Final Project

OR 7245

Project Report

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Introduction

Given the initial problem, there were seemingly two core methods identified to formulate the problem as a linear programming model:

1. Maximize the total radiation to cancerous (tumor) cells while abiding by the constraints
2. Minimize the total radiation to critical cells while abiding by the constraints

The choice of method could depend on the case, as a patient with more aggressive tumors could require aggressive treatment. In contrast, a patient with benign tumors might be able to combat the disease with less intense radiation treatment. Both formulations above are necessary for the problem. However, the isolation of the two can make this problem more susceptible to a linear program. Given its scalability related to later iterations of the problem, the team decided to frame the model as a minimization problem (2). Therefore, the overall objective was to minimize total radiation to critical cells given the scneario's constraints.

Problem Formulations

Formulation 1

For formulation 1, the overall objective is what was accomplished. Specifically, the model's objective was to minimize the total radiation from all beams being targeted at image pixels capturing critical areas. The constraints of this formulation were keeping each critical area pixel's radiation exposure under the maximum amount of radiation allowed to critical cells. Similarly, tumor cell pixels' total radiation exposure needed to meet the minimum amount of radiation to kill off tumor cells. The decision variable for this problem is the amount of times each beam is used (with varying strengths as to avoid integer constraints). The mathematical representation can be seen below:

Let $k :=$ set of beams such that $k \in \{1,...,b\}$

i, j: x, y pixel coordinates for each image where $i \leq$ height and $j \leq$ width

$b :=$ number of beams

$W_k :=$ matrix of constant beam weights for beam k

$T :=$ matrix representation for pixels with tumors with $T_{ij} = \begin{cases} 1, & \textit{if tumor present} \\ 0, & \textit{otherwise} \end{cases}$

$C :=$ matrix representation for pixels in critical area with $C_{ij} = \begin{cases} 1, & \textit{if critical} \\ 0, & \textit{otherwise} \end{cases}$

$U :=$ Upper limit of radiation allowed

$L :=$ Minimum radiation threshold required

<u>Decision Variable:</u>

$X_k :=$ number of times beam is used

$$Min \quad \sum_{\forall(i,j)} C' \sum_{k=1}^{b} X_k W_k$$

$subject\ to$:

$$C' \sum_{k=1}^{b} X_k W_k \leq U \forall\, C_{(i,j)} = 1$$

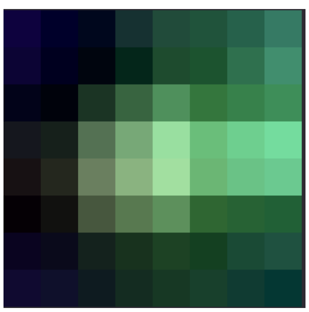
$$T' \sum_{k=1}^{b} X_k W_k \geq L \forall\, T_{(i,j)} = 1$$

$$X_k \geq 0 \;\forall\, k \in \{1,...,b\}$$

Formulation 1 Results

The results of formulation 1 can only be discussed when referring to the "small example." This is because the formulation, when applied to the "actual example," is infeasible. This was expected to happen as the large number of beams and large surface area of the image creates a complex model. Within this complex model, especially in the center of the image where the beam strength is the greatest (due to overlapping), it is expected that the radiation upper limit of 2 per pixel in critical areas is difficult to meet while also satisfying the lower bound of radiation of 10 on the tumor.

However, when considering the small example, there is a feasible optimal solution. The objective value was 0.0, meaning this was a “perfect solution” with no radiation present on critical areas. The algorithm also correctly chose to assign the beam strength’s to beams 0, 1, and 4 respectively with beam 0 being at 20, beam 1 being at 12.5, and beam 4 being 20. This was a great proof of concept for the model formulation since it worked exactly as designed. The light areas on the Maple visualization below correspond to the tumor areas and the darker areas correspond to the critical areas:

Optimal Solution	**Tumor Area**	**Critical Area**
	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

Formulation 1 Sensitivity Analysis

For the small example, sensitivity analysis shows that any values for the upper and lower radiation bounds will yield the objective value 0.0. This means that the current optimal basis for bounds of 2 and 10 respectively can be increased or decreased to meet fluctuations in these values. Because the objective function is 0, there is no contact between the beams and the critical area. Thus, the lower limit of radiation applied to the tumor area can be increased indefinitely and the basis will remain optimal. Additionally, the lower bound can take on values below 10 and the objective value will remain the same.

