# Help Cure Cancer

Course Project

OR7245: Network Analysis and Advanced Optimization

- Under Professor Ozlem Ergun

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# Contents

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# Motivation

Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. At low doses, radiation is used in x-rays to see inside your body, as with x-rays of your teeth or broken bones. At high doses, radiation therapy kills cancer cells or slows their growth by damaging their DNA. Cancer cells whose DNA is damaged beyond repair stop dividing or die. When the damaged cells die, they are broken down and removed by the body. Radiation therapy does not kill cancer cells right away. It takes days or weeks of treatment before DNA is damaged enough for cancer cells to die. Then, cancer cells keep dying for weeks or months after radiation therapy ends.

Radiation therapy seems like a method with no flaws. However, radiation not only kills the cancer cells, but it also affects nearby healthy cells, and this damage to healthy cells causes side effects. Furthermore, a target area of radiation (see Figure-1) is likely to contain not only tumorous areas but also critical areas where only a small amount of radiation (or none at all) is allowed. With a small number of beamlets, many beams may need to pass through the critical area to reach the tumorous region, making it difficult to deliver a high dosage over the tumorous region and low dosages over critical areas. This problem is particularly severe in the brain, where every non-cancerous cell is critical.

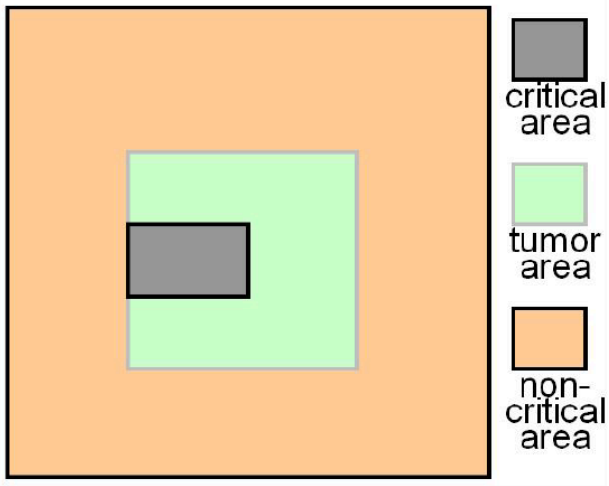


*Figure-1: Areas near a tumorous region*

Thus, the most crucial task is to determine the intensity levels to set for the beams for the radiation delivery so as to maximize the radiation dosage to the tumorous area while minimizing the dosage to the critical area.

# Provided Data

The following data has been provided by the radiotherapy oncologists:

- Sample 2D images of the tumorous and critical areas, along with a set of possible beamlet origins
- Each provided image has been transformed into a binary matrix where each element of the matrix corresponds to a pixel in the original image, where a 1 entry indicates the presence of the attribute shown in the image. For example, the binary matrix that corresponds to the tumor area will have a 1 entry if a tumor was present at the corresponding pixel and 0 otherwise. Note that the tumorous and critical areas need not be rectangular, and multiple tumorous regions may exist within the considered target region.
- The beamlet data has been converted to a set of relative intensity matrices, where each matrix corresponds to the relative intensity delivered by a particular beam, normalized between 0 and 1 inclusively. This is the data that captures the variation in the intensity of radiation as the beam passes through a region and also the imprecision in a particular beam. Each entry of a matrix again corresponds to a pixel in the image of the target area, such that an entry in the matrix is nonzero only if the beam passes through the corresponding pixel.
- The oncologists have provided 2 sets of data, one corresponding to a small example for testing purposes and another to an actual case of a patient with a brain tumor. We have transformed the data and provided them to you in 2 separate folders (*smallexample* and *actualexample*). Each folder contains information regarding the number of beams considered, the number of rows and columns in the provided images, and lower and upper limits on the amount of radiation delivery required over the tumorous areas and allowed over the critical areas, respectively.

**Goal:** The oncologist wants us to determine the intensity levels to set for the beams in the provided examples, but even more so, to provide general mathematical formulations and corresponding AMPL code that can then be used on other cases as well.

# Mathematical Formulation - Task 1

Rather than diving into solving the problem straightaway, we first looked at the data set that had been provided to us. We went through the folder '*max_matrix*', which essentially taught us how to read the beamlet matrices into AMPL and a set of basic AMPL code upon which we could use.

