

Forecasting the bladder tumor size and immune response of a patient over the time using a dynamic mathematical model

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Abstract

Bladder cancer is one of the most common malignant diseases in the urinary system and a highly aggressive neoplasm. The prognosis is not favourable usually and its evolution for particular patients is very difficult to find out. In this paper we propose a dynamic mathematical model that describes the bladder tumor growth and the immune response evolution. This model is customized for a single patient, determining appropriate model parameter values via model calibration. Due to the uncertainty of the tumor evolution, using the calibrated model parameters, we predict the tumor size and the immune response evolution over the next few months assuming three different scenarios: favourable, neutral and unfavourable. In the former, the cancer disappears; in the second a 5mm tumor is expected around the middle of August 2018; in the worst scenario, a 5mm tumor is expected around the end of May 2018. The patient has been cited around June 15th, 2018, to check the tumor size, if it exists.

Keywords: Bladder Cancer, Dynamic Model, Uncertainty Quantification, Model Calibration, Cancer Prognosis.

1 Introduction

Bladder cancer is one of the most common malignant diseases in the urinary system and a highly aggressive neoplasm [2, 5]. Around 80% of patients diagnosed with this cancer present a non invasive carcinoma that can be handled via a Trans Urethral Resection (TUR), a surgical endoscopic procedure to remove the tumor from the inner part of the bladder [4]. The bladder cancer is characterized by recursiveness for more than a half of the patients: the tumor appears again after a while and may progress to become a muscle invasive cancer. It is then, when the treatments turn more aggressive, including the removal of the bladder to avoid the spread of the cancer to other parts of the body [6].

The prognosis of bladder cancer is not generally good and after the TUR, the typical treatment consist of instillations of Bacillus Calmette-Guérin (BCG) into the bladder, with the aim that the BCG stimulates the patient's immune response against the cancer and then, the cancer cells may be eliminated [8].

Here, we propose a mathematical model to study the evolution of the bladder cancer of a patient where TURs and the administration of BCG have been considered in these evolution. To our knowledge, only in the paper [3], the authors introduce this kind of model using average parameter values obtained from several in silico patients data.

At this point, we must say that, even though our starting point is [3], we have to adapt the model to be applied with the available data of our patient, given that the available data are those the pathologist considers relevant to be analyzed in order to determine the evolution of the sickness rather than the data necessary for the model.

Thus, we are going to propose a model to describe the evolution of the bladder cancer, we will use data of a patient to determine the model parameters that describe the known evolution and use these model parameters to predict the evolution of the bladder cancer in the short-term. Due to the lack of data, we will perform the evolution taking into account three possible scenarios: favourable, neutral and unfavourable.

The paper is organized as follows. In Section 2, we will introduce the data available and the adaption of the model presented in [3]. In Section 3, we find the model parameter values that allow the model to describe the bladder cancer evolution until now. In Section 4, we predict the evolution of the size of the cancer over the next few months in three scenarios: favourable, neutral and unfavourable. Finally, we present some conclusions of the work.

2 Available data and model building

Typically, in the Spanish Region of Valencia, a patient goes to the family doctor or the hospital emergencies when he/she starts to urinate blood (hematuria).

Then, the patient is addressed to the urologist, who, using ultrasound images or a cystoscopy, diagnoses if there is a tumor. If so, the patient is treated by the doctors in the Urology Department. In our case, we are working with doctors belonging to the *Hospital Universitari i Politènic La Fe* [1] in Valencia, Spain. The doctors have collected biological tissues of patients suffering pT1G3 bladder cancer, a type of superficial bladder cancer. The usual protocol is to perform a TUR to the patient, then instillations of BCG and cytologies and cystoscopy for follow-up control and revisions. In case of recurrence, the doctors repeat the cycle describe above until the patient is completely healthy or the stage of the cancer increases and more aggressive treatments have to be applied.

Among the patients, we have chosen from the Hospital Universitari i Politènic La Fe database one with the complete medical history for our purpose. We are going to call this patient Patient X, and the available data and dates were collected and summarized in Table 1.