Formulation 2

Formulation 2 took a similar approach. However, the improvement from formulation 1 is the accountability to variation in upper and lower limits while maintaining feasibility. To accomplish this, slack was subtracted from the left-hand side (LHS) of the critical area constraint and added to the LHS of the tumor constraint. This way, an oncologist could increase the upper limit or decrease the lower limit while maintaining feasibility. Therefore, the slack also becomes a decision variable which we want to minimize for both constraints, implying addition to the minimization objective function. An arbitrary penalty can be assigned to the slack variables for the objective function. Different penalties for each allowable slack can be assigned based on oncologist knowledge, but were kept the same for this model. As such, the mathematical representation can be seen below:

Let M_T := penalty assigned to L ∀ (i,j) ∈ {T}

M_R := penalty assigned to L ∀ (i,j) ∈ {C}

Decision Variables:

X_k := number of times beam is used

S_T := Slack assigned to allow for lower limit (L) violation

S_R := Slack assigned to allow for upper limit (U) violation

$$Min \quad \sum_{\forall(i,j)} \left(C' \sum_{k=1}^{b} X_k W_k\right) + M_T S_T + M_R S_R$$

subject to:

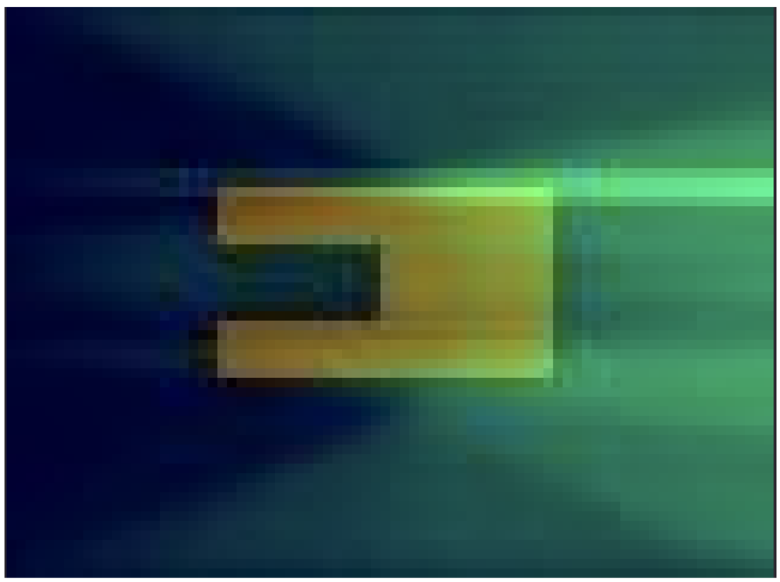
$$C' \sum_{k=1}^{b} X_k W_k - S_R \leq U \forall \, C_{(i,j)} = 1$$

$$T' \sum_{k=1}^{b} X_k W_k + S_T \geq L \forall \, T_{(i,j)} = 1$$

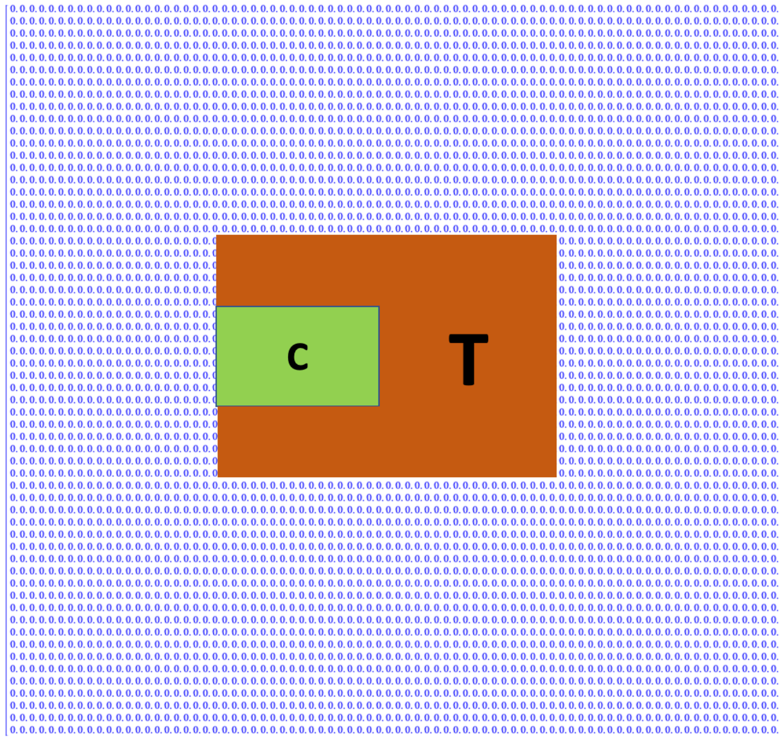
$$X_k \geq 0 \; \forall \, k \in \{1,...,b\}$$