Next, we looked at the data in folders '*smallexample*' and 'actual*example*'. The specifications provided were the following:

*Table-1: Parameters in the data sets provided*

| Parameters | smallexample | actual example |
|---|---|---|
| **Number of Beams ( = Beamlet Matrices)** | 5 | 126 |
| **Vertical Pixel resolution ( = Number of columns)** | 8 | 60 |
| **Horizontal Pixel resolution ( = Number of rows)** | 8 | 80 |
| **Maximum Dose Allowed over Critical Area** | 2 | 2 |
| **Minimum Dose Allowed over Tumor Area** | 10 | 10 |

The goal is to determine the intensity levels to set for the beams to maximize the radiation dosage to the tumorous area while minimizing the dosage to the critical area. Also, we had to make sure that the upper and lower limit of radiation over critical and tumor area respectively was satisfied.

The different parameters are as follows:

1. Number of beams (K): *num_beams*
2. Number of rows (m): *num_rows*
3. Number of columns (n)*: num_cols*
4. Beamlet matrix (B): *beams (k, i, j)*
5. Critical Matrix (C): *critical (i, j)*
6. Tumor Matrix (T): *tumor (i, j)*
7. Upper Limit for radiation on Critical area (u): *critical_upperlimit*
8. Lower Limit for radiation on Tumor area (l): *tumor_lowerlimit*

where i = row index,

j = column index

k = matrix index

The decision variable is the intensity levels of the various beams. Let this be '*weights (k)*' for each beamlet matrix (= W).

## Subtask - 1

We thought of a model that minimized the radiation dosage to the critical area subject to constraints of radiation dosage to every cell in tumor area to be greater than the lower limit and radiation dosage to every cell in critical area to be lower than the upper limit.

$$\text{minimize Critical\_Dosage: } \sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j)$$

subject to

(1) Cell Dosage over Tumor Area:

$$\sum_{k=1}^{K} W(k) \times B(k,i,j) \times T(i,j) \geq l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

(2) Cell Dosage over Critical Area:

$$\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) \leq u \times C(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) \geq 0, \forall k = 1,2,...,K$$

## Subtask - 2

The limits can be such that there are no feasible solutions. We would need to keep adjusting the limits until a feasible solution exists. To help with this process, we formulated a model that allows for a slight variation on the limits where it is necessary to ensure feasibility by penalizing whenever the critical constraint is violated.

1 new parameter was defined: penalize_critical ($p_c$)

1 new variable is also defined: *z (i, j)*

This variable z (i, j) is defined to account for the critical area constraint. It is similar to the way that a piecewise linear function is replaced.

$$\min z$$

$$\text{subject to } z \geq cx_i + d_i, \forall i$$

$$AX \geq b$$

Thus, the model is:

minimize Critical_Dosage: $\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k)\times B(k,i,j)\times C(i,j) + p_c \times (\sum_{i=1}^{m}\sum_{j=1}^{n} z(i,j))$

subject to

(1) Cell Dosage over Tumor Area:

$$\sum_{k=1}^{K} W(k)\times B(k,i,j)\times T(i,j) \geq l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

(2) Piecewise Linear for Critical area:

$$z(i,j) \geq \sum_{k=1}^{K} W(k)\times B(k,i,j)\times C(i,j) - u \times C(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) \geq 0, \forall k = 1,2,...,K$$

$$z(i,j) \geq 0, \forall i,j$$

## Subtask - 3

To address the problem that images are limited in resolution, we formulated a model similar to that of subtask-2 that penalizes radiation delivery to parts of the non-critical area that border a critical area.

For this, we generated a matrix that borders a critical area. Let this be called $C_b\ (i, j)$. This matrix is generated by running a Python code to find the neighbors of the critical area.

1 new parameter was defined: penalize_critical_boundary ($p_b$)

Thus, the model is:

minimize Critical_Dosage: $\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k)\times B(k,i,j)\times C(i,j) + p_c \times (\sum_{i=1}^{m}\sum_{j=1}^{n} z(i,j)) +$

$$p_b \times (\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k)\times B(k,i,j)\times C_b(i,j))$$

subject to

(1) Cell Dosage over Tumor Area:

$$\sum_{k=1}^{K} W(k)\times B(k,i,j)\times T(i,j) \geq l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

(2) Piecewise Linear for Critical area:

$$z(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) - u \times C(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) \geq 0, \forall k = 1,2,...,K$$

$$z(i,j) \geq 0, \forall i,j$$

## Subtask - 4

**Enhancement-1:** One possible enhancement could be a *gradual decreasing penalization* to the non-critical area in terms of closeness to the critical area. The more closer the non-critical cell to the critical area, higher the penalization for dosage to that cell. However, do not penalize after a certain distance from the critical area. For this, a distance threshold has been defined. This enhancement could decrease the damage that is done to the non-critical area, and thus not stop growth or kill any of the healthy cells. Additional data that is required for this enhancement is for the oncologist to provide a distance threshold. This model can be derived from model for subtask-3.

