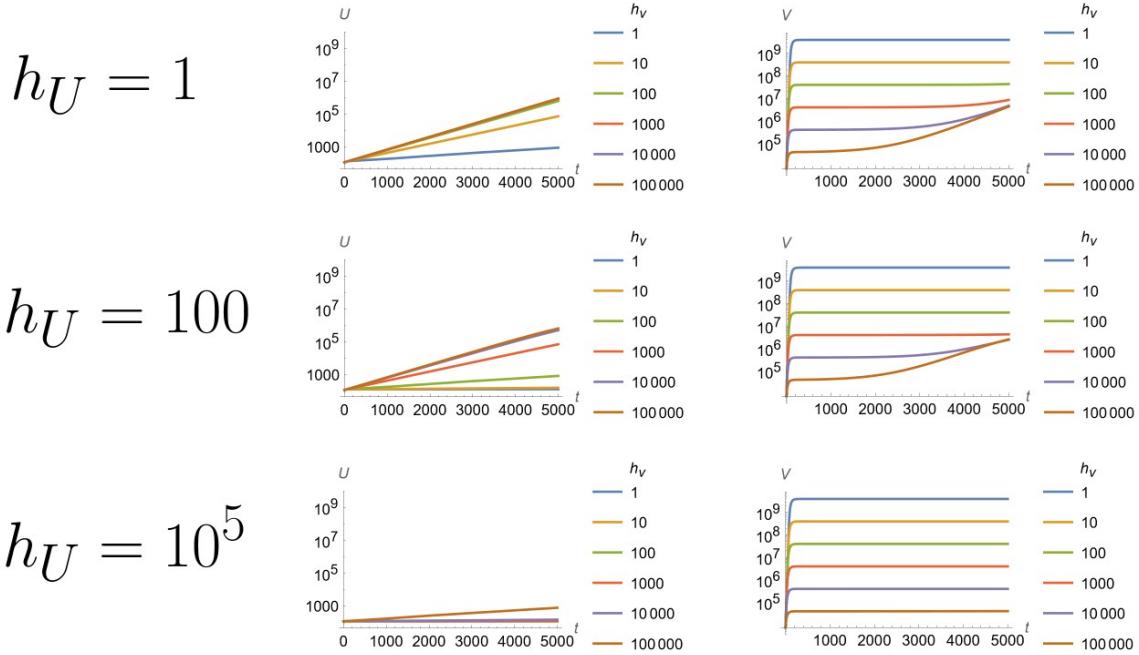


Figure 2.2: Comparing super long-term dynamics for the case when there's negative feedback on r_u and on r_v , with h_1 standing in as the feedback gain for negative feedback on r_u and h_2 standing in as the negative feedback gain on r_v .

DCCs [50, 56]. Stem cells had zero rate of apoptosis, assuming that CSCs had unlimited replicative potential. If the value of DCC death rate exceeds $\frac{\ln(2)}{T_p}$, then the model will predict no increase in CSC fraction. The value for c was found from the linear regression in Figure 2.3. Additionally, the value of \bar{p} was chosen from Yu et al's work, with the idea to make p close to .5 to not trivialize the increase of CSC fraction from a high value of p and thus make evaluating the effect of treatment more apparent. [44].

Feedback parameter values were selected for the purpose of showing the qualitative behaviour of the system. A coarse-grained parameter sweep among feedback gains was performed, with an example of such a parameter sweep shown in Figure 2.2. If we pay attention to the window of time between 0 and 2000 days, there's little difference between each of these simulations qualitatively: U increases slowly and V reaches equilibrium after awhile, despite quantitative differences. As such, feedback gain was set to 10^5 for the purposes of qualitative exploration.

Table 2.1: List of rate parameters and their values used for all simulations of dynamics.

Parameters	p	r_U	r_V	d	h_U	h_V	h_d	h_4	l	T_p
Values	0.505	$\frac{\log(2)}{3.9}$	$\frac{\log(2)}{3.9}$	$\frac{\log(2)}{5*3.9}$	10^5	10^5	$\frac{10^5}{3}$	10^9	10^5	3.9
Units	none	$\frac{\text{cell}}{\text{day}}$	$\frac{\text{cell}}{\text{day}}$	$\frac{\text{cell}}{\text{day}}$	$\frac{1}{\text{cell}}$	$\frac{1}{\text{cell}}$	$\frac{1}{\text{cell}}$	$\frac{1}{\text{cell}}$	$\frac{1}{\text{cell}}$	day
References	s.t. (see text)	[50, 56]	[50, 56]	s.t.	s.t.	s.t.	s.t.	s.t.	s.t.	[44]

2.2 Simulating Radiotherapy

$$\mu' = \mu + c \cdot g$$

$$U' = (U + \min(1, \mu') \cdot V) \cdot SF_U,$$

$$V' = (1 - \min(1, \mu')) \cdot V \cdot SF_V$$

where

$$SF_U = e^{-g(\alpha_U + \beta_U g)}$$

$$SF_V = e^{-g(\alpha_V + \beta_V g)}$$

Figure 2.1 represents a summary of how the model couples glioblastoma dynamics and treatment. After initializing the simulation with observed amounts of CDC and DCC, the tumor grows unperturbed until radiotherapy scheduling commences, when dynamical growth stops in order to change in population levels from μ to μ' , U to U' , and V to V' . μ is the fraction of DCCs that are to be reprogrammed into U . This change re-initializes the system of equations before it continues the dynamics that ceases with the next fraction of radiotherapy. This happens for n fractions of d doses, with each business day counting as a single fraction. This kind of radiotherapy scheduling is called “fractionated radiotherapy”.

Best fit in Figure 2.3 gives rise to c . With signaling factors like survivin as representatives of

Table 2.2: Radiosensitivities for GBM line U373. Fit by Victoria Yu.[45]

α	β	α_U	β_U	α_V	β_V
0.17	0.02	0.01	1.77e-7	0.125	0.028

μ , we also allow for μ to decay dynamically according to

$$\frac{d\mu}{dt} = \sigma(\bar{\mu} - \mu).$$

We set $\bar{\mu}$ to 0, assuming that survivin plays no other role in cell dynamics.

2.2.1 Radiotherapy Model

SF_U and SF_V indicates the fraction of the population that survived radiotherapy for stem cells and differentiated cells, respectively. To calculate this surviving fraction, we use the linear-quadratic model, which assumes that single-stranded and double-stranded DNA damage determine the surviving fraction (SF) of cancer cells when afflicted with a single dose of g Grays:

$$SF = e^{-\alpha g - \beta g^2} = e^{-g(\alpha + \beta g)}.$$

The α and β coefficients are cancer-specific and correspond to the radiosensitivity of the tumor to single and double-stranded DNA damage, respectively. These can be empirically measured, and for the glioblastoma cell line we're considering, we have such coefficients. Not only for the whole tumor, but also for each sub-population of cancer cell in our model [57, 45]. In other words, we can extend the model to more than one cell type, as we've previously seen in the definitions of SF_U and SF_V . The

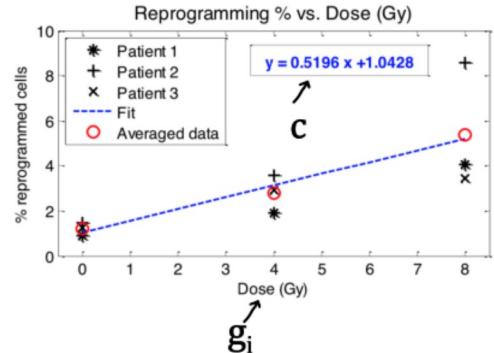
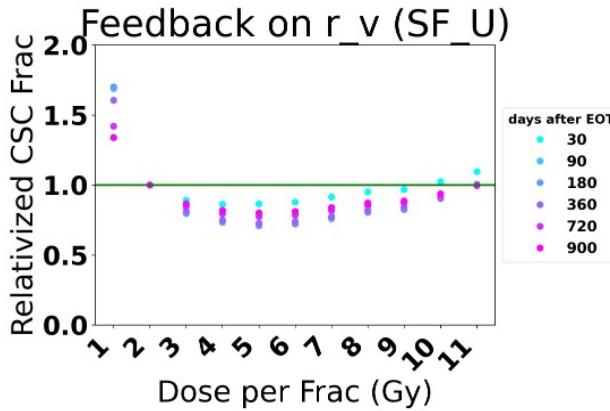
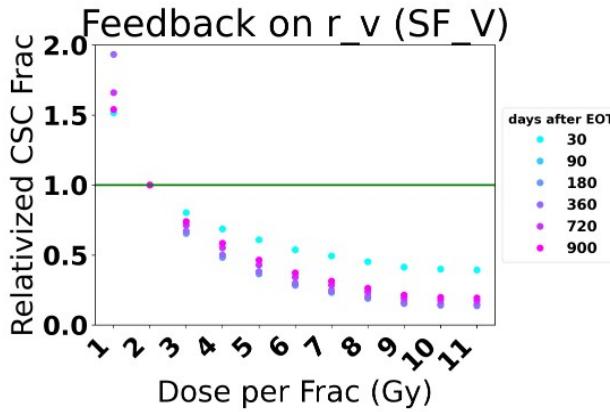


Figure 2.3: Figure describing relationship between $\mu \cdot 100\%$ and dose reproduced and modified from Victoria Yu's thesis.[45]

reader may have observed that the equation for U' multiplies V with SF_U instead of with SF_V . We could model reprogramming due to radiotherapy in the latter format, but there is an underlying uncertainty in exact choice of radiotherapy behavior. One would assume that there is no increase in the total cell population due to reprogramming, but the protective aspect of survivin makes this unclear. Do cells survive before reprogramming, or do they reprogram before dying off? The former entails compounding V with SF_V , and the latter V with SF_U . At the same time, radiotherapy outcomes do not improve with higher doses. After moderate hypofractionation, it gets worse. Between the two, only $V \cdot SF_U$ follows this pattern, as we can see in Figure 2.4.