Formulation 2 Results

With the slack variables introduced, the model was able to find an "optimal solution" to the actual example problem in addition to the small problem (the result for the small problem was the same as Formulation 1 since no slack was needed for the solution there). This time, the model resulted in being solved using dual simplex after 248 iterations. The objective value was extremely high ~57,679,887 due to the 100,000 penalty placed on both tumor and critical slack variables. This meant that critical areas which were not only hit by radiation, but also over the allowed threshold of radiation. In this formulation, the same penalty was put on both slacks, the violations are considered equally important. However in a real-world scenario a doctor may choose to prioritize one over the other. The image created using Maple for the second formulation can be seen below:



Optimal Solution to Formulation 2 depicted using Maple



Approximate depiction of critical and tumor area

Judging solely based on the output image, the formulation with slack is able to avoid the critical area and deliver a large amount of radiation to only the tumor area. The heatmap from Maple shows a high level of radiation in the exact shape of the tumor and a very dark area in the critical area which is promising. However, at closer inspection of the model results, the answer is not quite “optimal”.

The first sign of this is evident that since without slack variables, this formulation is infeasible. However, looking at the slack variables it becomes clear why this is the case. While the majority of slack variables in the critical area are considered to be low (<= 3), there are a few slack variables in the critical region which are found to be extremely high with the top 3 being ~42, ~30, and ~24. This represents danger to the patient's vital organs and is a sign that the formulation should be adjusted to avoid this large slack on the critical area. Within the tumor, the slack values were typically under 2, however there were some relatively high slack values as well with multiple reaching levels over 9. This indicates that the tumor is not being fully treated and should also be a concerning sign.

Between the two categories of slack violations, the critical area slacks should be considered to be a higher priority to change as they cause harm to the patient. However, if aggressive treatment is needed, doctors may prioritize killing the tumor and accepting collateral damage to critical areas.

Formulation 2 Sensitivity Analysis

As described, the solution for formulation 2 includes slack variables in the optimal solution. Because of the large penalty assigned to the slacks, the dual prices of 60 variables is -100000. By changing the upper bound of the treatment area by 1, the objective function is decreased by over 6.5 million (~11.2%). Decreasing the lower bound by 1 unit results in an objective function decrease of over 7 million (~12.3%).

Formulation 3

In addition to Formulation 2's improvement to the model, the third formulation must account for cells neighboring the critical area (pixels). The goal here is to also minimize radiation exposure to these cells, while maintaining the same goals as previous formulations. Thus, the decision variables from Formulation 2 remain, and the only thing to change about this model is the objective function, which can be seen mathematically below. Also, there is a constant value (which can be assigned by the oncologist) to reduce the penalty for hitting the neighboring cells on the objective function.

Let D := matrix representation for pixels neighboring the critical area with

$$D_{ij} = \begin{cases} 1, & \textit{if bordering tumor area and no tumor is present} \\ 0, & \textit{otherwise} \end{cases}$$

q := reduced penalty for hitting neighboring cells to the critical area

Decision Variables:

X_k := number of times beam is used

S_T := Slack assigned to allow for lower limit (L) violation

S_R := Slack assigned to allow for upper limit (U) violation

$$Min \sum_{\forall (i,j)} (C' \sum_{k=1}^{b} X_k W_k + M_T S_T + M_R S_R + qD' \sum_{k=1}^{b} X_k W_k)$$

subject to:

$$C' \sum_{k=1}^{b} X_k W_k - S_R \leq U \forall \; C_{(i,j)} = 1$$

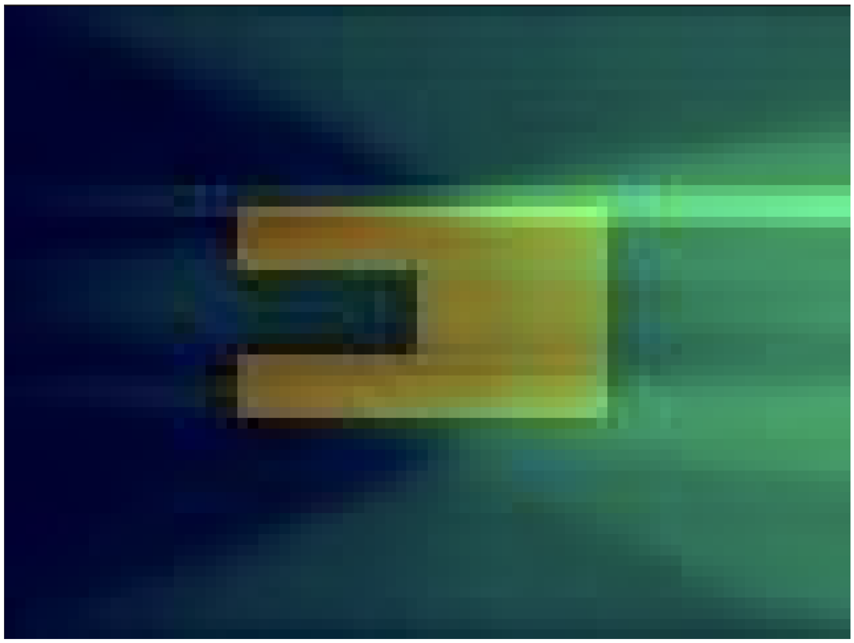
$$T' \sum_{k=1}^{b} X_k W_k + S_T \geq L \forall \; T_{(i,j)} = 1$$

