FINAL PROJECT SEMESTER 8 - 2022

COMBINED CHEMO AND RADIATIVE THERAPIES IN CANCER TREATMENT

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Contents

1 Introduction

To finish this fourth year of our degree in the major "Applied mathematics and modeling", we had to choose a subjet for the semester project. We wanted to work on a concrete subject that can concern everyone. Thereby, having the possibility to apply our skills in a new area, by modeling and understanding the evolution of tumor cell density according to the treatment, appeared like a good opportunity. The aim of the project is to see how a simple mathematical model can show the efficiency of new cancer therapies combining clinical chemotherapy and radiation treatment sequences, answering the following question:

To what extent can the combination of radiotherapy and chemotherapy be more effective than using only one of those therapies?

Firstly, we will describe the process in a theoretical setting, explaining some important keystones in order to make the subject understandable, then we do a presentation of our computational part, including several tests and some explanations of the obtained results.

2 Model for cancer growth and therapy

2.1 Definition of Cancer

Cancer is a disease that is characterized by the uncontrolled proliferation of cells that have been genetically mutated in a "harmful" way. These cells proliferate to form tumors (from 100,000 cells), which become dangerous when the cancer cells start spreading to neighboring areas instead of remaining clustered together (metastasis).

There are various medical solutions to slow down the proliferation of cancer cells, including chemotherapy, radiotherapy, which we will define later, as well as combined therapy, which consists combining these two treatments.

2.2 Tumor Growth Modeling

A tumor is an abnormal mass of tissue that forms when cells grow and divide more than they should or do not die when they should.

Tumors may be benign (not cancer) or malignant (cancer). Benign tumors may grow large but do not spread into, or invade, nearby tissues or other parts of the body. Malignant tumors can spread into, or invade, nearby tissues. They can also spread to other parts of the body through the blood and lymph systems.

The tumor growth can be modelled as an Exponential growth, meaning that the tumor can grow exponentially without any capacity constraints until the death of the patient. Nevertheless, this process is only biologically sound in case of small tumors.

Therefore, one usually uses the Gompertz Model, to consider the increased of the tumor volume. It is described by:

$$\frac{dN(t)}{dt} = \rho N(t) \log\left(\frac{K}{N(t)}\right)$$

with N is the evolution of tumor cell number, ρ the growth rate and K the carrying capacity.

2.3 Radiation Effect Modeling

Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill carcinogenic cells and shrink tumors. Radiation therapy most often uses X-rays, but protons or other types of energy also can be used. It is a local treatment, that is not harmful by itself but can cause side effects afterwards. Radiation therapy damages cells by destroying the genetic material that controls how cells grow and divide. 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. While both healthy and cancerous cells are damaged by radiation therapy, the goal of this treatment is to destroy as few healthy cells as possible. Normal cells can often repair much of the damage caused by radiation.

Commonly, the quantitative prediction of radiation effects is done with a linear quadratic model.

It describes that the number of surviving cells after being irradiated by a certain dose of radiation takes the form of an exponential function with a linear and a quadratic term.

This model is described by :

$$\frac{dN(t)}{dt} = -(\alpha d(t) + \beta d(t)^2)N(t)$$

with α the patient-specific radiosensitivity parameter and $\frac{\alpha}{\beta}$=10. There can be a correlation between the two parameters α and ρ.

2.4 Chemotherapy Effect Modeling

Chemotherapy is a treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. It affects all cells of the body.

Chemotherapy may be given by injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery or radiation therapy.

Though chemotherapy is an effective way to treat many types of cancer, chemotherapy treatment also carries a risk of side effects. Some chemotherapy side effects are mild and treatable (nausea, vomiting, hair loss) while others can cause serious complications (heart problems, nerve damage).

Each chemotherapy session is called a cycle. Each cycle is followed by a rest period. This period helps the body to recover from the effects of the chemotherapy.

The chemotherapy effects can be simulated with the log cell kill model. It subtracts a certain fraction of cancer cells based on the drug concentration.

The model can be described by :

$$\frac{dN(t)}{dt} = -\beta_c C(t) N(t)$$

with β_c the chemotherapy effect per dose and $C(t)$ the drug concentration for a certain time t.