(a) The radiotherapy model when using SF_U does lead to non-monotonicity when varying RT dose.



(b) The radiotherapy model when using SF_V does not lead to non-monotonicity when varying RT dose.

Figure 2.4: Comparing dose-response curves of two distinct radiotherapy models.

2.2.2 Radiotherapy Scheduling

Conventional fractionated radiotherapy for glioblastoma is set to 2 Gray applied over 30 consecutive weekdays, or 30 fractions. While we can calculate different radiotherapy schedules by delivering 60 Gray over a given number of days, we can use Biologically Equivalent Dose (BED) to make a fairer comparison of the effect that radiotherapy has on a given tumor. BED tells us what the expected effect of a radiotherapy schedule is. BED can be calculated using the radiosensitivity parameters α and β of the whole tumor, and is derived from multiplying SF with itself n times as a measure of the total efficacy of treatment after the radiotherapy schedule is complete. [57]

$$BED = n g \left(1 + \frac{g}{\frac{\alpha}{\beta}} \right).$$

It is worth noting that hypofractionated scheduling of radiotherapy glioblastoma - where fewer fractions with larger doses than conventional are used - has been found to be a safe alternative. In moderate amounts, it does not do worse than conventional treatment and can even improve outcomes, in some cases.

2.2.3 c : % Reprogrammed Per Gray

The coefficient c is critical to the simulation. If we look at Figure 2.3, we can see a few data points where the kind of radiation amount is on the horizontal axis and % of DCC reprogrammed is in vertical axis. It is measured as the percentage of DCC reprogrammed into CSC per Gray of radiation. We will use the value of 0.5138 % reprogrammed DCC per Gray that was obtained by Victoria Yu by fitting data from “Radiation-induced reprogramming of breast cancer cells.”[58] This value was in turn derived from FACS-purified fresh tissue ALDH1-negative samples from 3 patients that was irradiated and then measured for ALDH1

five days later. As ALDH1 is a stemness factor in breast cancer, this acts as a reasonable proxy for measuring de-differentiation due to radiotherapy only.

Chapter 3

Results

3.1 Conditions for Accelerated Re-Growth and CSC Enrichment

We have found that, alongside the feedforward regulation, reprogramming, and radiotherapy, that at least one of the birth or death rates of V need feedback in order for the model to produce the enrichment of CSC that drives accelerated re-growth of glioblastoma and development of resistance.

In order to see that, let us observe dynamics for when there are no forms of feedback. Since the style of Figure 3.1a will be used throughout the paper, we describe the line types used here.

- **Green** line indicates no treatment has been done to the tumor.
- **Cyan** line indicates treatment has been applied but there is no reprogramming.
- **Purple** line indicates that there is treatment and reprogramming is allowed.

3.1. CONDITIONS FOR ACCELERATED RE-GROWTH AND CSC ENRICHMENT

Let us consider cases where there is not an increase in CSC fraction after treatment. In Figure 3.1a, there is no feedback in the system. We can see exponential growth take place for the total tumor population (bottom left), with CSC's growing slowly enough to appear like they are saturated (top left) due to the 50.5% chance of self-renewal p used for all simulations shown (Table 2.1 has all of them) and DCC's dominating the population size (top right). The CSC fraction plot all but confirms this last statement (bottom right). Even with radiation and reprogramming providing a boost in CSC numbers over the case without treatment, the actual increase of CSC fraction of the case with full treatment and reprogramming over the case without treatment is negligible. Without feedback, there is neither any notable increase in CSC fraction nor of the total tumor volume. When we consider the addition of only negative feedback on division of CSC in Figure 3.1b, the outcome is similar to that of Figure 3.1a for CSC volume, DCC volume, total cell volume, and CSC fraction over time. When looking at the graph of CSC volume over time, regulating the rate of CSC division flattened the slow growth when using feedback on r_U versus not using feedback, and the DCC dynamics are largely unchanged over moderately long times. Negative feedback on probability of self-renewal was considered but reducing the probability of stem cells forming unilaterally makes CSC enrichment unlikely, per Figure 3.1c. Additional examples where adding negative feedback on p in conjunction with other kinds of feedback are supplied in Figure 6.3. All share the same pattern of lacking enrichment in CSC fraction in the case of radiotherapy and reprogramming versus the untreated case. As such, they are ignored as potential mechanisms for CSC fraction enrichment in this context of this model.

We now turn our attention to cases where CSC fraction does increase over time after treatment. In Figure 3.2a, the only parameter changed from 3.1a is h_V , the gain of negative feedback on r_V , from 0 to 10000 to take population effect of growth into account, per Table 2.1. Here we can see a dramatic change in dynamics. In the bottom left graph of Figure 3.2a, we see that the total cell count with reprogramming and radiotherapy has increased over the total cell count without treatment, which clearly indicates accelerated re-growth.

At the same time, the bottom right graph indicates that the fraction of stem cells that has grown due to radiotherapy is nearly a hundred times larger than that without treatment. Hence we can say that if these conditions hold, then accelerated re-growth and CSC enrichment occurs in patient-relevant timescales. In Figure 3.2b, a similar outcome occurs when making h_d the only feedback gain with a positive value d by going from 0 to $\frac{10000}{3}$, per Table 2.1. While feedback on r_U does not contribute to accelerated re-growth and CSC fraction increase, combining it with other forms of feedback does somewhat affect CSC dynamics. For example, when combining the feedback on r_U and d , as seen in Figure 3.2c, the effect of increasing feedback gain for h_d on dynamics for both cell types is largely unchanged except for much slower growth after treatment. Figure 6.2 in the Appendix shows the remaining combinations of feedback that can be used on the system. In each of these, the qualitative nature of the dynamics is largely unchanged and the actual quantities are within an order of magnitude of each other. Thus, when using feedback on r_V or d in conjunction with radiotherapy and reprogramming (purple line), the system experiences accelerated regrowth and increased CSC fraction.

3.2 Varying Radiotherapy Scheduling

Next, we wanted to ask if our model, when supplied with the appropriate feedbacks, point to hypofractionation as an alternative to conventional radiotherapy scheduling [59, 60, 61, 64, 63, 62]. To this end, we calculated the BED of conventional radiotherapy, picked whole number values for radiotherapy doses between 1 and 11 Gray, and calculated the weekdays it would take to match that BED. If the number weekdays calculated was not a whole number, then they would be rounded down. Radiotherapy in each case of radiation and fractions of radiation was applied on consecutive weekdays. With these schedules, we calculate temporal trajectories of CSC and DCC under each of these radiotherapy schedules for every combina-

Doses	1	2	3	4	5	6	7	8	9	10	11
Fractions	66.	30.	18.	12.	9.	7.	5.	4.	4.	3.	2.
BEDs	73.76	74.12	73.06	70.5	71.47	71.65	63.82	62.12	74.12	65.29	50.47

Table 3.1: List of alternative radiotherapy schedules used and their corresponding BED values. We assume that treatment occurs on every consecutive weekday.

tion of feedbacks. It isn't necessary to see each and every one of them, but notable examples will be shown here.

In Figure 3.3, we vary dose and measure CSC fraction for other schedules relative to that of the conventional schedule of radiotherapy. A green line in each of these radiotherapy-varying graphs is drawn for comparison of nonconventional treatment with conventional treatment. Without any kind of feedback, per Figure 3.3a, there is a monotonic increase in CSC fraction as dose is increased. However, in Figure 3.3b, we can see that having at least feedback on d or r_V results in a non-monotonic response. In particular, at intermediate values of radiation per dose, hypofractionation is better than conventional in terms of measuring of CSC fraction.