**Enhancement-2:** Another enhancement could be to restrict the radiation dosage on the tumor area by putting an upper limit on it. This could help to decease the radiation dosage to the non-critical area. This model can be derived from model for subtask-4: enhancement-1.

**Enhancement-3:** While the solutions discussed so far aim at penalizing the excess radiation dosage on the critical cells, one might be not able to escape damage to the critical cells if the radiation is beyond the upper limit specified. One additional measure could be to forgo the critical cells that have been affected as lost cause and try to minimize the number of critical cells exposed to excess radiation. To this effect, we can add an additional variable that tracks the number of critical cells with excess radiation and add a penalty multiplier of this variable to the objective of the model of subtask-3.

## Subtask - 5

**Enhancement-1:** This model can be derived from model for subtask-3 with the addition of the following parameters:

- Distance-to-Critical Matrix: Distance of cells from boundary of critical area. This is used for gradual decrease in penalty. Let this matrix be $D_c\ (i,j)$.
- A distance threshold that does not penalize cells that are further away from this threshold. Let this be $d_t$.

Also, a new variable similar to z in subtask-3 is defined. This distance_clipped be $DC\ (i,j)$.

minimize Critical_Dosage: $$\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) + p_c \times (\sum_{i=1}^{m}\sum_{j=1}^{n} z(i,j)) +$$

$$p_b \times (\sum_{i=1}^{m}\sum_{j=1}^{n} DC(i,j))$$

subject to

(1) Cell Dosage over Tumor Area:

$$\sum_{k=1}^{K} W(k) \times B(k,i,j) \times T(i,j) \geq l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

(2) Piecewise Linear for Critical area:

$$z(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) - u \times C(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

3) Piecewise Linear for Boundary area:

$$DC(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times (d_t - D_c(i,j)) \times (1 - C(i,j) - T(i,j)), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) \geq 0, \forall k = 1,2,...,K$$

$$z(i,j) \geq 0, \forall i,j$$

$$DC(i,j) \geq 0, \forall i,j$$

**Enhancement-2:** This model can be derived from model for subtask-4: enchantment-1 with the addition of the parameter:

- Upper Limit for radiation on Tumor area ($u_t$): *tumor_upperlimit*

minimize Critical_Dosage: $\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) + p_c \times (\sum_{i=1}^{m}\sum_{j=1}^{n} z(i,j)) +$

$$p_b \times (\sum_{i=1}^{m}\sum_{j=1}^{n} DC(i,j))$$

subject to

(1) Cell Dosage over Tumor Area:

$$u_t \times T(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times T(i,j) \geq l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

(2) Piecewise Linear for Critical area:

$$z(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) - u \times C(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

3) Piecewise Linear for Boundary area:

$$DC(i,j) \geq \sum_{k=1}^{K} W(k) \times B(k,i,j) \times (d_t - D_c(i,j)) \times (1 - C(i,j) - T(i,j)), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) \geq 0, \forall k = 1,2,...,K$$

$$z(i,j) \geq 0, \forall i,j$$

$$DC(i,j) \geq 0, \forall i,j$$

# Implementation in AMPL - Task 2

*Table-2: File names used for the two examples*

| File Names | for smallexample | for actualexample using updated model |
|---|---|---|
| | | |
| **Model** | small_model.mod | actual_model.mod |
| **Data** | small_data.dat | actual_data.dat |
| **Run** | small_run.run | actual_run.run |
| **Output for Weights** | weight_results.out | actual_results.out |
| **Output for weights * Beams** | small_results.out | actual_results.out |

For all subtasks, the visualization is not clear for *smallexample* since the dimension is $8 \times 8$, which is very small. Thus, it is not attached in the report.