$$X_k \geq 0 \; \forall \; k \in \{1,...,b\}$$

Formulation 3 Results

The result of the new border penalty formulation on the small problem produced the exact same result except for a new optimal solution value of 68.5. This is due to the small penalty on the border of the critical area which overlaps with the tumor since the algorithm "must" push beams to meet those constraints and “accepts” the penalty of hitting the border. No slack is utilized here which shows the correct approach of the model accepting the border penalty over the much larger penalty of not treating the tumor properly or having a high level of radiation on a critical area.

Moving to the actual example, the results can be seen in the Maple visualization below:



Optimal solution to the new formulation with a penalty for hitting the critical border

Based on both the visualization as well as the data-output, the optimal solution for this formulation is extremely similar to the previous solution from Formulation 2. This is due to the same reasons as the similarity in the small problem. The algorithm accepts the relatively small penalty resulting from hitting the border of the critical area while it tries to minimize the large penalty resulting from using the slack variables to meet the tumor and critical area treatment constraints. The new optimal solution here is ~57,680,218, slightly higher than the previous one from Formulation 2 and was found using dual simplex.

This problem could be addressed by speaking to doctors and deciding exactly how to prioritize and penalize penalties depending on their view of the risks associated with either breaking the critical and tumor constraints or hitting the border.

Formulation 3 Sensitivity Analysis

Sensitivity analysis for formulation 3 yielded similar results and insights to that of formulation 2.

Enhancements:

Enhancement 1

A major issue in the administration of radiation therapy is ensuring that a patient's movement during the therapy does not reduce the effectiveness of the treatment. Variables such as the patient's breathing pattern and heart contractions can move the target area a matter of millimeters, enough to negatively impact the accuracy of the radiation beams. This first enhancement aims to combat this by minimizing the total number of beams used to meet the upper and lower limits specified by the oncologist. The objective function would switch to minimization of the total number of beams used while keeping the same constraints. No additional data would be necessary outside of the upper and lower limits of the radiation needed for the critical areas and tumor areas, respectively. Limiting the number of total beams used would have adverse effects on critical area impact due to patient movement as well as an overall time reduction due to a decreased number of total beams used.

Enhancement 2

Currently, the oncology department provides images of the tumor area in 2D space. This means photos of the area are taken from the z-plane. Additionally, the beams are cast on the 2D plane corresponding to the image of the tumor area. Enhancement 3 would ask the oncology department for images taken from either the x or y-plane. Doing this would allow the team to create a 3D image of the tumor area. With this, the team would be able to analyze the effectiveness of the beams on different planes and check if further optimization can be achieved in doing so. This would require additional photos and more details on the feasible directions of the radiation beams. The decision variables and constraints would remain from the original problem, but would better capture the actual treatment. Furthermore, the image can gain a 4th dimension of whether the tumor cells are malignant or benign, increasing the amount of decision variables.

Enhancement 3

Radiation beams enter the patient at a specified intensity and dissipate radiation as the beam travels through the patient. Enhancement 3 looks to alter the strength at which the beam enters the patient. Ideally, this would allow the radiation to dissipate before reaching the critical areas. The objective function would remain the same as the original model formulation but the team would introduce a data set of possible beam strength multipliers for each beam. This would effectively increase the number of possible beam combinations by a factor of unique strength multipliers. For example, if the vector b_1 = [0.75, 0.5, 0.25] representing the possible strength adjustments for a beam, the beam X_1 would now be considered as four unique beams (decision variables), each with different beam strengths but the same directionality. The oncology department would have to provide the feasible strength multipliers for each available beam. For the sake of this problem, the strength of the beam would only be reduced rather than increased. This is because increasing the strength of the beam by a factor of 2 would be the same as using 2 of the beam.

Enhancement 4

Chemotherapy can be prescribed in conjunction with radiation treatment to weaken the cancer cells and ultimately minimize the required radiation[1]. However, the chemotherapy process takes several months and tends to have more side effects[2]. Radiation treatment, on the other hand, is more targeted than chemotherapy. Yet, radiation beams hit non-cancerous cells in their path to the tumors, mostly killing these cells (which should be avoided) and can cause unhealthy levels of toxicity in the bloodstream. Therefore, chemotherapy is helpful to try to lessen the amount of radiation required, and then radiation can finish the removal process. In contrast, radiation can be used to fight most of a tumor, and chemotherapy can then be used to flush out any cancerous cells that were missed or are in very sensitive areas (neighboring critical pixels).

