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Mathematical modeling of the dynamics of the bladder cancer and the immune response applied to a patient: Evolution and short-term prediction

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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 favorable 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: favorable, neutral and unfavorable. In the former, it is not expected any trace of the cancer in the middle of September 2018 (after 16 months). In the neutral scenario, at the same date, a 7-8 mm tumor is expected. In the worst case, a 40 mm tumor is expected. The patient was cited on September 10th, 2018, to check the tumor size and, according to the doctors, there was no sign of recurrence. It seems that we are in the favorable scenario. The patient will be called again for follow-up in mid-2019.

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 [5, 12]. 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

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the tumor from the inner part of the bladder [9]. In this procedure, a catheter is introduced by the urethra until arriving to the bladder. With a camera attached to the top of the catheter, the tumor is found with a sight inspection and then removed using a scalper. There is no need of cutting into the abdomen, and therefore, it is considered a minor surgery.

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 become more aggressive, including the removal of the bladder to avoid the spread of the cancer to other parts of the body [14].

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 [17].

When BCG instillations are administered, the BCG cells attach to the urothelial cells and they get internalized by the bladder cancer cells. Because of this, the bladder cancer cells release substances such as cytokines and antigen presentation, which promotes the immune cells recruitment and suppression activity [17].

Despite the advancements in molecular biology techniques [6] and the knowledge of the cancer stages and the treatments [1, 2], it is not well known the mechanisms of bladder cancer evolution in particular patients, why and when some of them heal and others have recurrences. In fact, the treatment protocols have not changed in the last 25 years.

With the aim of providing some light to the problem of customizing the evolution of bladder cancer and its treatment, 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 the evolution. Also, we consider in the model the immune response caused by the apparition and growth of the tumor and the interaction of cancer cells with the immune system. To our knowledge, only in the paper written by Bunimovich-Mendrazitsky et al. [7], the authors introduce a model of this kind using average parameter values obtained from several in silico patients data.

At this point, we must say that, even though the antecedent of Bunimovich-Mendrazitsky et al. [7] has been very valuable to develop our model, we had to design our own model. This is because our model has to be applied with the available data of our patients, given that the available data are those the anatomic pathologist doctors consider relevant to be analyzed in order to determine the evolution of the sickness rather than the data we could consider as necessary for the model. Also, our model should describe properly the clinic practice in the Hospital Universitari i Politècnic La Fe [4] in Valencia, Spain, where we collaborate with the doctors of the Urology Department and the Pathology Department. Furthermore, we introduce into the model new recent findings related to the interaction between inflammatory and tumor cells.

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

The paper is organized as follows. In Section 2, we introduce the data available collected from the Hospital Universitari i Politècnic La Fe. In Section 3 we build the model describing the evolution of the tumor size and the immune response in stages determined by the medical protocols. In Section 4, we find the model parameter values that allow the model to describe the bladder cancer evolution until now and we show the result of the calibration. In Section 5, we predict the evolution of the size of the tumor and the immune system over the next few months in three scenarios: favorable, neutral and unfavorable. Also, we describe the patient's follow-up actions done. Finally, we present some conclusions of the work.

2 Available data

Typically, in the Spanish Region of Valencia, a patient goes to the family doctor or the emergencies of the hospital when he/she starts to urinate blood (hematuria). Then, the patient is addressed to the urologist, who, using ultrasound images or a cytoscopy, diagnoses if there is a tumor inside the bladder. 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 Politècnic La Fe. The doctors have collected biological tissues of patients suffering pT1G3 bladder cancer, a non muscle-invasive stage of the bladder cancer. Then, the usual protocol is

- to perform a TUR to the patient.
- After the TUR, the anatomic pathologist doctor, observes the tumor and measures the tumor size (diameter) and the immune response in the tumor microenvironment by counting the inflammatory cells (CD3, CD20, CD56, CD68, CD138, FoxP3 and tryptase). With the collected data, the anatomic pathologist doctor reports the urologists;
- to administer instillations of BCG;
- to perform cytologies and cystoscopies for follow-up control and revisions.