Date	Activity	Tumor size	Inflammatory cells/field
01/Mar/2012	Ultrasound	3-5 mm	-
14/Jun/2012	TUR	25 mm	260
15/Feb/2015	Cystoscopy	1-2 mm	-
28/Apr/2015	TUR	5 mm	515
30/Jan/2017	Cystoscopy	20 mm	-
14/Mar/2017	TUR	30-35 mm	508

Table 1: Data corresponding to Patient X, who had the first symptoms in March 2012. Since then, the Patient X has suffered three TURs and has been treated with three BCG instillation sessions, each one after each TUR.

Besides the information provided in Table 1, instillation dates are also known. BCG instillations were made the following days: 10/Aug/2012, 26/May/2015 and 27/Apr/2017, after each TUR. Doses introduced in the bladder consisted of 81 ml of BCG colonies instilled weekly during six weeks.

From paper [3], we have adapted the model there to our available data and to describe properly the clinic practise in the Hospital Universitari i Politènic La Fe. First, let us denote $E(t)$ as the average inflammatory cells in a microscopy field of view, $T_u(t)$ as the radius (size) of the tumor cells non infected by BCG, $T_i(t)$ as the radius (size) of the tumor cells infected by BCG, $B(t)$ as the milliliters of BCG inside the bladder and $b(t)$ as the milliliters of BCG injected in one or several doses at the time instant t .

Thus, in the first stage, the tumor is growing, no treatment is administered until TUR is performed and only inflammatory cells may interact with the tumor. The tumor growth is modeled by $T_u(t+1) = T_u(t) + kT_u(t)$, where k is the tumor growth rate (exponential growth). Inflammatory cells kill tumor cells at rate p_6 and it is modeled by the term $-p_6E(t)T_u(t)$ (Figure 1). Parameter p_6 measures the effectiveness of the immune system to kill tumoral cells. Also, the production of inflammatory cells increases in presence of tumoral cells and it is modeled by the term $\alpha T_u(t)$, where α is the inflammatory cells production

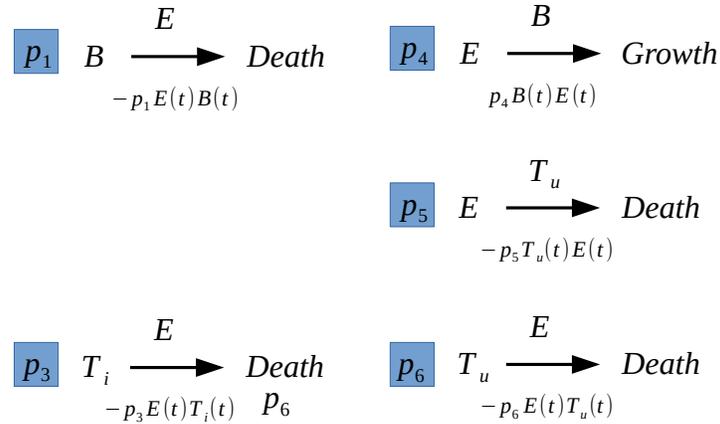


Figure 1: Interaction between BCG $B(t)$, inflammatory cells $E(t)$, tumoral cells $T_u(t)$ and tumoral cells infected by BCG $T_i(t)$, and their corresponding rates p_1 , p_3 , p_4 , p_5 and p_6 .

rate.

Then, TUR removes the tumors and after a while, BCG treatment is administered. The tumor is still growing because, although the doctors do their best, the complete removal is almost impossible [9]. But now, tumoral cells are infected by BCG and attacked by the immune system in a more aggressive way than the attack to non-infected cells. Here, infected tumoral cells and BCG have been introduced and we have to describe how they interact. First, the terms $-\mu_1 B(t)$ and $-\mu_2 E(t)$ describe the natural deaths of BCG and inflammatory cells, respectively, being μ_1 and μ_2 their death rates. Now, the interactions (Figure 1):

- the death of BCG because their interaction with inflammatory cells is modeled by $-p_1 E(t)B(t)$;
- the death of infected tumor cells because of inflammatory cells is modeled by $-p_3 E(t)T_i(t)$;
- the growth of inflammatory cells because of BCG is modeled by $p_4 B(t)E(t)$;
- the death of inflammatory cells because of uninfected tumor cells is modeled by $-p_5 T_u(t)E(t)$.