In regards to total tumor size, we see in Figure 3.4 a parallel story of feedbacks necessary for producing non-monotonicity, but with a small twist. Through hypofractionation at moderately higher doses with the feedback on DCC growth or on death do we see a reduction in tumor size relative to tumor size due to conventional radiotherapy (Figure 3.4b). When neither of the necessary feedbacks are included, a monotonic response arises (Figure 3.4a). The twist is that the addition of negative feedback on CSC division rate weakens this effect some time after the end of treatment (Figure 3.4c).

3.3 Analytical Insights

To see how these results depend on the parameters, we performed long-term analysis of a transformation of the model. If we define:

$$N = U + V$$

$$u = \frac{U}{N}$$

$$v = \frac{V}{N} = 1 - u,$$

then we arrive at the following system of equations by applying the division rule of differentiation:

$$\frac{du}{dt} = (2p - 1 - u)r_u u - (r_v - d)u(1 - u) \quad (3.1)$$

$$\frac{dN}{dt} = N(r_u u + (r_v - d)(1 - u)) \quad (3.2)$$

With this system of equations, we can directly analyze the long-term stability of the CSC fraction. Note that feedback forms can be freely added to the system in the same manner as the original one in (U, V) coordinates, albeit with the new definitions, i.e. $\frac{1}{1+hV} = \frac{1}{1+h(1-u)N}$. Additionally, the analysis performed does not calculate a long-term value for N , as this system does not stop growing over time, even under feedback. Fixing N for the total population's expected values can be done without affecting the category of stability in the u -direction. We can start to see why this is the case when we consider the feedbacks in the (u, N) space. Here h_j denotes a feedback gain coefficient and r_i indicates a division rate for

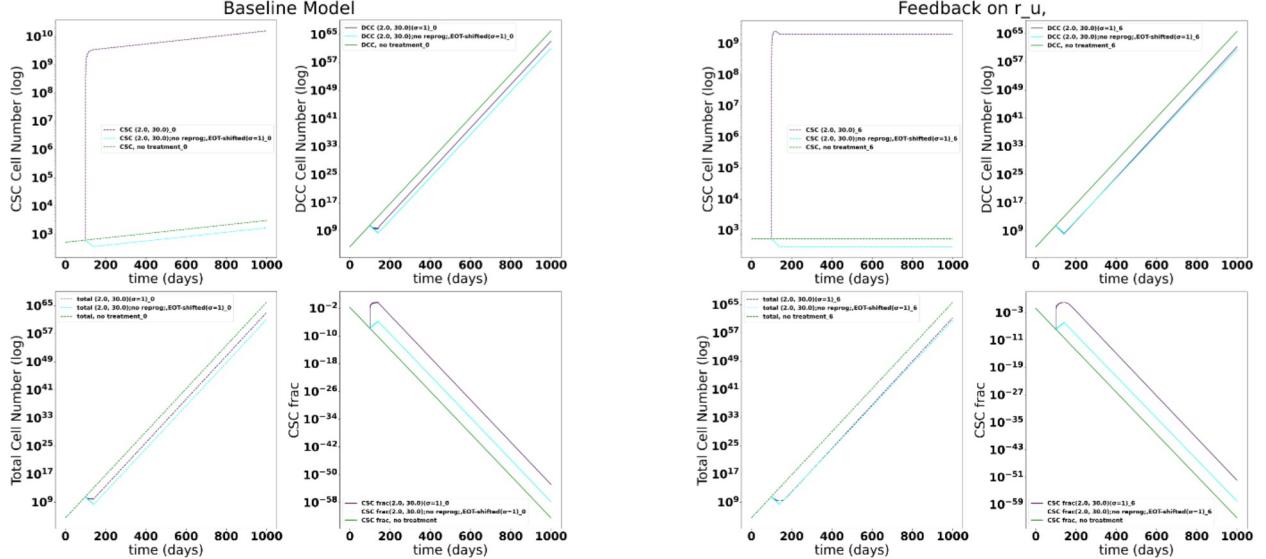
CSC or DCC for the sake of speaking of negative feedback within the system generically.

$$\lim_{N \rightarrow \infty} \frac{r_i}{1 + h_j V} = \lim_{N \rightarrow \infty} \frac{r_i}{1 + h_j(1 - u)N} = 0 \quad (3.3)$$

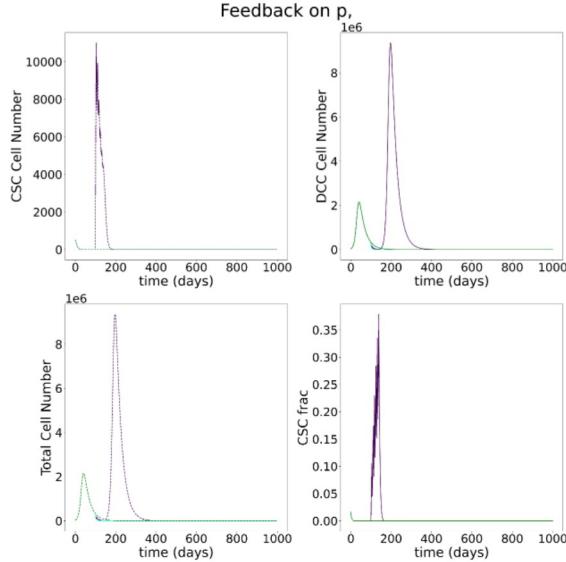
$$\lim_{N \rightarrow \infty} d + \frac{(1.1r_V - d)(1 + h_d V)}{1 + h_d V} = \lim_{N \rightarrow \infty} d + \frac{(1.1r_V - d)(1 + h_d(1 - u)N)}{1 + h_d(1 - u)N} = 1.1r_V \quad (3.4)$$

If r_V has feedback then Equation (3.4) turns into (3.3). This effectively means that the $\lim_{N \rightarrow \infty} \frac{du}{dt}$ for any feedback regime will result in N falling out of the equation, meaning that N has no influence on long-term dynamics for CSC fraction. Figure 3.5 characterizes how $\frac{du}{dt}$ does not change when varying N except for a small region near 0. But due to how large N is at the beginning per Figure 3.1 and 3.2, we can safely assume that choice of N does not affect our analysis for long-term stability and thus can calculate \bar{u} . This statement is true for all feedback combinations.

Figures 3.6 and 3.7 feature phase diagrams for the system generated in Mathematica. Generally, without treatment, there is an increase in CSC fraction due to the addition of feedback and there is only one steady state value \bar{u} that's smaller than 1 and larger than 0. In each of these subfigures, we can see the pace at which each system approaches its single equilibrium \bar{u} . In particular, the more components V regulates via feedback, the higher the value of \bar{u} , and the system's growth is slower without the addition of feedback on r_v .



(b) Temporal dynamics for the baseline model with the addition of negative feedback on r_U . No accelerated re-growth or CSC enrichment can be found here.



(c) Temporal dynamics for the baseline model with the addition of negative feedback on p only. Not only is there no accelerated regrowth, but the ODE is pushed into quantities which are practically zero and no clear increase in CSC fraction over time in any case.

Figure 3.1: Green line indicates no treatment has been done to the tumor. Cyan line indicates treatment has been applied but there is no reprogramming. Purple line indicates that there is treatment and reprogramming is allowed. Y-axes are as follows starting from the top left and going clockwise: CSC number, DCC number, CSC fraction, total cell number.