Provided this treatment addition, a new model could be formulated which minimizes the total cancer treatment time while abiding by other constraints on how much radiation is actually allowed (with a allowed blood toxicity constraint), consecutive weeks of each treatment, and the existing constraints. This would be especially helpful in treating malignant tumors that need to be killed ASAP with chemotherapy not being an option. Accordingly, the oncologist could adjust the amount of radiation allowed, pushing the limits of tolerable blood toxicity if it means the patient's life would be in imminent danger, regardless of the radiation. Introducing time into the model, though, does incorporate another dimension of variables. Data would need to be gathered on the accepted frequency/duration of treatment to decide how granular the decision variables should be (day/week/month).

As an alternative, since chemotherapy does affect non-cancerous cells, a constraint could be set to minimize combined exposure from chemotherapy and radiation to the non-cancerous cells (separated by critical area or not). Also, multipliers can be assigned to each form of treatment where radiation effects are seen as stronger. This problem's objective could minimize total treatment exposure to non-tumorous cells. To keep the model as a linear program without integer constraints, the multipliers could also be decision variables. The multiplier values could then be categorized by range, bucketing various treatments by their intensity. For example, more frequent chemotherapy sessions would have a higher multiplier, with a similar representation for the radiation multiplier. This could limit the amount of decision variables introduced (whether to perform treatment daily, weekly, or monthly) by incorporating a one-step logic supplement to the problem to categorize the results. That is, the range of the multiplier will correspond with a category for potential strength of treatment option. This setup would require data on the relative strengths of each treatment, which could also be interpreted as a relative success rate given the nature of the case and patient conditions.

Once chemotherapy is included in the discussion, another constraint that can be added regardless of decision variables and objective function is a cost constraint. This constraint can address expense concerns, as not everyone can afford the same types of treatment. Furthermore, this model could even be generalized to help patients before meeting oncologists. Using the cost constraint, patients can try to maximize treatment while maintaining the cost limit.

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[1] https://pubmed.ncbi.nlm.nih.gov/9928562/

[2] https://www.curetoday.com/view/combining-radiation-and-chemotherapy-may-improve-outcomes

This would make more sense then minimizing cost in most cases, as patients likely put more value on their treatment quality than the value of money.

Next, as mentioned before, a possible symptom of radiation treatment can be hazardous blood toxicity levels. Therefore, there should be a constraint that sets a maximum threshold for allowed radiation to mitigate the risk of toxicity. Also, since chemotherapy weakens the immune system, the constraint should decrease according to a recursive function week over week since the patient likely would be able to handle less radiation healthily in later weeks than the beginning ones. This function would be defined by an expert, with an original threshold also set by an expert. Similarly, the lower limit for required radiation will also likely reduce week over week. This would come as the tumor cells would be weakened by the chemotherapy and previous radiation sessions. Like the blood toxicity constraint, the lower limit should decrease according to a function based on historical research and on a case-by-case basis.

To account for the difference in strength of treatment between chemotherapy and radiation, an expert could decide a constant to multiply the radiation decision variables by, which will be called the “damage” constant.

Enhancement 5 Summary

As discussed above, there are numerous enhancements considered for a chemo-radiation treatment schedule. The team deemed it appropriate to include all enhancements in a single model formulation. The enhancements chosen for this model with respective variable decisions can be seen below:

1. Create a 12-week schedule for chemotherapy and radiation treatment while minimizing the exposure to the critical areas and cells neighboring the critical areas.
2. Introduce a constraint that limits radiation treatment due to blood toxicity concerns. The value for this function decreases linearly for this formulation. The initial value for the RHS of the constraint was set accounting for solutions from previous formulations for the original problem to provide context.
3. Adjust the RHS of the lower limit constraint for the tumor treatment, as the lower limit will decrease as the tumor cells become weaker from prior radiation treatment and chemotherapy sessions. The value for this function decreases linearly for this formulation. The initial lower limit value was set based on the original problem.
4. Multiply the radiation treatment by a “damage” constant to account for its added effectiveness over chemotherapy treatment. For the purposes of this model, the damage constant was set to 3, as chemotherapy takes about 3X as long as radiation treatment[3].