The last term to be modeled is the interaction between tumoral cells in presence of BCG (Figure 2). In this case, the tumoral cells become infected at rate p_2 , and the involved bacillus of BCG die. The term modeling this interaction is given by $p_2 B(t)T_u(t)$ and affects negatively the tumoral cells and BCG and positively the infected tumoral cells.

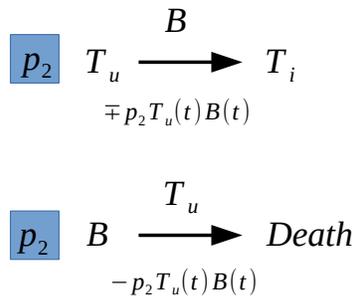


Figure 2: Interaction between BCG $B(t)$ and tumoral cells $T_u(t)$, with the corresponding rate p_2 .

Then, gathering all the above terms, the evolution of the dynamics of the tumoral cells, inflammatory cells and BCG can be modeled using the following system of difference equations:

$$E(t+1) = E(t) - \mu_2 E(t) + \alpha T_u(t) + p_4 B(t) E(t) - p_5 T_u(t) E(t), \quad (1)$$

$$T_u(t+1) = T_u(t) - p_2 T_u(t) B(t) - p_6 E(t) T_u(t) + k T_u(t), \quad (2)$$

$$T_i(t+1) = T_i(t) - p_3 E(t) T_i(t) + p_2 T_u(t) B(t), \quad (3)$$

$$B(t+1) = B(t) - \mu_1 B(t) - p_1 E(t) B(t) - p_2 T_u(t) B(t) + b(t), \quad (4)$$

where the parameters have been collected in Table 2.

3 Model calibration

In order to find the model parameters that make the model to be as close as possible to the data of Table 1 in the corresponding time instants, we define the following fitting function F :

INPUT: Model parameter values $(k, \alpha, \mu_1, \mu_2, p_1, p_2, p_3, p_4, p_5, p_6)$.

Step 1. Substitute the model parameter values into the model (1)-(4).

Step 2. Run the model and retrieve the model output for tumor size and inflammatory cells per field in the same time instants as those in Table 1.

Step 3. Calculate the root mean square between the model output retrieved in Step 2 and the data in Table 1.

Model calibration has been made in stages, because it is not a continuous process due to the sudden extraction of the tumor with TURs and a calibration period is established for each operation. Besides, not all parameters are considered constant over the time. Immune response (whose related model parameters

Parameter	Description	Term
k	Uninfected tumor cells growing rate.	$kT_u(t)$
α	Production rate of inflammatory cells because of tumor cells.	$\alpha T_u(t)$
μ_1	BCG natural death rate.	$-\mu_1 B(t)$
μ_2	Inflammatory cells natural death rate.	$-\mu_2 E(t)$
p_1	BCG death rate because of inflammatory cells.	$-p_1 E(t)B(t)$
p_2	Tumor cell infection rate because of BCG.	$p_2 T_u(t)B(t)$
p_3	Infected tumor cells death rate because of inflammatory cells.	$-p_3 E(t)T_i(t)$
p_4	Inflammatory cells growth rate because of BCG.	$p_4 B(t)E(t)$
p_5	Inflammatory cells death rate because of uninfected tumor cells.	$-p_5 E(t)T_u(t)$
p_6	Tumor cell death rate because of inflammatory cells (effectiveness).	$-p_6 E(t)T_u(t)$

Table 2: Model parameters, description and modeling term. Positive terms mean growth of cells and negative terms mean death or removal of cells.

are the growing rate p_4 and the effectiveness rate p_6) is considered variable over the time.

For Patient X there are three different stages. The first stage starts the 01/Mar/2012 and lasts until 09/Aug/2012. In this first stage there are two different groups of parameters: the constant ones (k , α , μ_1 , μ_2 , p_1 , p_2 , p_3 and p_5) and the varying over the time ones (p_4 and p_6) which are valid until the first BCG instillation occurs.

Together with the model parameters, the initial size of the tumor is unknown. Nevertheless, there is a diagnostic test made the 01/Mar/2012 where there is not any tumor evidence because the cystoscopy test is not positive if the tumor size is smaller than 5 mm. However, according to medical criteria, the tumor size cannot be smaller than 3 mm. Therefore, the initial size is also a parameter to be calibrated between the aforementioned values.