## Subtask-1

**For actualexample:**

When we used the model (described in Task-1 Subtask-1) for the actualexample, many of the constraints in (2) were violated. Since the actualexample has data for an actual patient with a brain tumor, violating any constraint for cell dosage over critical area would be devastating for the patient. Thus the model was modified to penalize for every constant in (2) that is violated.

1 new parameter was defined:

$$\text{penalize (p)} = 10$$

The updated model is as follows:

minimize Critical_Dosage:

$$\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j) + p \times \sum_{i=1}^{m}\sum_{j=1}^{n}((\sum_{k=1}^{K} W(k) \times B(k,i,j) \times C(i,j)) - u \times C(i,j))$$

subject to

(1) Cell Dosage over Tumor Area:

$$\sum_{k=1}^{K} W(k) \times B(k,i,j) \times T(i,j) >= l \times T(i,j), \forall i = 1,2,...,m; j = 1,2,...,n$$

$$W(k) >= 0, \forall k = 1,2,...,K$$

**Visualization in MAPLE**

The output file for both examples (i.e., output for weights * beams) is used to visualize the radiation dosage in MAPLE. The output files are '*small_results.out*' and '*actual_results.out'* for *smallexample* and *actualexample* respectively.

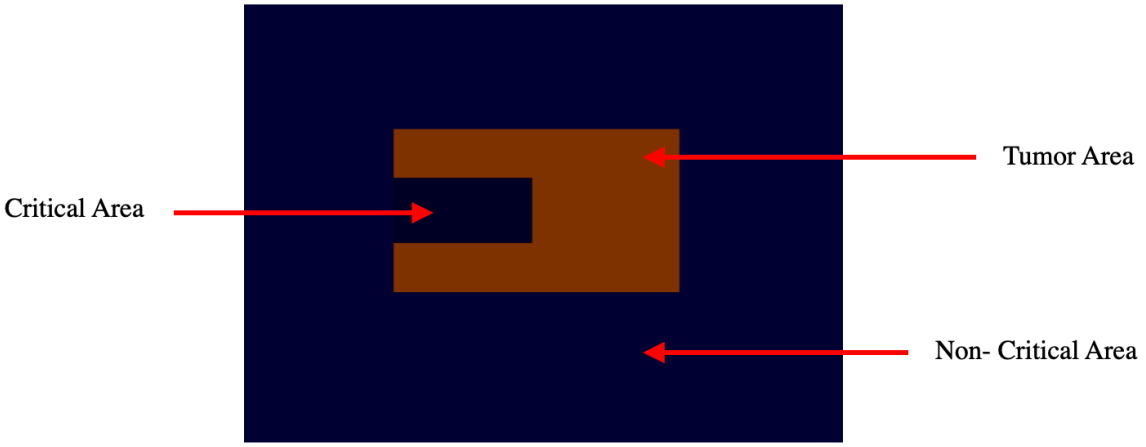


*Figure-2: Tumor, Critical, and Non-critical areas*

As we can see in figure-2, the target area is covering the critical area. So we have to be careful while sending dosage to the tumor area.

*Figure-3: Radiation Dosage over the cell for actualexample*

In figure-3, the radiation dosage can be identified by the bright colors. We observe that the tumor area is getting radiation properly. However, a little of the radiation is also sent to the critical area. Further, a lot of the healthy cells are also getting radiation.

## Subtask - 2

Let the value of parameter penalize_critical ($p_c$) = 10.

**Visualization in MAPLE**

The output file for both examples (i.e., output for weights * beams) is used to visualize the radiation dosage in MAPLE. The output files are '*small_results.out*' and '*actual_results.out'* for *smallexample* and *actualexample* respectively.

*Figure-4: Radiation Dosage over the cell for actualexample*

As seen in figure-4, the visualization is same as for subtask-1 for *actualexample*. This is due to the fact that the updated model for *actualexample* in subtask-1 is written in a similar manner to the model in subtask-2. Thus there is no difference in the radiation dosage to all the cells in subtask-1 and subtask-2.

## Subtask - 3

Let the value of penalize_critical_boundary ($p_b$) = 5.

This model penalizes radiation delivery to parts of the non-critical area that border a critical area. For this, a matrix is generated that borders a critical area. Let this be called $C_b\,(i, j)$. This matrix is generated by running a Python code to find the neighbors of the critical area.

**Visualization in MAPLE**

The output file for both examples (i.e., output for weights * beams) is used to visualize the radiation dosage in MAPLE. The output files are '*small_results.out*' and '*actual_results.out'* for *smallexample* and *actualexample* respectively.