In case of recurrence, the doctors repeat the cycle described above until the patient is completely healthy or the cancer has increased and invaded the bladder muscle layer. In this latter case, more aggressive treatments have to be applied.

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

The anatomic pathologist doctor, in their practise, measures the number of inflammatory cells as the average of five countings from different parts of the tumor microenvironment that they observe through a 40x microscopy lens. This is what is called "average inflammatory cells per microscopy field" (right column in Table 1). We gather all the types of the inflammatory cells assuming a joint effect against the tumor cells.

Apart from the information provided in Table 1, instillation dates are also known. BCG instillations were started the 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 once per week during six weeks.

3 Model building

To design a reliable model, we are going to take into account the available data and their magnitudes, describing properly the clinic practice in the Hospital Universitari i Politècnic La Fe, and including recent discoveries about the interaction between tumor cells and the immune system, and facts do not considered in literature, mainly: (a) the fact that the immune system also attacks non-infected tumor cells [13]; (b) in the interaction between tumor cells and inflammatory cells, the tumor cells can kill inflammatory cells [10]; and (c) the immune response is only dependent on tumor cells [11].

The model is going to be built in two stages. It is natural, because from the tumor detection and diagnosis to the first TUR, there are only two interacting actors: the tumor cells and the immune system. However, after the first TUR and the application of the BCG treatment to the patient, tumor cells, infected tumor cells, BCG and the immune system, all of them, interact. This latter interaction will be repeated every time a new TUR is performed and BCG administered.

3.1 Modeling the first stage

As we mentioned before, at this stage only tumor cells and inflammatory cells interact. Then, following the units of the data collected in Table 1, we define $T(t)$ as the diameter of the tumor at the day t and $I(t)$ as the average number of inflammatory cells per microscopy field at the day t. In the following we abbreviate it and we name $I(t)$ as inflammatory cells.

For model building, let us consider the following assumptions:

A1 the tumor grows following the classical exponential growth difference equation, $T(t+1) = T(t) + kT(t)$, where k is the growth rate;

A2 the inflammatory cells kill the tumor cells and reduce the tumor size [13]; it is modeled by the term $\lambda_2 I(t)T(t)$ where λ_2 is the killing rate;

A3 the inflammatory cells increase because of the presence of tumor cells [11]. It is modeled by the term $b_1 T(t)$, where b_1 is the increase rate;

A4 the encounters of inflammatory cells with the tumor cells provokes the inactivation (death) of the inflammatory cells [10]; it is modeled by the term $\lambda_1 I(t)T(t)$ where λ_1 is the killing rate;

A5 the natural death of the inflammatory cells is modeled by the term $d_1 I(t)$ where d_1 is the death rate.

In the Figure 1 we can see how every assumption contributes to the model building in this first stage.

Therefore, the dynamics of the tumor growth and the inflammatory cells and their interaction in the first stage is given by the following system of difference equations

$$\begin{array}{rcl} T(t+1) & = & T(t) + kT(t) - \lambda_2 I(t)T(t), \\ I(t+1) & = & I(t) - d_1 I(t) + b_1 T(t) - \lambda_1 T(t)I(t), \end{array} \tag{1}$$

where the time t is in days, $T(0)$ is the initial diameter, $I(0)$ is the initial average number of inflammatory cells per microscope field (see Table 1), being $t = 0$ the day 01/Mar/2012.

We point out the importance of the parameter λ_2 because it measures the effectiveness of the immune system to kill tumor cells and reduce the tumor size.

Remark 3.1 *At this point, it is usual to perform a dynamic analysis of the model in order to obtain information about the studied phenomenon. Then, the fixed points of the model (1) are:* $T = 0$ *and* $I = 0$ *for the tumor-free scenario, and*

$$T = \frac{kd_1}{\lambda_2 b_1 - \lambda_1 k}, I = \frac{k}{\lambda_2},$$

for the scenario where we reach a tumor with constant size. In this latter scenario, T *is positive if* $\lambda_2 b_1 > \lambda_1 k$*. However, because of cancer cells anomalous and high growth rate, if the rates* λ_2, b_1 *and* λ_1 *have similar magnitudes and* k *is much greater than them, the condition* $\lambda_2 b_1 > \lambda_1 k$ *will not be satisfied. Moreover, the physicians say that situations where the tumor reaches a constant size because of the immune system are very rare due to the aggressive grade of the bladder tumor (grade 3) [16].*

Therefore, in this case, the dynamic analysis show an unrealistic behavior and does not provide new relevant information on the phenomenon.