The second stage goes from 10/Aug/2012 to 25/May/2015. When the instillation is performed, the values of p_4 and p_6 change again. In this case, we do not know the value of the resulting tumor left inside the bladder after the instillations, therefore, this value is another parameter to be calibrated.

The third stage goes from 26/May/2015 to 26/Apr/2017. When the BCG instillation is performed, the values of p_4 and p_6 change again. The resulting tumor size after the TUR is also unknown and it is also calibrated.

For model calibration, we minimize function F in stages, as described, using the rPSO algorithm [7].

4 Results

The calibrated parameter values for the Patient X are shown in Table 3.

Parameters	Value	Parameters	Value
k	0.01563	$T_u(TUR_1)$	0,02
α	0.005	$p_4(TUR_1)$	1e-4
μ_1	0.8	$p_6(TUR_1)$	1.62e-5
μ_2	0.0005		
p_1	8e-5	$T_u(TUR_2)$	0.02
p_2	1e-3	$p_4(TUR_2)$	5.6e-4
p_3	1e-4	$p_6(TUR_2)$	6.3e-6
p_4	0.0		
p_5	0.0		
p_6	0.0		
$T_u(0)$	5.0		
$E(0)$	260		

Table 3: Model parameter values calibrated for Patient X. Observe that parameters p_4 and p_6 appear three times in the table and change over the time. Values accompanying TUR_1 and TUR_2 correspond to the variable parameters after the TUR_1 and TUR_2 , respectively.

Parameter p_6 in the first stage is zero because the tumor cells growth parameter k also includes the possible decrease because of the normal activity of the immune system. The following p_6 values obtained in the next stages reflects the increasing activity of the immune system because of BCG compared to the normal activity.

In Figure 3, the evolution of the tumor size and the immune system development are shown. In the lower figure (tumor size) the sudden drops correspond to TURs, when the tumor is removed. Then, it starts to grow again. Respect to the upper figure (immune response), we can see a quick increasing after TUR corresponding to the BCG instillations and how it influences the immune response. The saw teeth appearing when BCG is administered are due to the weekly doses of BCG instilled.

Due to the uncertainty in the future evolution, in order to predict the dynamics of the bladder cancer for Patient X, three different scenarios have been considered. In the favourable scenario the response of the immune system is greater than the second stage. The neutral scenario consists of the same response of the immune system as in the third stage, that is to say, the immune system response remains constant. The unfavourable scenario is based on the fact that the response of the immune system decreases in the same proportion as it decreased from the second to the third stage. In Table 4 the values of the parameters corresponding to the described scenarios are shown.

The day 0 in the figures correspond to 01/Mar/2012, coinciding with the first ultrasound test pointed out in Table 1.