The formulation can be seen mathematically below:

[3] https://www.diffen.com/difference/Chemotherapy_vs_Radiation_Therapy

Enhancement Formulation

Let g := treatment length (weeks)

t := week number of treatment such that t ∈ {0,...,g}

y_t := upper limit on radiation associated with blood toxicity danger for week t

L_t := Lower limit on radiation associated with week t

d := treatment strength associated with radiation relative to chemotherapy

Decision Variables:

R_{kt} := number of times beam k is used on week t

H_t := strength of chemotherapy treatment on week t

S_{Tt} := Slack assigned to allow for lower limit (L) violation

S_{Rt} := Slack assigned to allow for upper limit (U) violation

$$Min \quad \sum_{t=0}^{g}\left[\sum_{\forall(i,j)}(dC'\sum_{k=1}^{b}(R_{kt}W_k) + H_t + M_T S_{Tt} + M_R S_{Rt}) + q\sum_{\forall(i,j)}(dD'\sum_{k=1}^{b}(R_{kt}W_k) + H_t)\right]$$

subject to:

$$C'(H_t + d\sum_{k=1}^{b}R_{kt}W_k) - S_{Rt} \le U \; \forall \, t \in \{1,...,g\}, \; \forall \, C_{(i,j)} = 1$$

$$T'(d\sum_{k=1}^{b}R_{kt}W_k + H_t) + S_{Tt} \ge L_t \; \forall \, t \in \{1,...,g\}, \; \forall \, T_{(i,j)} = 1$$

$$\sum_{k=1}^{b}R_{kt}W_k \le y_t \; \forall \, t \in \{1,...,g\}$$

$$y_{t+1} = f(y_t) = y_t - \frac{1}{12}y_0$$

$$y_0 = 5$$

$$L_{t+1} = f(L) = L_t - \frac{1}{12}L_0$$

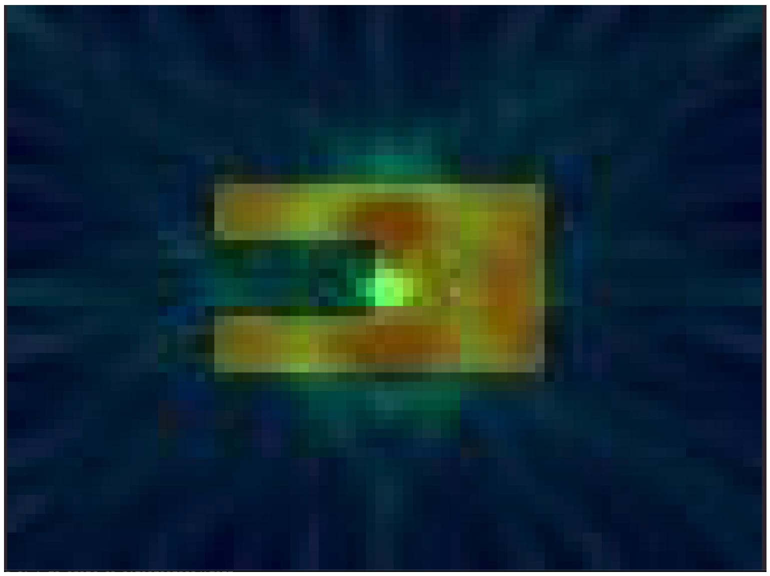
$$L_0 = 10$$

$$X_k \ge 0 \; \forall \, k \in \{1,...,b\}$$

Enhancement Results

The enhancement was feasible and solvable by the barrier optimizer. While the final solution value here was ~216,792, this number is extremely high due to the amount of slack involved in obtaining a solution and the increased number of times slack was used over the course of the 12 treatment “sessions” in the 12 week period. This number is lower than the previous optimal solutions as the penalties used for breaching the critical and tumor constraints were set at 100 and 50, respectively. This was done to make the model prioritize meeting the critical constraints over the tumor constraint in order not to cause harm to the patient's vital critical area.

Looking at the visualization obtained from Maple, there is a notably different solution approach to treating the tumor than from before. In the previous visualizations, the algorithm has tried to treat the tumor by focusing on beams from the right of the image moving towards the left. However, here, the treatment is much more balanced and coming from all around the tumor. While this is able to provide a higher level of treatment to the tumor, it also results in slightly more of the critical area receiving radiation.



Optimal Solution for Enhancement

The main decision variables in this model, the amount of each beam used per week, provide the treatment schedule that pairs with the chemotherapy-by-week decision variables. The visualization above is a total summary of all treatments over the 12 weeks and can be thought of as each week's treatment stacked above one and other. If this image was broken out into 12 separate images, it would display a fainter glow over the tumor for each week. The summary of treatment scheduling graphs shows us how the treatment progresses over the course of the 12 weeks. Radiation is utilized the most in the early stages of treatment and then is rapidly decreased. Chemo is used in a steadily increasing manner for the first 10 weeks and then rapidly decreased for the last 2 weeks of treatment. The number of beams utilized remains relatively similar over the course of treatment.