3.2 Modeling the second stage

This second stage starts when the 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 ("seed and soil" theory)[18]. Apart from the tumor cells and the inflammatory cells, in this stage, BCG appears via instillations and the effect of the BCG is to infect tumor cells to get marked facilitating the attack of the inflammatory cells in a more aggressive way. This way, the action of the inflammatory cells is much more effective than without BCG and this is called specific immune response [17]. Thus, infected tumor cells have to be considered in this stage too.

Then, let us denote by $B(t)$ the milliliters of BCG inside the bladder, $b(t)$ the milliliters of BCG injected in one or several doses per day t and $T_i(t)$ as the diameter of the tumor cells infected by BCG, at the time instant (day) t.

For model building this second stage, let us consider the following assumptions:

A6 when a bacillus encounters a tumor cell, the tumor cell becomes infected and the bacillus gets attached to the tumor cell [17]. This is modeled by the term $\tau_2 T(t)B(t)$ where τ_2 is the infection rate. This term affects decreasing $T(t)$, increasing $T_i(t)$ and decreasing $B(t)$;

A7 in **A3**, inflammatory cells increase because of tumor cells, and now, also because the infected ones. It is modeled by the term $b_2 T_i(t)$ where b_2 the apparition rate of the inflammatory cells because the infected tumor cells;

A8 the death of the inflammatory cells because the infected tumor cells [13]. This is modeled by the term $\tau_1 T_i(t) I(t)$ where τ_1 is the death rate;

A9 the growth of inflammatory cells because of BCG [8]. This is modeled by $\tau_5 B(t) I(t)$ where τ_5 is the growth rate;

A10 the death of infected tumor cells and the reduction of its size because of inflammatory cells [17]. This is modeled by $\tau_4 I(t) T_i(t)$ where τ_4 is the death rate;

A11 the natural disappearance of BCG by urination is modeled by the term $d_2 B(t)$, where d_2 is the urination rate. According to the treatment protocol of the Spanish Minister of Health [3], when the BCG instillations are introduced into the bladder, the patients urinate it about two hours after the procedure. The BCG cells are internalized by the tumor cells [17]. If the BCG cells that are not internalized and would stay long time in the bladder, there could be an infection. The urination expels all the BCG cells before they start to die.

A12 the death of BCG because the inflammatory cells attack BCG [8]. This is modeled by $\tau_3 I(t) B(t)$ where τ_3 is the death rate;

In the Figure 2 we can see how every assumption contributes to the model building in this second stage.

It is important to remark that the effectiveness of the BCG treatment is based on the fact that parameter τ_4 **(A10)** is much greater than λ_2 **(A2)** because BCG infects the tumor cells and facilitates the detection and destruction by the inflammatory cells (specific immune response). All the above model parameters and their description have been summarized in Table 2.

Then, gathering all the above terms, the evolution of the dynamics of the size of tumor, inflammatory cells and BCG can be modeled using the following system of difference equations (time t in days):

$$\begin{array}{rcl} T(t+1) & = & T(t) + kT(t) - \lambda_2 I(t) T(t) - \tau_2 B(t) T(t), \\ I(t+1) & = & I(t) - d_1 I(t) + b_1 T(t) - \lambda_1 T(t) I(t) + b_2 T_i(t) \\ & & -\tau_1 T_i(t) I(t) + \tau_5 B(t) I(t), \\ T_i(t+1) & = & T_i(t) + \tau_2 T(t) B(t) - \tau_4 I(t) T_i(t), \\ B(t+1) & = & B(t) - d_2 B(t) - \tau_2 T(t) B(t) - \tau_3 I(t) B(t) + b(t). \end{array} \tag{2}$$