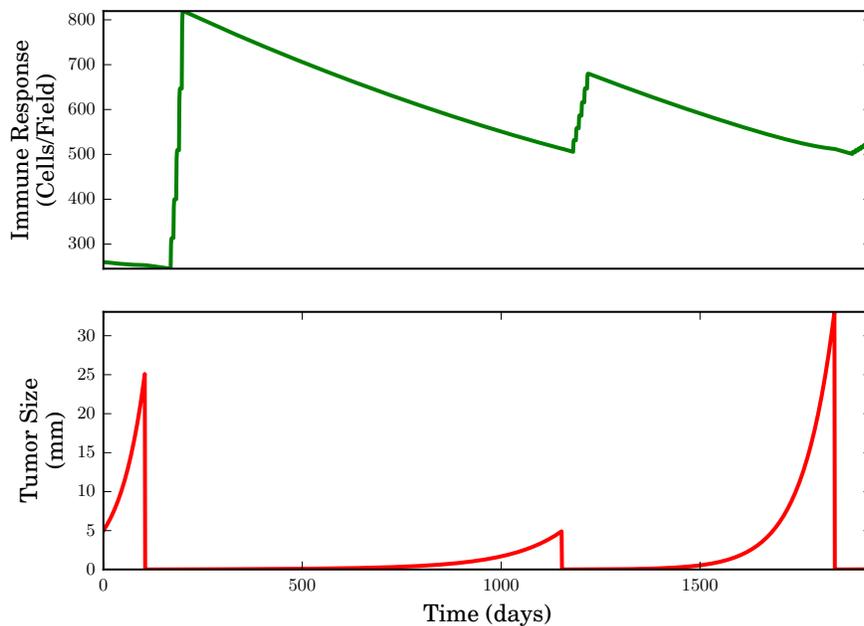


Figure 3: Here we show the graphs with the evolution of the immune response (upper) and the tumor size (lower) with the parameters obtained in the model calibration. The sudden drops in the lower graph correspond to the TURs, when tumors are removed. The sudden increasing in the upper graph correspond to the administration of the BCG. Time $t = 0$ corresponds to 01/Mar/2012.

Parameters	Favourable scenario	Neutral scenario	Unfavourable scenario
p_4	1e-3	5.6e-4	1.14e-4
p_6	3.62e-5	6.3e-6	2.45e-6
Date tumor size 5mm	No tumor	15/Aug/2018	25/May/2018

Table 4: Model parameter values in the three different scenarios: favourable, neutral and unfavourable.

In Figures 4, 5, 6, the prediction in the different scenarios are shown. The prediction starts in the dashed black vertical line. In the favourable scenario, the BCG treatment is successful and the tumor does not grow anymore after instillation treatment is finished. In the neutral scenario, bladder cancer recurrence with a tumor of size 5 mm is predicted for the 15/Aug/2018 and recurrence is expected. In the unfavourable scenario, bladder cancer recurrence with a tumor of size 5 mm is predicted for the 25/May/2018.

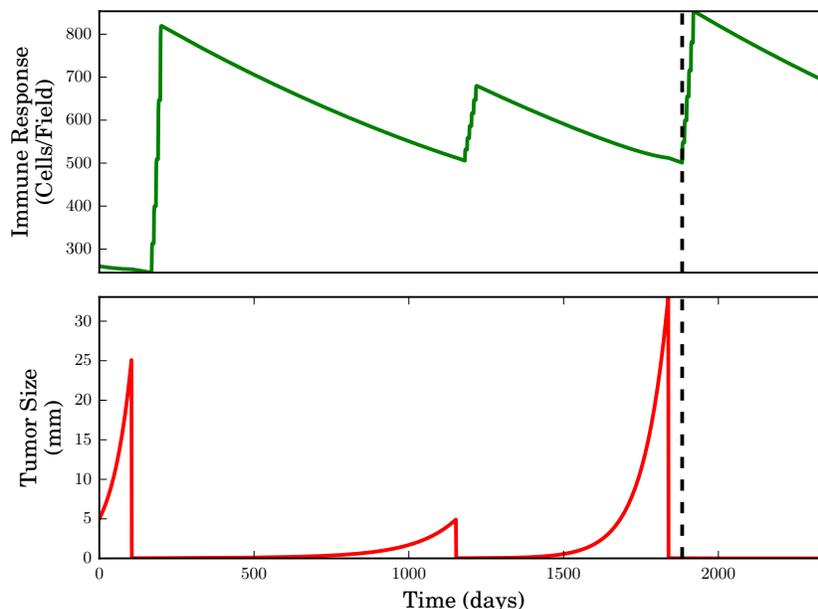


Figure 4: Favorable scenario. The prediction appears on the right of the dashed vertical black line. It can be seen that the tumor does not grow anymore, that is, the BCG treatment can kill the remainder tumor cells. Time $t = 0$ corresponds to 01/Mar/2012.

5 Conclusion

In this paper, we present a dynamic mathematical model to describe the evolution of a bladder tumor in a given patient. The model is calibrated in several stages and the obtained parameters allowed us to give a prediction about the tumor growth over the next few months in three scenarios: favourable, neutral and unfavourable. To our knowledge, this is the first approach of this type applying the model to a given patient and the results seem promising.

Some predictions have been made and they will be checked in the near future. In fact, the Patient X will be called in the middle of June to measure the size of the tumor, if it exists. If the tumor is not present, the Patient X will be called in the middle of September for another medical revision.