Moreover, the implementation of chemotherapy proved to be highly useful. The model chose to supplement the radiation with chemotherapy during every week of the 12 week treatment. The amount of chemotherapy used increased each week from ~1.86 in the first to ~1.99 in week 9 and then sharply decreased in week 10 and 11 with only 1.6 and 0.63 used respectively. This can likely be attributed to the gradually decreasing need for tumor damage as the tumor became weaker (the lower limit declined).

Table 1: Summary Results by Week

Week	# of Beams Used	Total Beam Multipliers	Total Chemo Used	Critical	Tumor
0	78	254.88	1.86	166.49	463.32
1	78	233.05	1.87	157.64	414.96
2	78	211.24	1.89	147.68	366.7
3	78	198.72	1.9	142.42	318.35
4	78	175.95	1.92	119.08	270.12
5	78	152.72	1.93	95.48	221.75
6	78	138.78	1.94	84.63	173.41
7	78	122.99	1.96	60.3	125.09
8	78	101.81	1.97	23.5	83.34
9	78	115.31	1.99	43.28	30.89
10	76	51.14	1.6	0	0
11	76	22.53	0.63	0	0

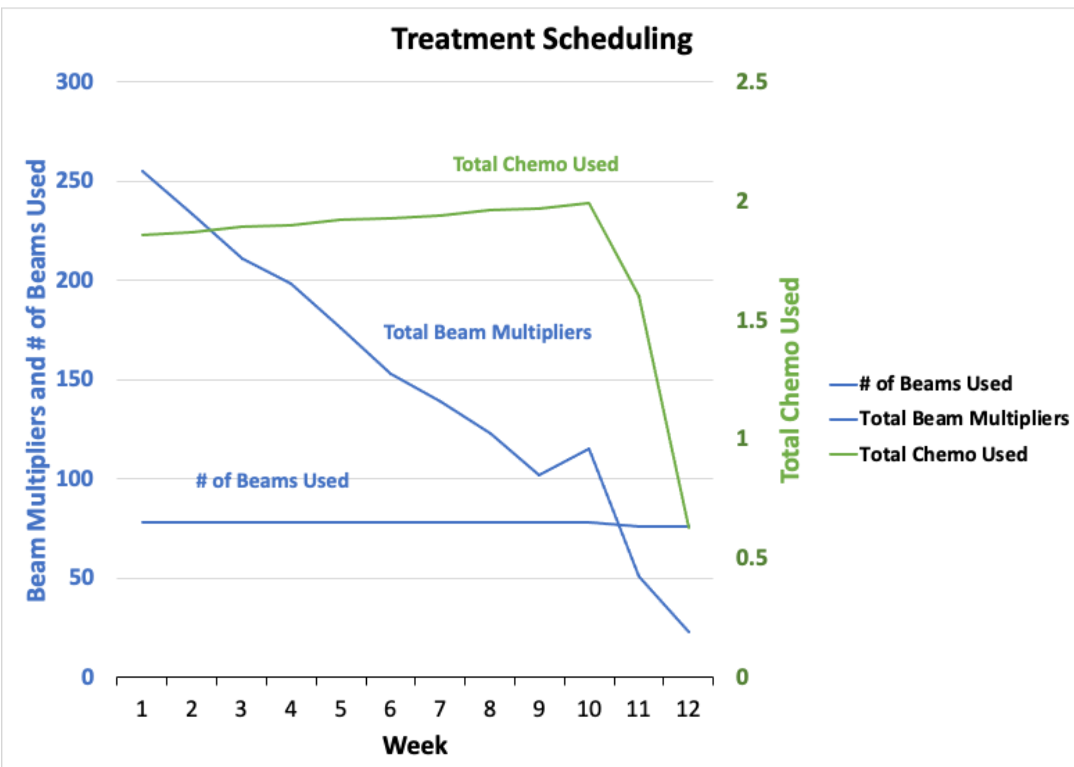


Chart 1: Summary of treatments by type and week

When inspecting the slack decision variables, the enhanced treatment method coupled with the strategy of prioritizing safety of the patients' critical area over treating the tumor reduces the maximum slack values from over 40 in previous solutions to about 23 as the maximum. There are also a lower number of slack variables in use to meet the critical area constraints. This formulation also positively impacted the tumor slack constraints. A large majority of the slack values were below 1 while the maximum amount of slack for these constraints was about 8, while larger slack values were rare. The total amount off slack used decreased each week and finally moved to 0 in weeks 11 and 12 where the model did not need to utilize the slack variables.