*Figure-5: Radiation Dosage over the cell for actualexample*

As seen in figure-5, the visualization is different from that for subtask-1 for *actualexample*. This is due to the fact that this model penalizes radiation delivery to parts of the non-critical area that border a critical area. Thus there is less radiation dosage to the non-critical area than the previous subtasks.

## Subtask - 4

**For Enhancement-1:** Let the distance threshold, $d_t = 3$.

*Figure-6: Radiation Dosage over the cell for actualexample*

As seen in figure-6, the visualization is different from that for the previous subtasks for *actualexample*. This is due to the fact that this model has a *gradual decreasing penalization* to the non-critical are in terms of closeness to the critical area. The more closer the cell to the critical area, higher the penalization for dosage to that cell. However, the model does not penalize after a certain distance from the critical area. Thus there is less radiation dosage to the non-critical area than the previous subtasks. The bright colors fade as you go further away from the critical area.

**For Enhancement-2:** Let Upper Limit for radiation on Tumor area ($u_t$) = 70.

*Figure-7: Radiation Dosage over the cell for actualexample*

The radiation dosage is same as that of enhancement-1 since the cluster of bright colors is the same in both the visualizations.

# Discussion

Each of the subtasks in Task-2 has a different model, and thus a different objective function value for both the data sets- *smallexample* and *actualexample*.

*Table-3: Objective function values for the two examples*

| Subtasks | Objective Value for smallexample | Objective Value for actualexample |
|---|---|---|
| **1** | 0 | -83.481.41 |
| **2** | 0 | 10325.26 |
| **3** | 246.4 | 10668.90 |
| **4: enhancement-1** | 669.71 | 11158.57 |
| **4: enhancement-2** | 669.71 | 11158.57 |

From subtask-1 to subtask-4 (enhancement-1), we observe that the objective function value increases as we go from one subtask to the other. This is because each of these subtasks builds from the previous subtask by adding a penalization term to the objective. The common part in all these subtasks is to minimize the radiation dosage to the critical area. The objective value increases when:

- there is radiation dosage to the non-critical area (subtask-3 and subtask-4-enhancement 1).
- there is no feasible solution due to the limits and thus there is relaxation of the limits (subtask-2).

The difference in these objective function values is also seen by the visualization of the radiation dosage to the cells. The radiation dosage is marked by the bright colors in the visualizations. In subtask-3, the radiation dosage to the non-critical area is less than in subtask-2. Thus, there is a decrease in the bright color in the radiation dosage to the non-critical area in subtask-3. Similarly, the radiation dosage to the non-critical area in subtask-4 (enhancement-1) decreases gradually as you go further away from the critical area into the non-critical area. This can be seen by the fading away of the bright colors in the non-critical area.

There is no change in objective value from enhancement-1 to enhancement-2. This means that the constraint for upper limit to the radiation dosage is satisfied for all cells in the tumor area. This constraint can be made tighter. The same is observed from the visualization of the 2 enhancements. The radiation dosage is same for both the enhancements since the cluster of bright colors is the same in both the visualizations.

## Sensitivity Analysis on Parameters

- **For Subtask-3:** The y-axis is the objective function and the x-axis is the penalty on critical area for different ratio of penalize_critical_boundary ($p_b$) to penalize_critical ($p_c$). As you can see in figure-7, the objective value increases as the ratio of penalties increases. However, the number of penalized critical cells and the number of penalized critical boundary cells remain almost constant throughout. Thus the increase in the objective function value is solely due to the increase in the ratio of penalties. This can also be seen in figure-8 where the y-axis is the logarithmic of objective value.