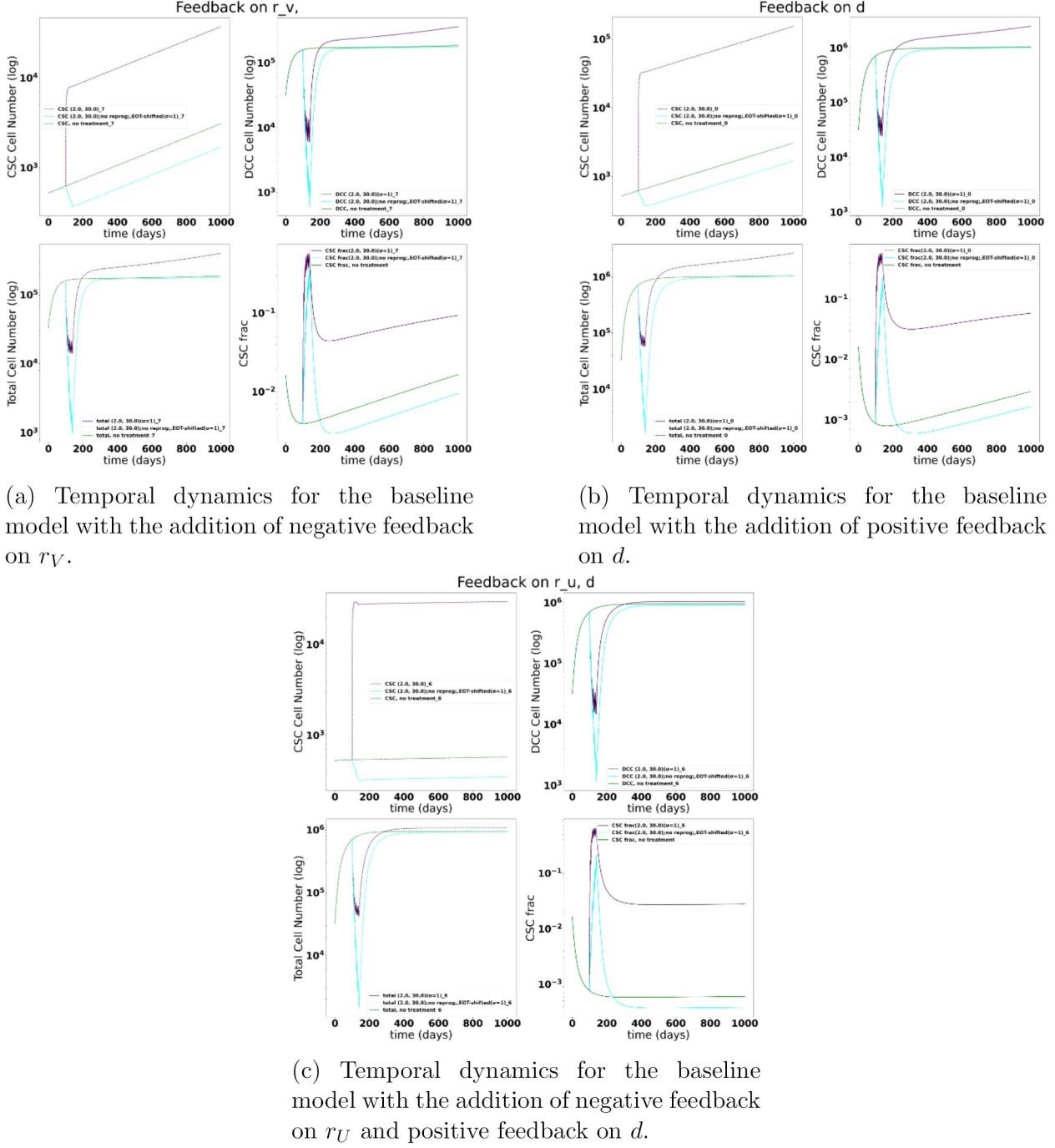
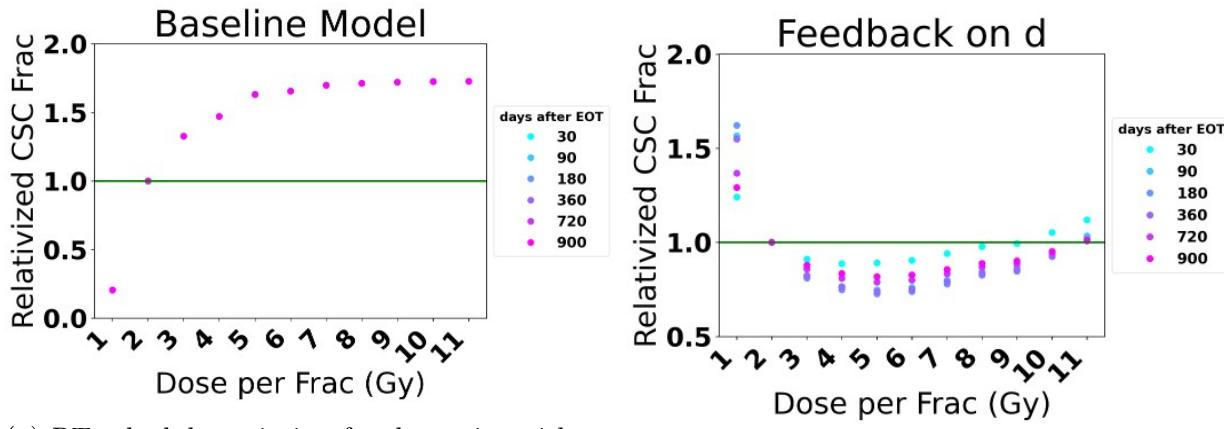


Figure 3.2: Here we can see that each combination here leads to tumor accelerated re-growth and CSC enrichment, with the primary difference between each case being the slower growth of DCC and CSC in the case in Figure 3.2c. **Green** line indicates no treatment has been done to the tumor. **Cyan** line indicates treatment has been applied but there is no reprogramming. **Purple** line indicates that there is treatment and reprogramming is allowed. Y-axes are as follows starting from the top left and going clockwise: CSC number, DCC number, CSC fraction, total cell number.



(a) RT schedule variation for dynamics without feedback on r_V or d leads to monotonic response. Here, no feedback is used.

(b) RT schedule variation for baseline dynamics involving feedback on r_V or d leads to non-monotonic response. Here, feedback on d is used.

Figure 3.3: Characteristic plots comparing radiotherapy schedules for particular feedback regimes in terms of CSC fraction. The y-axis is “relativized” because it measures the CSC fraction at a particular dose divided by the CSC fraction of conventional dose at a given time point. EOT is End of Treatment, and time is relativized to EOT because that will let us fairly assess the consequences of each treatment schedule. The green line denotes when the tumor size at a certain time point for a non-conventional treatment schedule matches that of the conventional treatment schedule.

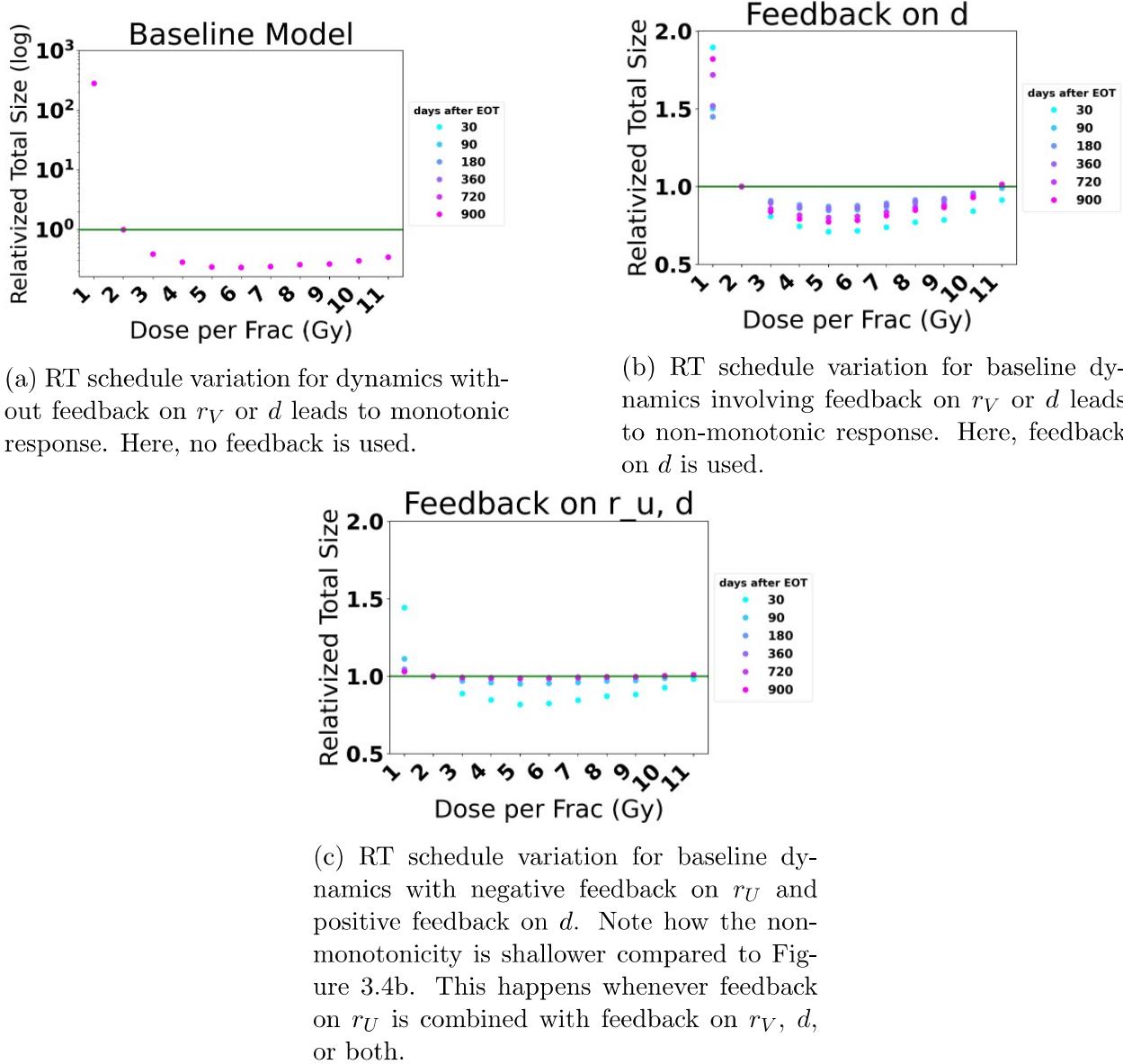


Figure 3.4: Characteristic plots comparing radiotherapy schedules for the effect of particular feedback regimes on total tumor size. The y-axis says “relativized” because it measures the total tumor size at a particular dose divided by the total tumor size of conventional dose at a given time point. EOT is End of Treatment, and time is relativized to EOT because that will let us fairly assess the consequences of each treatment schedule. The green line denotes when the tumor size at a certain time point for a non-conventional treatment schedule matches that of the conventional treatment schedule.