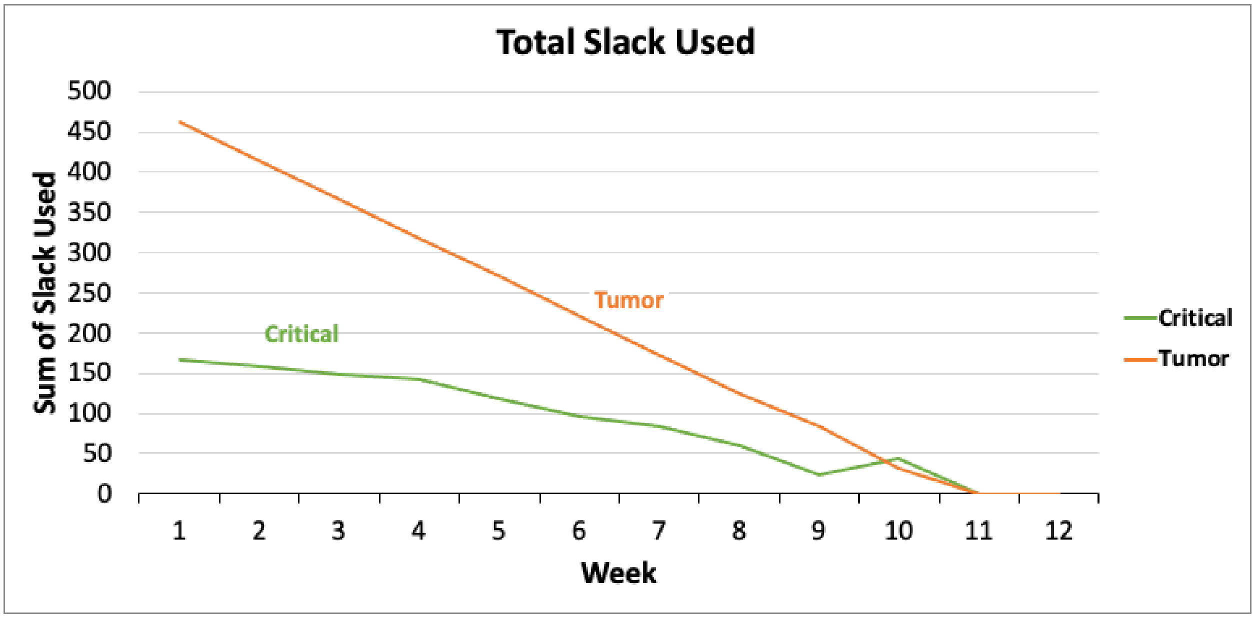


Chart 2: Sum of slack decision variables used each week by area type

Enhancement Sensitivity Analysis

For the enhanced model, sensitivity analysis was used to determine the sensitivity of the right hand side constraints. The team first looked at the upper bound set on the radiation of the critical area. The first set of constraints limits the amount of treatment to the critical area specified by the upper bound. The sensitivity analysis of the upper bound shows that to keep the current basis optimal, the upper bound constraint cannot be changed. Additionally, because the upper bound stays constant week over week, each constraint for the critical area was analyzed because it corresponds to the same right hand side value. The allowable range was calculated using the minimum upper bound and the maximum upper bound for the right hand side. In other words, to keep an optimal basis, the critical area upper bound cannot be changed.

The second set of constraints is the minimum radiation required for treating the tumor area. This value decreases week over week and therefore must be analyzed for a specified week. In the sensitivity analysis conducted, the lower bound set forth by the team was analyzed. This was performed because week 1 determined the remainder of the week's tumor radiation requirements. The minimum and maximum values for the lower bound to keep the basis optimal are 9.99995 and 10.00004 respectively. The team concluded that the lower bound limit must stay the same to keep the basis optimal. Because there are a large number of decision variables that share the same right hand side value, it is expected that the bounds would not have large ranges to keep the optimal basis.

Finally, the team analyzed the blood toxicity constraints with right hand side values y_t. These values also change week over week from the initially specified limit. The team set the limit to be 5 for the actual example and ensured that the toxicity from the beams is less than the limit. Because the values for blood toxicity decrease over each week, the team again looked at the sensitivity for week 1 of treatment. Sensitivity of the right hand side determined that the current basis is optimal for all values of blood toxicity equal to 3.4456 and higher in week 1.

After conducting sensitivity analysis on the right hand side of the constraints, it is evident that the current formulation does not have tight constraints for the blood toxicity. For this formulation, the objective value is 216792. Decreasing the blood toxicity constraint to 4 yields the same objective value function. Retesting the model with an upper bound value of 4, lower bound value of 9, and blood toxicity constraint of 4 yielded similar results. The upper and lower bound were tight where the blood toxicity could be decreased to 2.15 and increased indefinitely. This tells the team that the doctors can be more aggressive with the blood toxicity constraint than the team was when testing the model.