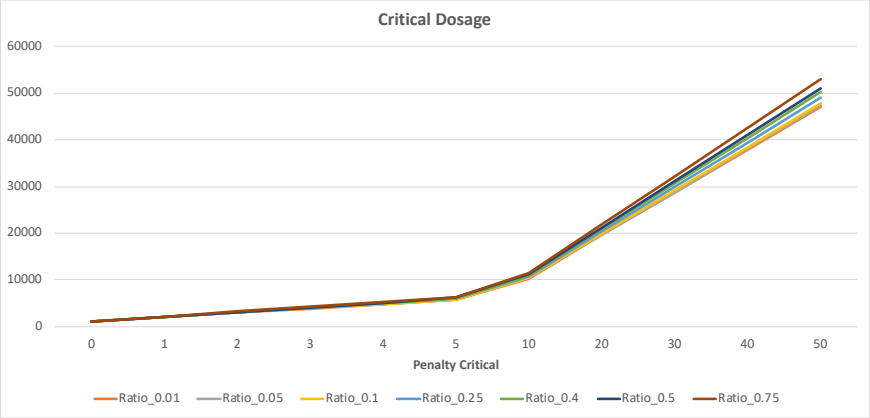


*Figure-8: Objective function value for different Ratio of $p_b/p_c$*

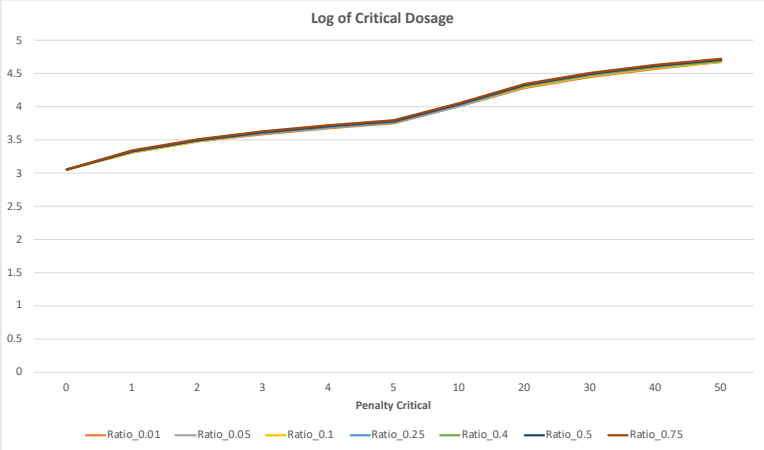


*Figure-9: logarithmic of Objective function value vs Ratio of $p_b/p_c$*

- **For Subtask-2**: The y-axis is the objective function and the x-axis is the penalize_critical ($p_c$). As you can see in figure-9, the objective value increases as the penalty increases. However, the number of penalized critical cells remains the same throughout. Thus the increase in the objective function value is solely due to the increase in the penalty.

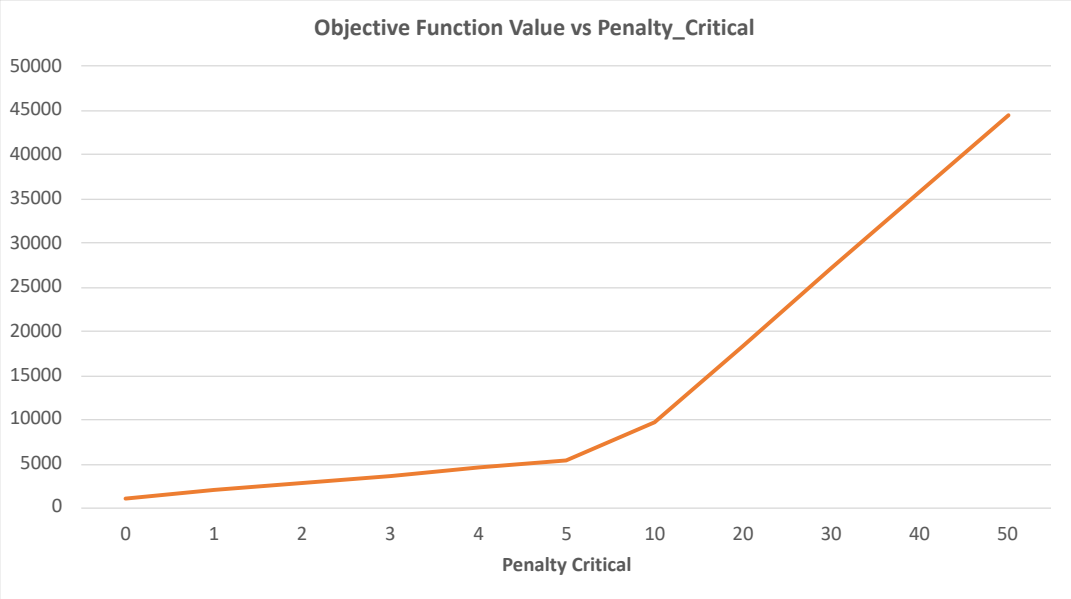


*Figure-10: Objective function value vs $p_c$*