The $C(t)$ is assumed as an exponential decay process, equal to :

$$C(t) = C_{max} e^{-\frac{\ln(2)}{halflife} t}$$

2.5 Final Model

As our goal is to study combined chemo and radiative therapies, we need to combine our three models to obtain the following differencial equation:

$$\frac{dN(t)}{dt} = \underbrace{\rho N(t) \log\left(\frac{K}{N(t)}\right)}_{\text{Growth}} \underbrace{-\beta_c C(t) N(t)}_{\text{Chemotherapy}} \underbrace{-(\alpha d(t) + \beta d(t)^2) N(t)}_{\text{Radiation}}$$

However, not only this modeling will be studied. We will focus also on the growth of the tumor alone and the separated effect of chemo therapy and radiative therapy.

3 Numerical Methodology and Experiments

3.1 Initialization

To start the numerical simulation of our problem, we had to initialize problem parameters. As we have no knowledge regarding this area, we had to lead some researches in order to find the best values. We found some mean value for most of parameters thanks to the article[1]. For example, we took a carrying capacity of 20, and we decided to start with 5 cancer cells.

[1] C. Geng, H. Paganetti, and C. Grassberger. Prediction of treatment response for combined chemo- and radiation therapy for non-small cell lung cancer patients using a bio-mathematical model. *Scientific Reports*, 7, 2017

One of the difficulties was to find the maximal injection dose for the chemotherapy and the radiotherapy (C_{max}, d_{max}) and the half-life of the chemotherapy. As it was too difficult to find some information on internet, we asked some friends who are working in this area as nurses, and they gave us a very useful article[2]. We found out that the maximum injection dose for the radiotherapy was around 2 Gy. Going past this value can be dangerous for the patient.

[2] S. Petit and F. Castaldo. Les anticancéreux oraux. *Onconews*, 8, 2014

For the chemotherapy, the value of C_{max} has large variation; it goes from 0.5 to 3 mg. We therefore decided to choose a mean value around 1.5 mg.

Here are our final values :

```
alpha=0.16
beta=alpha/10
betaC=0.028
pho=7.23*10**-3
K=20
N=5
n=365
time=365
hf=23
Cmax=1.5
dmax=2 #2 gy sinon trop dangereux pour le corps
lambdat=0.03
eps=1e-3
Nmax=10000
```

3.2 Chosen Method

As we had to solve a first order differential equation, we could choose between Explicit Euler and Runge Kutta. As Runge Kutta is a fourth order method and is more stable than the Explicit Euler, we decided to take this one. The formula is :

$$y_{n+1} = y_n + h\left[\frac{1}{6}k_1 + \frac{1}{3}k_2 + \frac{1}{3}k_3 + \frac{1}{6}k_4\right] \quad \text{avec} \quad \begin{cases} k_1 &= f(t_n, y_n) \\ k_2 &= f(t_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_1) \\ k_3 &= f(t_n + \frac{1}{2}h, y_n + \frac{1}{2}hk_2) \\ k_4 &= f(t_n + h, y_n + hk_3) \end{cases}$$

We discretized our model over one year (T=365), with a step equal to one (n=365), representing a day.

3.3 Chemo and Radio therapies separatly

First of all, we want to model the case where there is no treatment. There will only be the tumor and we will see an exponential growth as mentionned before.

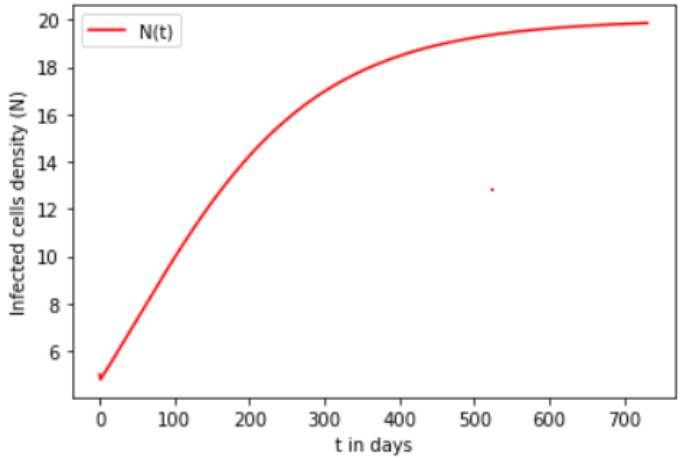

Figure 3.1: Evolution of the tumor cell density without treatment

We can see that the tumor stops growing at one point when the tumor cells density reach the carrying capacity K.