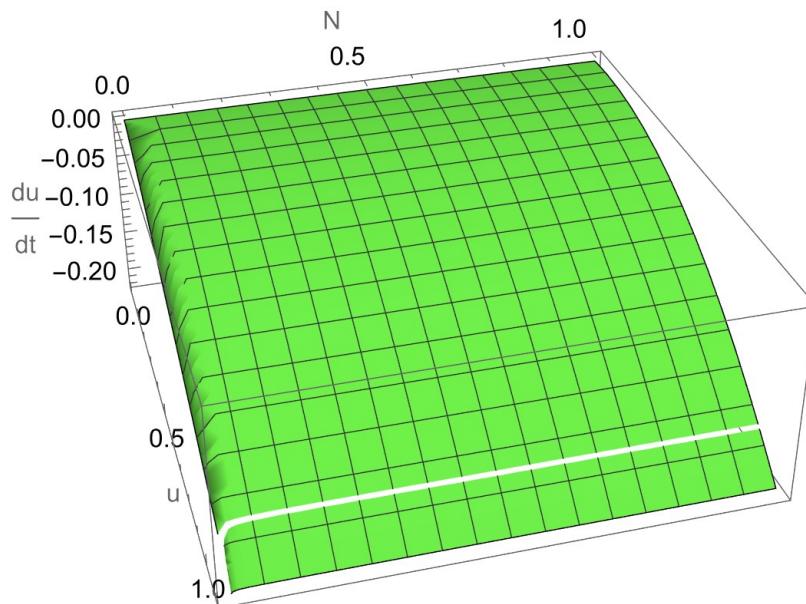


Figure 3.5: Case where there is only feedback on r_V . The fact that the 3D plot does not change in the N direction except for very small values of N indicates that \bar{u} does not depend on N .

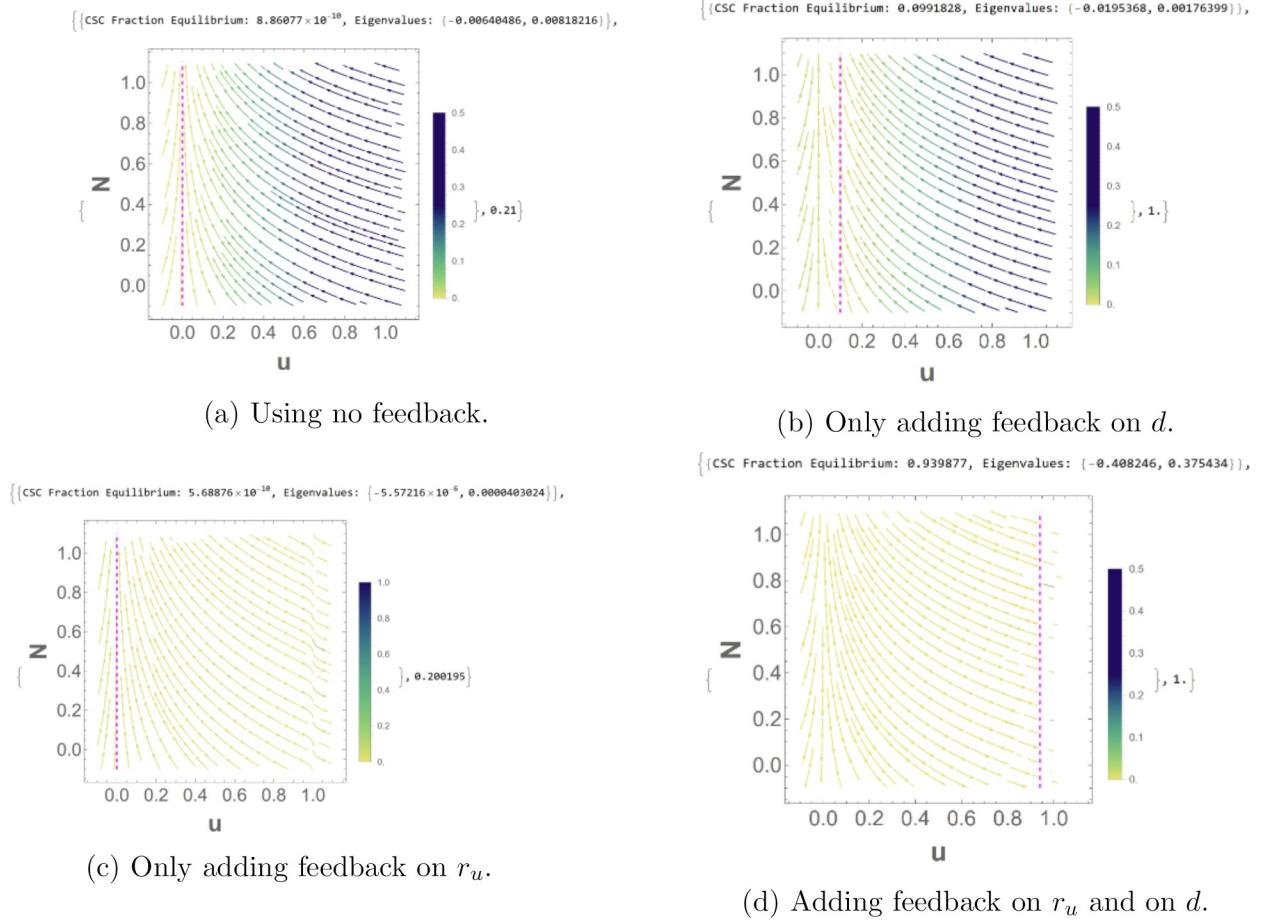


Figure 3.6: Comparing the phase diagrams of the model with the feedforward circuit and various feedbacks added to it (no feedback on r_v is used here). The magenta line indicates the value of \bar{u} calculated and given above the plot.