At this point, we must say that model parameters λ_2, τ_4 and τ_5 are going to be variable over the stages. They are responsible of the immune response before and after the administration of the BCG. Then, after the first BCG administration, the immune system is highly stimulated and the values of the model parameters λ_2, τ_4 and τ_5 reach their highest values. If more BCG administration is necessary, the stimulation of the immune response is not as well as in the first time and the model parameter values λ_2, τ_4 and τ_5 use to decrease as

the stages goes on. This is natural taking into account the behavior of the immune response (sudden increase because of BCG and slow decrease) and noting that the output returned by the model of the immune response cannot overpass certain values in order to keep the model credibility (around 800).

4 Model calibration

Model calibration has been made in stages, because it is not a continuous process due to the sudden extraction of the tumor with TURs. For Patient X there are three different stages, separated by TURs:

1. the first stage starts the 01/Mar/2012 and lasts until 14/Jun/2012;
2. the second stage starts the 15/Jun/2012 and lasts until 28/Apr/2015;
3. the third stage from the 29/Apr/2015 to 14/Mar/2017.

Predictions will be made for dates after the 14/Mar/2017, considering the instillations administered 27/Apr/2017 and during 6 weeks, once per week.

In the first stage, the model is given by the system (1). The system (2) will be used for the second and third stage, and also for predictions.

4.1 Calibration of the first stage

Taking into account the lack of data because of the nature of its measurement and the large number of model parameters, we have to consider the reduction of the parameters space in order to guarantee reliable calibrations. Looking at the data about the size of the tumor in the Table 1, considering only the growth tumor model $T(t+1) = T(t) + kT(t)$ and performing a calibration of the parameter k in the three stages, we can obtain that parameter k cannot be greater that 0.0204. k is the growth tumor rate and it is much greater than the usual growth rates for healthy cells, by definition of cancer. Therefore, the parameters related with the growth and death of cells, b_1, b_2, d_1, d_2, should be smaller than k. Similar reasoning can be done for the remainder parameters insofar they are involved in the growth or death of the cells and BCG.

Furthermore, Table 1 shows small changes in the inflammatory cells per field in second and third TURs, where the immune system has been changed because of the instillations of BCG. We are going to assume the same behavior before the first TUR, what means that initially, we expect around 260 inflammatory cells the 01/Mar/2012.

As we mentioned above, although the doctors do their best, the bladder is not completely free of tumor cells after the TUR. Therefore, we are going to consider that the diameter of the tumor after a TUR will be determined by the model after the calibration. This size is small enough to be considered the bladder gets "clean" after a TUR and permits the tumor keep growing, which we know that happens because of recurrences.

Now, 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_1:

INPUT: Model parameter values $(k, \lambda_1, \lambda_2, d_1, b_1)$;

Step 1. Substitute the model parameter values into the model (1);

Step 2. Run the model and retrieve the model output for tumor size and average 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.

For model calibration, we minimize the function F_1 in this stage using the rPSO algorithm [15], and the model parameter values are given in Table 3.

The calibration procedure allowed us to determine more precisely the initial conditions $T(0) = 4.64$ mm and $I(0) = 265$.

4.2 Calibration of the remainder stages

Once the first stage has been calibrated, the parameters k, λ_1, d_1, b_1 are known and only the remainder parameters have to be calibrated in the second stage. As we mentioned above, the model parameters λ_2, τ_4 and τ_5 are going to be variable over the stages, meanwhile the remainder model parameters will remain constant over the stages. Now, for the calibration in the second stage, we propose the following fitting function F_2:

INPUT: Model parameter values $(\lambda_2, d_2, b_2, \tau_1, \tau_2, \tau_3, \tau_4, \tau_5)$. The model parameters k, λ_1, d_1 and b_1 are those with the values given in Table 3;

Step 1. Substitute the model parameter values into the model (2);

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.

For model calibration in the second stage, we minimize the function F_2 using the rPSO algorithm [15], and the model parameter values are given in Table 4.