Afterwards, we will add a certain treatment.

We start with the chemotherapy. We test a first treatment (treatment1) where we apply chemotherapy the first and the last three months of the year.

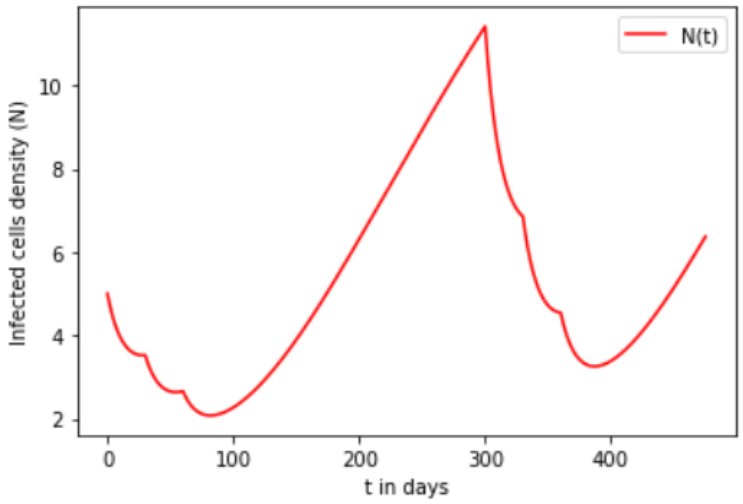

Figure 3.2: Evolution of the tumor cell density for treatment1

As a result of an ordinary differential equation, we expect to have a fonction which is C^1, which is not the case. This can be explained by the fact that the chemo and radio therapies are discrete (We use them in a certain interval). Therefore, some corner points are observed on our graphics.

We also tried a second treatment (treatment2) where we apply the chemotherapy once a month during one year.

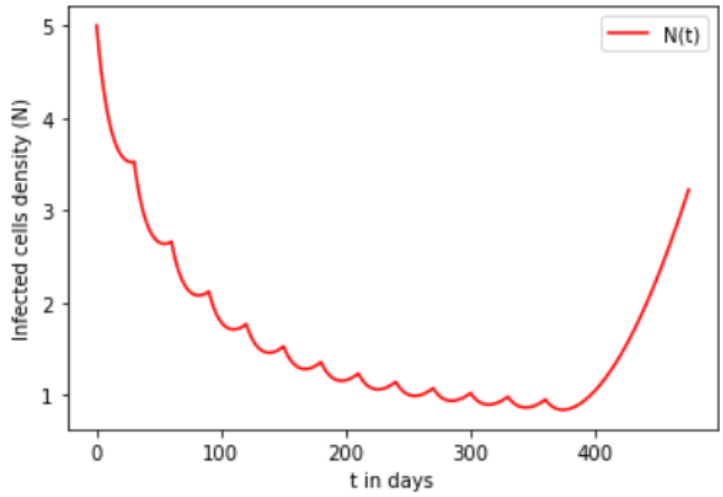

Figure 3.3: Evolution of the tumor cell density for treatment2

We observe that those kinds of treatments reduce the tumor cell density by following an exponential decrease. However, even if we use this treatment for a long time, as soon as we stop it, the tumor will start growing up again.

Then, we chose to model the radiotherapy only. By following some treatments that are considered in some articles, we apply the radiotherapy 5 days a week, during 3 random weeks over 2 months. We repeat this process two times during the year. We obtain the following results.