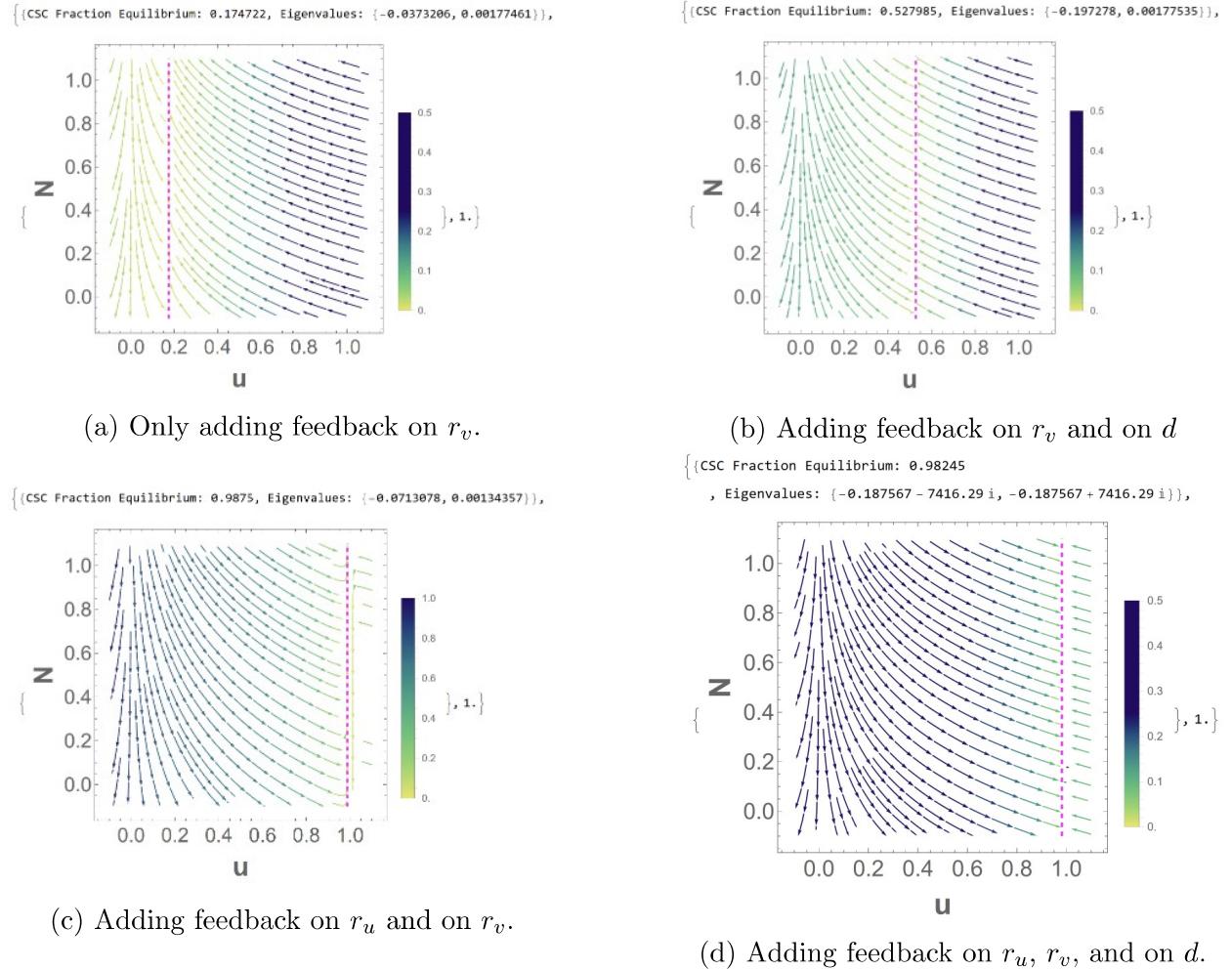


Figure 3.7: Comparing the phase diagrams of various feedback regimes, assuming the feed-forward circuit is in use and coupled with feedbacks that involve r_v . The magenta line indicates the value of \bar{u} calculated and given above the plot.

Chapter 4

Discussion

The combination of feedforward regulation, reprogramming, and radiotherapy, and negative feedback on r_V , positive feedback on d , or both, are necessary in order for accelerated re-growth and sustained CSC fraction elevation to take place. See Figure 4.1 for a visualization. There may be other forms of feedback yet to be explored that are entailed by this phenomenon, however.

The fact that the phase diagrams point to a single value of \bar{u} suggests that there isn't a new level of CSC fraction that holds in the long term. The temporal dynamics for one case are in Figure 4.2 to demonstrate this. While the results in the section on temporal dynamics is sufficient for the median lifespan of glioblastoma patients, this does point to the transient nature of CSC enrichment within this model. The model used by Rodrigues-Brenes

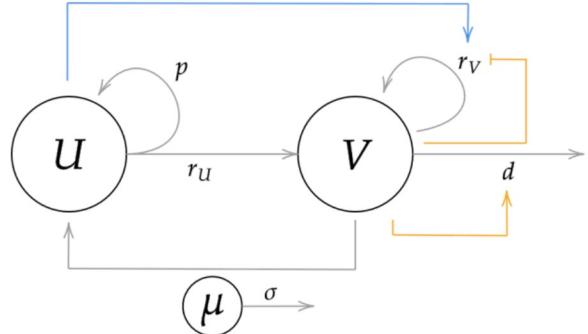


Figure 4.1: A diagram summarizing the feedbacks that, in conjunction with RT and reprogramming, result in tumor accelerated regrowth and CSC enrichment. At least one of the gold arrows is enough.

et al. used feedback on division rates and also additional compartments within the model to create permanent long-term changes in CSC fraction. However, model extensions that produce multiple steady states in the space of fractions of stem and non-stem cells would provide a result distinct from previous work that has studied multistability in the context of cell counts or populations [65].

There are some plausible biological interpretations for the positive feedback on DCC death. It may represent a logistic growth term of sorts, where crowding or resource competition ends up reducing the DCC population. There is experimental evidence to give at least some credence to this finding, in particular regard to positive feedback on death. Necrosis induced by neutrophils can stimulate GBM growth, which means that death can drive overall cell growth through allowing space for growth. [66] Iron dependency and ferroptosis seem to be at the heart of this mechanism. [67, 68].

In addition to providing potential mechanisms for tumor accelerated re-growth and CSC enrichment, our model indicates that the radiotherapy schedules we used at 5 Gray would be optimal for reducing CSC fraction, though the other schedules between 3 and 7 Gray are at a similar level of improvement compared to the 5 Gray schedule. This recapitulates observations of the improvement to treatment outcome that moderate hypofractionation can bring to elderly glioblastoma patients. Many clinical papers have confirmed this in patients, so there may be use for the model to help provide targets for combination therapy. [59, 60, 61, 64, 63, 62]

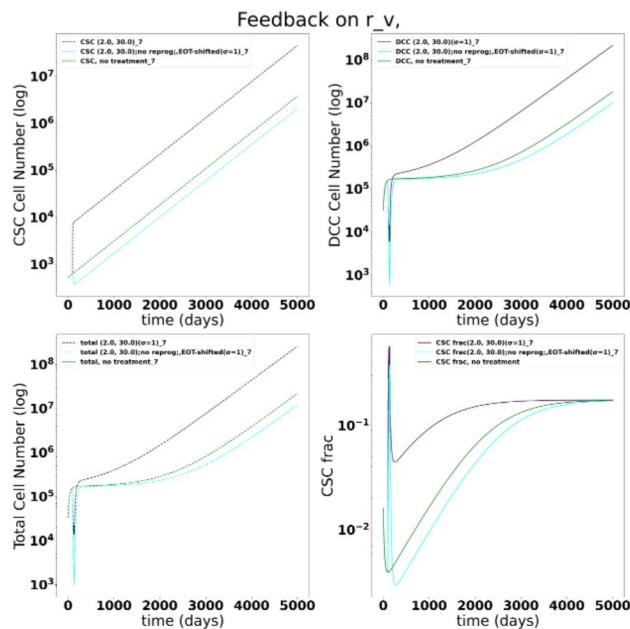


Figure 4.2: Extension of Figure 3.2a into a longer time scale, indicating that the increase is temporary, albeit after a long time under the given parameter values specified.

Chapter 5

Next Steps

5.1 Adding Stages and Combinatorial Feedback for Multistability

The reported results regarding long-term changes in the CSC fraction and overall tumor size are transient and thus dependent on the parameters. However, by introducing combinatorial feedback (i.e. having positive and negative feedback from V act simultaneously onto U), changes in CSC fraction may become permanent through multistability and would expand the predictive potential of a mathematical model of glioblastoma that combined feedback, de-differentiation, and treatment[65]. This would allow us to identify permanent changes in the system if treatment is sufficiently influential on the population levels. Additionally, considering such feedback in the context of the CSC fraction-total cell number system would extend Kunche et al's paper since they used feedback on systems of populations of cells and not of cell fractions.

5.2 Extending to a Hybrid Model

Additionally, while the ODE-based model has allowed us to directly analyze the system, expanding to an ABM may help with addressing the unmet needs described in the introduction. One assumption of the model that allowed us to use an ODE-formulation was the homogeneous application of radiation to the entire tumor. However, radiotherapy and chemotherapy is usually more targeted [69, 70], not to mention the inherent heterogeneity cancers like glioblastoma possess [71]. While a partial differential equation (PDE) model is able to capture spatiotemporal heterogeneity, there is an issue of the stem cell population usually being orders of magnitude smaller. Since populations are represented as concentrations or volumes, a population that should be zero will be instead nearly zero, i.e. overrepresented. Thus, the difference in scale of populations might not be accurately captured by a PDE model since it is a continuous model and not a discrete one. Using discrete cell counts would allow us to bypass this issue. One more potential use for the agent-based model would be to implement multiscale dynamics, specifically in the form of intracellular dynamics with intercellular dynamics regarding de-differentiation, as the consequences of the application of radiation to specific regions of the tumor span the intracellular and intercellular and manifest themselves differently in the short-term and in the long-term [72, 73]. Additionally, the production and dissemination of factors of de-differentiation spans several timescales.

5.3 Deriving the Radiotherapy Equations

While our model of radiotherapy is based on the linear-quadratic model, the fact that survivin levels and export correlate with radiation damage [14, 74] lead us to believe that it would be during radiotherapy that reprogramming would have the most effect. In other words, we would like to justify the equations used in 2.2.

Let u and v represent CSC and DCC volumes, with ρ describing the rate of reprogramming and δ_u and δ_v representing death due to radiation for CSC and DCC, respectively.

$$\frac{du}{dt} = \rho v - \delta_u u \quad (5.1)$$

$$\frac{dv}{dt} = -\rho v - \delta_v v \quad (5.2)$$

we can arrive at a set of equations that we later use for the effect of radiotherapy.