When we have more data available, we will be able to check the validity of our approach, performing better and more accurate predictions, giving tools to the doctors to administer treatments, to schedule the patient's revisions and, in the future, to determine the best strategies to improve the patient's health avoiding tumor recurrences, if possible.

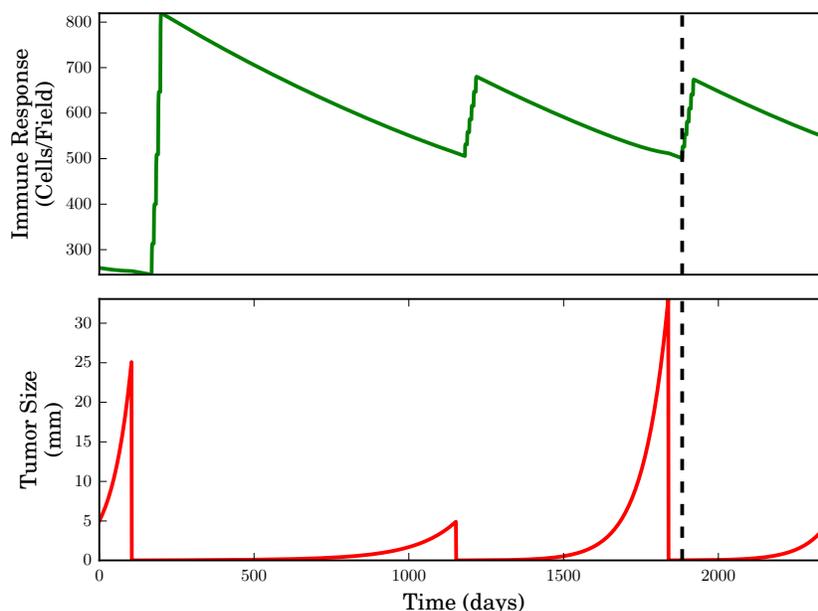


Figure 5: Neutral scenario. The prediction appears on the right of the dashed vertical black line. After a while, the tumor grows again and a recurrence is expected, reaching the size of 5mm in the middle of August 2018. Time $t = 0$ corresponds to 01/Mar/2012.

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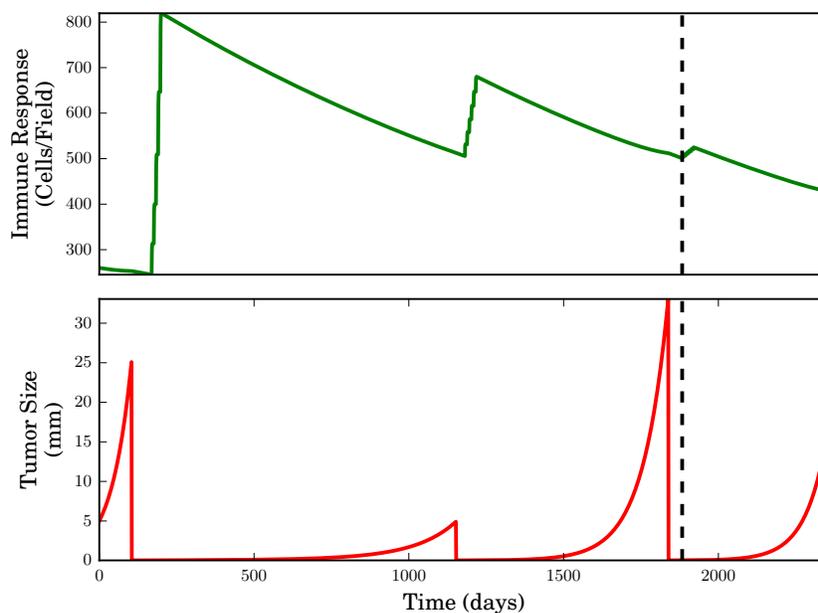


Figure 6: Unfavourable scenario. The prediction appears on the right of the dashed vertical black line. Here the effect of BCG is almost inexistent and the tumor grows quickly reaching the size of 5mm at the end of May 2018. Time $t = 0$ corresponds to 01/Mar/2012.

patients with stages TA and t1 transitional cell cancer of the bladder followed for at least 20 years. *The Journal of Urology*, 153(6):1823–1827, jun 1995.

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