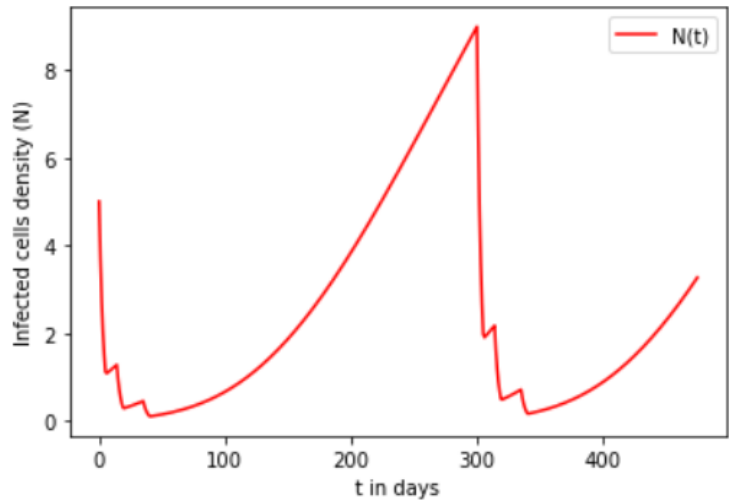

Figure 3.4: Evolution of the tumor cell density for treatment1

We do exactly the same, but three times per year, to simulate a whole year of radiotherapy.

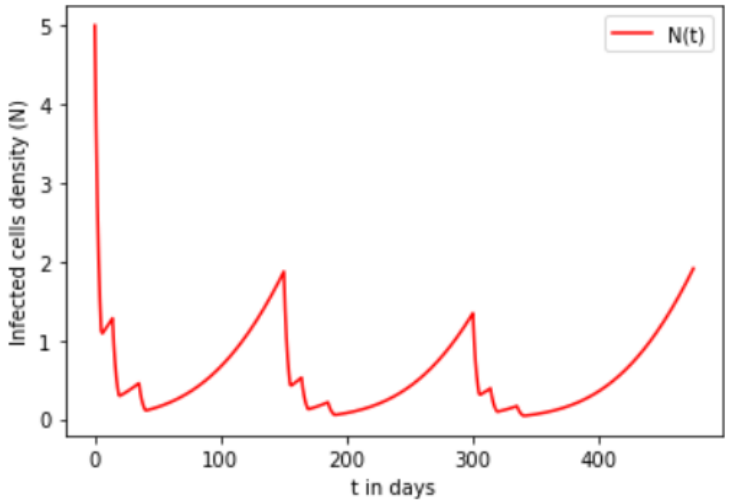

Figure 3.5: Evolution of the tumor cell density for treatment2

After each week of radiotherapy, the tumor cell density decreases drastically but we notice that it never kills the tumor. Indeed, at the end of the treatment the tumor cell density increases again.

We can conclude that the radiotherapy seems not effective enough and that it might be wise to combine both radio and chemo therapy.

3.4 Combined therapy

Afterwards, we therefore tried to do quite the same treatments, by combining chemo and radio therapies.

- In the first treatment (treatment1) we apply the radiotherapy when the chemo is at Cmax/2, during the first and the last 3 months of the year.
- In the second one (treatment2), we do exactly the same process but during the whole year.
- And in the third one (treatment3), we just tried to do 3 months of chemo followed by two months of radiotherapy.

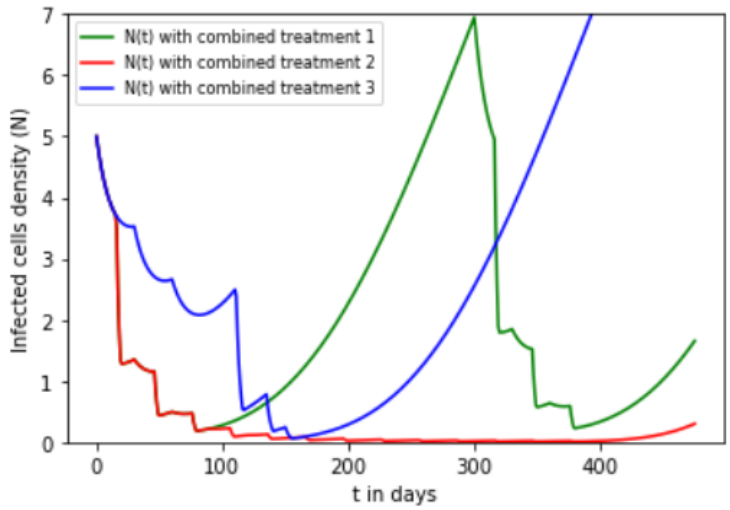

Figure 3.6: Comparaison of the evolution of the tumor cell density for each treatment

We can observe that the decrease is more significant than when we were using one of those therapies. We can verify it by printing the minimum value reached during each treatment.

```
Minimum for chemo during the first and the last 3 months ->  2.079
Minimum for chemo during the whole year ->  1
Minimum for radio during the first and the last 2 months ->  0.109
Minimum for radio during the whole year ->  0.041
Minimum for combined therapy while applying radio when chemo is at Cmax/2 during the first and the last 3 months ->  0.182
Minimum for combined therapy while applying radio when chemo is at Cmax/2 during the whole year ->  0.008
```

In each case, the tumor cells density goes under 1, but it never kills the disease. The best treatment here appeared to be the combined chemo and radio therapy during the whole year.