The form of the model above falls under the following assumptions:

- The timescale of radiation is quicker than that of a cycle of proliferation, so cell division is dwarfed by cell death in these rate equations.
- Reprogramming happens dynamically during this timeframe.
- The radiotherapy happens during a very short amount of time, labeled Δ .

With these two key assumptions, we can solve the system.

$$v_\Delta = v_0 e^{-\delta_v \Delta} e^{-\rho \Delta}$$

$$u_\Delta = u_0 e^{-\delta_u \Delta} + \frac{\rho v_0}{\rho + \delta_v - \delta_u} (e^{-\delta_u \Delta} - e^{-\delta_v \Delta} e^{-\rho \Delta})$$

Let us grant the interpretation that

$$e^{-\delta_v \Delta} = SF_V = e^{-g(\alpha_V + \beta_V g)},$$

with an equivalent definition for SF_U . At the same time, let us suppose $\rho \Delta = \mu$. Then we

can find the following:

$$v_\Delta = v_0 S F_V e^{-\mu}$$

$$u_\Delta = u_0 S F_U + v_0 \frac{\mu}{\mu + g(\alpha_V - \alpha_U) + g^2(\beta_V - \beta_U)} (S F_U - S F_V e^{-\mu})$$

$S F_V e^{-\mu}$ is a negligible amount since $S F_V$ and $e^{-\mu}$ are small numbers, which means that with this model there is a cross-term between the amount of DCC and the fraction of CSC that survive treatment. However, the fraction $\frac{\mu}{\mu + g(\alpha_V - \alpha_U) + g^2(\beta_V - \beta_U)}$ does not neatly correspond to the radiotherapy equations used to generate earlier results since the fraction is roughly approximated by a $\frac{1}{g}$ relation not present in the equations used. As-is, the approach somewhat corresponds to the radiotherapy equations used in the model used to generate the results of the paper.

Chapter 6

Conclusion

This thesis featured a model of the dynamics of glioblastoma undergoing radiotherapy and simulated different conditions and regimes of feedback. A combination of dedifferentiation, radiotherapy, and feedback on division or death rate of DCC is necessary and sufficient for CSC enrichment and tumor recurrence in patient-relevant timescales. The model also indicates that changing from conventional radiotherapy to hypofractionation (higher dose, fewer fractions) can provide more effective treatment schedulin. Despite the limitations investigated regarding long-term stability of the system's steady state, the present model still can characterize dynamics at patient-relevant timescales.

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Appendix: Derivation of Radiotherapy Equations

Let us for now slightly generalize the equations to the following:

$$\frac{du}{dt} = \rho_u v - \delta_u u \quad (6.1)$$

$$\frac{dv}{dt} = -\rho_v v - \delta_v v \quad (6.2)$$

Looking at (6.2) we integrate over the interval $[0, \Delta]$. Noting that the form of the differential equation matches that of the exponential, we can state that it evaluates to

$$v(\Delta) \equiv v_\Delta = v_0 e^{-\delta_v \Delta} e^{-\rho_v \Delta}.$$

Now, looking at the (6.1),

$$\frac{du}{dt} = \rho_u v - \delta_u u \quad (6.3)$$

$$= \rho_u v_0 e^{-\delta_v t} e^{-\rho_v t} - \delta_u u \quad (6.4)$$

$$\frac{du}{dt} + \delta_u u = \rho_u v_0 e^{-\delta_v t} e^{-\rho_v t} \quad (6.5)$$

$$e^{\delta_u t} \left(\frac{du}{dt} + \delta_u u \right) = (\rho_u v_0 e^{-\delta_v t} e^{-\rho_v t}) e^{\delta_u t} \quad (6.6)$$

$$\Rightarrow \frac{d}{dt} \left(e^{\delta_u t} u \right) = (\rho_u v_0 e^{-\delta_v t} e^{-\rho_v t}) e^{\delta_u t} \quad (6.7)$$

$$\int_0^\Delta \frac{d}{dt} \left(e^{\delta_u t} u \right) dt = \int_0^\Delta (\rho_u v_0 e^{-\delta_v t} e^{-\rho_v t}) e^{\delta_u t} dt \quad (6.8)$$

$$e^{\delta_u \Delta} u - u_0 = \int_0^\Delta \rho_u v_0 e^{(\delta_u - \delta_v - \rho_v)t} dt \quad (6.9)$$

$$= \frac{\rho_u v_0}{(\delta_u - \delta_v - \rho_v)} \int_0^{(\delta_u - \delta_v - \rho_v)\Delta} e^s ds \quad (6.10)$$

$$= \frac{\rho_u v_0}{(\delta_u - \delta_v - \rho_v)} (e^{(\delta_u - \delta_v - \rho_v)\Delta} - 1) \quad (6.11)$$

$$e^{\delta_u \Delta} u = u_0 + \frac{\rho_u v_0}{(\delta_u - \delta_v - \rho_v)} (e^{(\delta_u - \delta_v - \rho_v)\Delta} - 1) \quad (6.12)$$

$$u(\Delta) \equiv u_\Delta = e^{-\delta_u \Delta} u_0 + e^{-\delta_u \Delta} \frac{\rho_u v_0}{(\delta_u - \delta_v - \rho_v)} (e^{(\delta_u - \delta_v - \rho_v)\Delta} - 1) \quad (6.13)$$

$$u_\Delta = e^{-\delta_u \Delta} u_0 + \frac{\rho_u v_0}{(\delta_u - \delta_v - \rho_v)} (e^{(-\delta_v - \rho_v)\Delta} - e^{-\delta_u \Delta}) \quad (6.14)$$

$$u_\Delta = e^{-\delta_u \Delta} u_0 + \frac{\rho_u v_0}{(\rho_v + \delta_v - \delta_u)} (e^{-\delta_u \Delta} - e^{(-\delta_v - \rho_v)\Delta}) \quad (6.15)$$

$$\text{If } \rho_u = \rho_v \equiv \rho, \quad (6.16)$$

$$u_\Delta = e^{-\delta_u \Delta} u_0 + \frac{\rho v_0}{(\rho + \delta_v - \delta_u)} (e^{-\delta_u \Delta} - e^{(-\delta_v - \rho)\Delta}) \quad (6.17)$$

Additional Figures

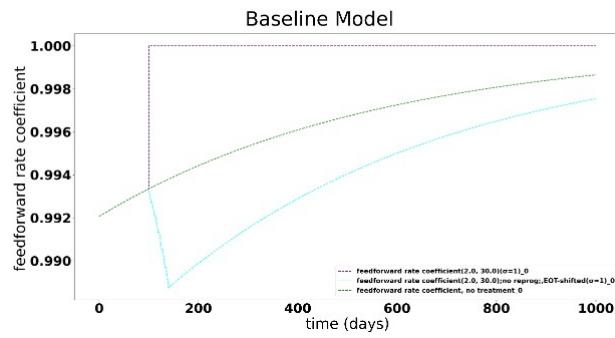
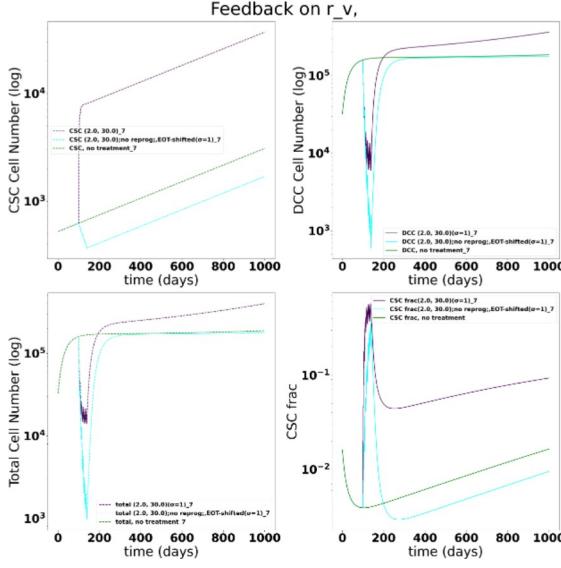
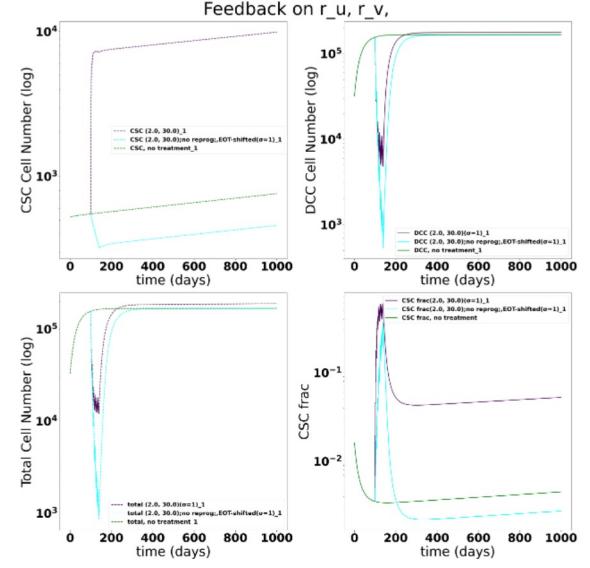


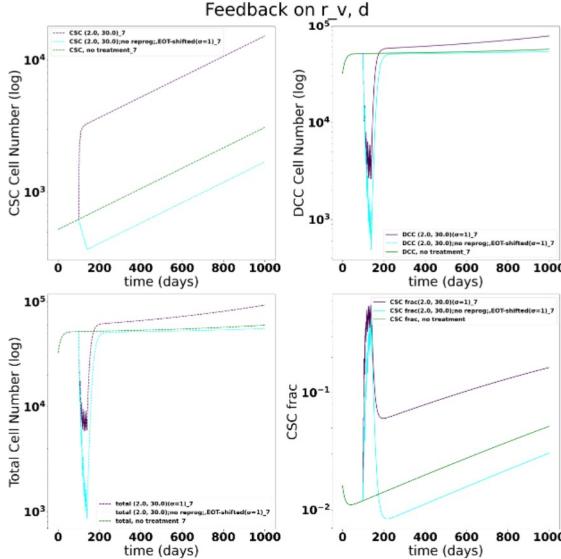
Figure 6.1: Y-axis measures the value of the relative feedforward term for the baseline model, which is between 0 and 1. We can see that feedforward regulation does not contribute much to the dynamics of the model since it's tuned to be saturated. Green line indicates no treatment has been done to the tumor. Cyan line indicates treatment has been applied but there is no reprogramming. Purple line indicates that there is treatment and reprogramming is allowed.



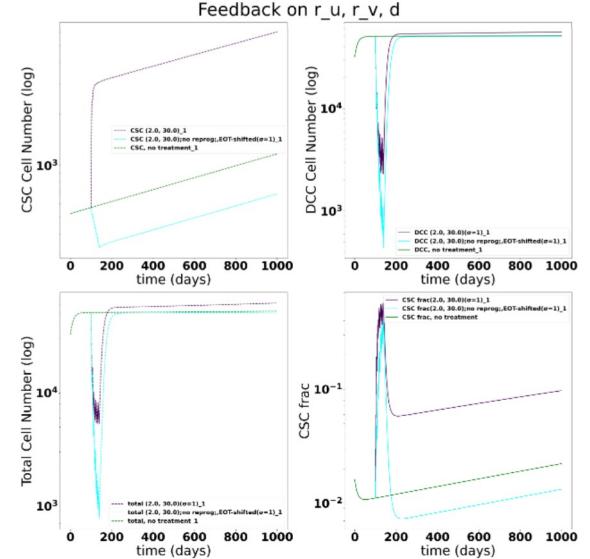
(a) Temporal dynamics for the baseline model with the addition of negative feedback on r_V .



(b) Temporal dynamics for the baseline model with the addition of negative feedback on r_U and r_V .

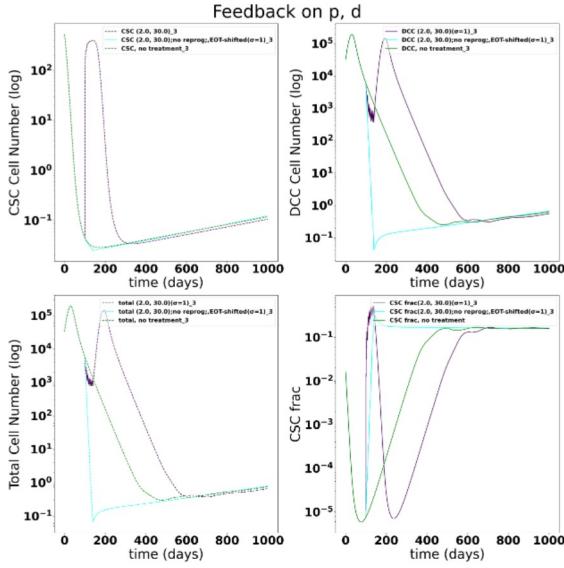


(c) Temporal dynamics for the baseline model with the addition of negative feedback on r_V and positive feedback on d .

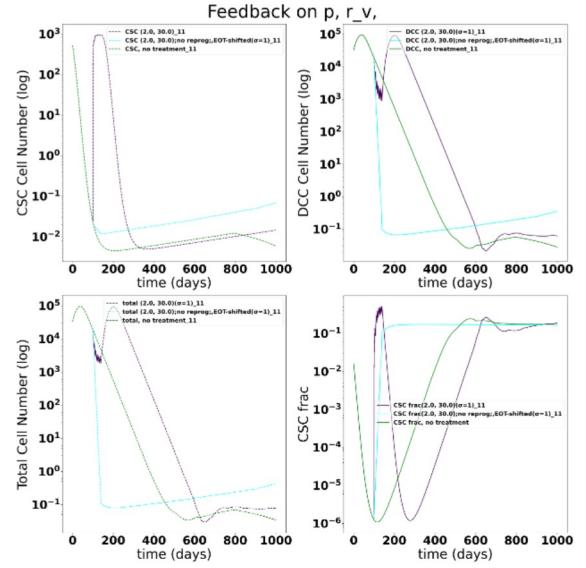


(d) Temporal dynamics for the baseline model with the addition of negative feedback on r_U and r_V and positive feedback on d .

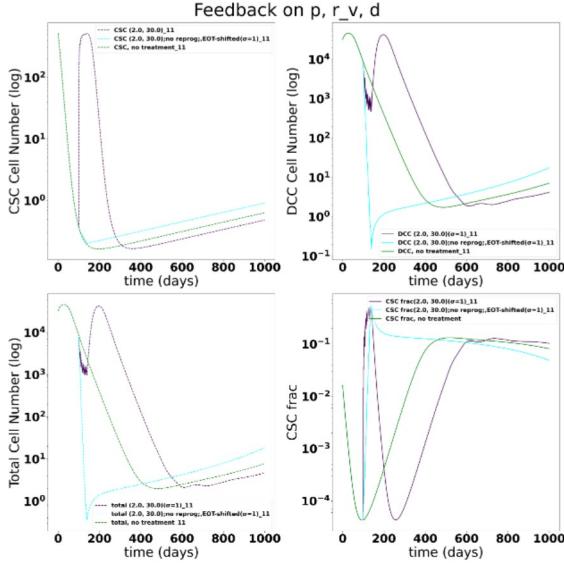
Figure 6.2: Here we can see that every combination here leads to tumor accelerated regrowth and CSC enrichment. **Green** line indicates no treatment has been done to the tumor. **Cyan** line indicates treatment has been applied but there is no reprogramming. **Purple** line indicates that there is treatment and reprogramming is allowed. Y-axes are as follows starting from the top left and going clockwise: CSC number, DCC number, CSC fraction, total cell number.



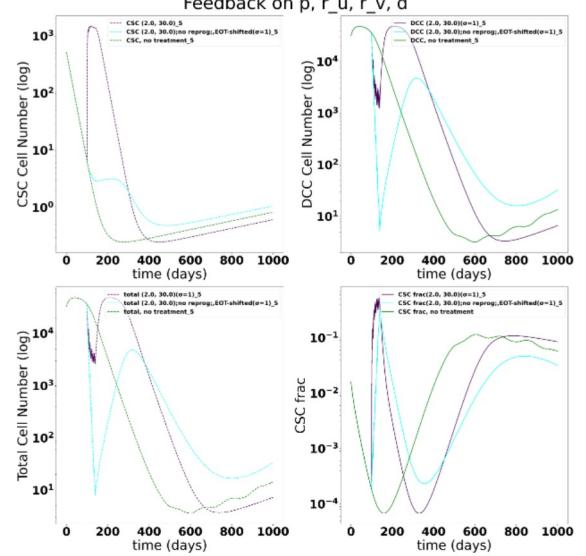
(a) Temporal dynamics for the baseline model with the addition of negative feedback on p and positive feedback on d .



(b) Temporal dynamics for the baseline model with the addition of negative feedback on p and r_v .



(c) Temporal dynamics for the baseline model with the addition of negative feedback on p , on, r_v , and positive feedback on d .



(d) Temporal dynamics for the baseline model with the addition of negative feedback on p , on r_u , on r_v , and positive feedback on d .

Figure 6.3: Here are some examples of the application of negative feedback on p in conjunction with some other forms of feedback. All share the same pattern of a temporary CSC enrichment in the case of radiotherapy and reprogramming versus the untreated case. **Green** line indicates no treatment has been done to the tumor. **Cyan** line indicates treatment has been applied but there is no reprogramming. **Purple** line indicates that there is treatment and reprogramming is allowed. Y-axes are as follows starting from the top left and going clockwise: CSC number, DCC number, CSC fraction, total cell number.