Now the question that we can think about is : would modifying the Cmax and the dmax be sufficient to eradicate the tumor ?

We now put Cmax and dmax at 3. Here is the result :

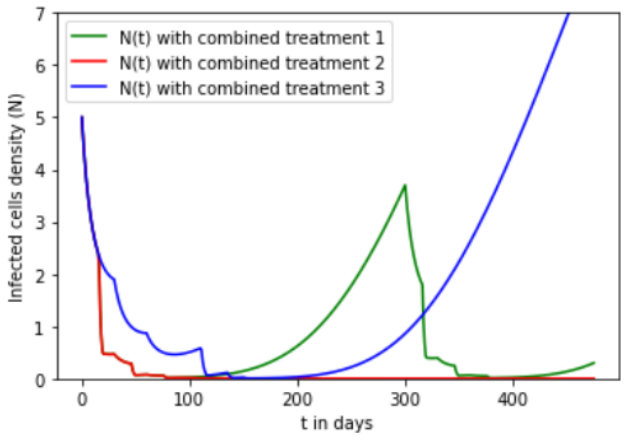

Figure 3.7: Comparaison of the evolution of the tumor cell density for treatment1, treatment2 and treatment3 with Cmax and dmax at 3

We can see that the second treatment is effective enough to eradicate the tumor, contrary to the two others. We could think that it's a good point but the dose administrated to the patients would be too high, and it would be too dangerous for them.

One of the treatments that is actually used today is to do like 3 months of chemotherapy and then, when the tumor cells density would be over 2 for example, we would apply the radiotherapy. Here is an example :

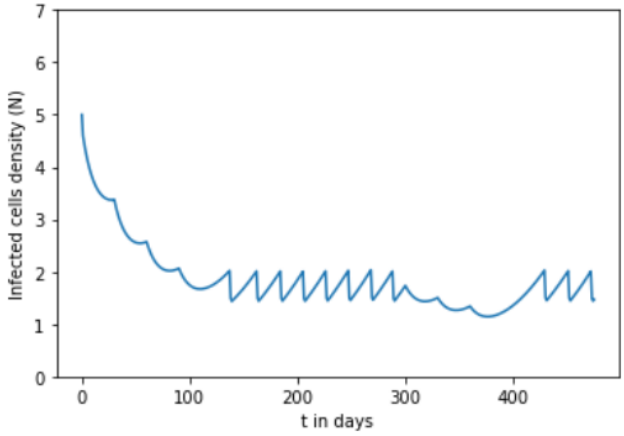

Figure 3.8: Comparaison of the evolution of the tumor cell density for treatment1, treatment2 and treatment3 with Cmax and dmax at 3

4 Conclusion

To conclude, we can say that applying radiotherapy and chemotherapy at the same time is more efficient than using one of them in many cases. Even if we cannot eradicate the disease, it doesn't mean that our results are bad. Cancer is a disease which has no remedy for now and the only thing that we can do is to make it stable as possible. Thus, the idea would be to use chemotherapy, and then, when the tumor cells density would be over a certain value, apply the radiotherapy.

5 Appendix

Below, you can find the code for our all project :

`https://colab.research.google.com/drive/1CZGz86-NINGgtYYRoupTX6ygav_HhQc3?usp=sharing`

6 Bibliography

C. Geng, H. Paganetti, and C. Grassberger. Prediction of treatment response for combined chemo- and radiation therapy for non-small cell lung cancer patients using a bio-mathematical model. *Scientific Reports*, 7, 2017.

S. Petit and F. Castaldo. Les anticancéreux oraux. *Onconews*, 8, 2014.

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