Now, for model calibration in the third stage, the model parameter values $k, \lambda_1, d_1, b_1, d_2, b_2, \tau_1, \tau_2, \tau_3$ have been calculated and only $\lambda_2, \tau_4, \tau_5$ have to be calibrated again, using the fitting function F_2 where, now, the unknown model parameters are only $\lambda_2, \tau_4, \tau_5$. Then, using the rPSO algorithm [15], the calibrated model parameters are given in Table 5. It can be seen that the model parameter values satisfy the restrictions stated through this section.

In Figure 3, we can see the result of the calibration, that is, the evolution of the tumor size and the immune system development. 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 they influence the immune response. The saw teeth appearing when BCG is administered are due to the weekly doses, once per week, of BCG instilled.

5 Predictions and patient's follow-up

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 takes the maximum possible values that allow the reliability of the values corresponding to the immune system response, usually less than the values as after the first TUR (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 6 the values of the parameters corresponding to the described scenarios are shown.

In Figures 4, 5 and 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 seem to grow in the prediction time interval until 15/Sep/2018, after the third instillation treatment is finished. In the neutral scenario, bladder cancer recurrence with a tumor of size 7-8 mm is predicted for the 15/Sep/2018. In the unfavourable scenario, bladder cancer recurrence with a tumor of size 40-42 mm is predicted for the 15/Sep/2018.

5.1 Patient's follow-up

Patient X was called for a revision the 15/Mar/2018 (10 months after the last administration of BCG) and, after a cystoscopy, the doctors did not find any trace of bladder cancer. Then, she was called again the 6/Jun/2018 (13 months after the last administration of BCG) where the cytoscopy was inconclusive. A week later, a molecular test called XPERT Bladder Cancer Monitor was performed with negative results.

The model in the unfavorable and neutral scenarios, predicts tumor of sizes 9.2 mm and 2.4 mm for 6/Jun/2018. Therefore, the unfavorable scenario is discarded for Patient X. The neutral scenario gives a tumor size not visible in a cytoscopy, although the XPERT Bladder Cancer Monitor test could detect.

The following revision was 10/Sep/2018 (16 months after the last administration of BCG). According to the doctors, there was no sign of recurrence. Thus, it seems that Patient X is in the favorable scenario. Anyway, the patient will be called again for follow-up in mid-2019, where the favorable scenario predicts the apparition of new tumors.

6 Conclusion

In this paper, we build a dynamic mathematical model to describe the evolution of the size of a bladder tumor and the immune system response in a given patient. The model is calibrated in several stages determined by the TURs included in the hospital protocol and the obtained parameters allow us to give a prediction about the tumor growth and the immune system response over the next few months in three scenarios: favorable, neutral and unfavorable. To our knowledge, this is the first approach of this type applying the model to a given

patient and the results seem to be promising, insofar the doctors of the Hospital Universitari i Politècnic La Fe have scheduled patient's revisions following the predictions given by the model.

Some predictions have been made and they are going to be checked with programmed patient's revisions. Some scenarios have been discarded, but others have to be examined in the near future. In fact, the Patient X will be called in mid-2019 to measure the size of the tumor, if it exists.

This is a working model, built *ad-hoc* to be adapted to the data provided by the Hospital Universitari i Politècnic La Fe and applied to a particular patient. If this experience with Patient X gives us reliable results, the model will be calibrated for more patients using more data in order to predict the future evolution of this disease in each one of them. In fact, the doctors are working on obtaining more information and data about the patient's evolution to feed the model. Moreover, improvements of the model are also contemplated.

Thus, 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, with an important saving of time and resources.

Furthermore, the model and the obtained results indicate us that it would be interesting to administer the BCG as soon as possible in order to improve the effect against the remainders of the tumor after the TUR. We suggested this to the doctors, nevertheless, this kind of changes involve variations in the hospital's protocol and it takes time and bureaucracy.

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Conflict of interest

The authors declare no potential conflict of interests.

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Figures

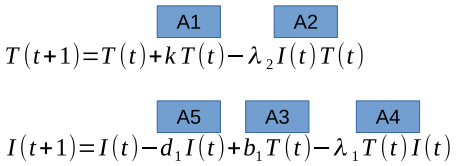

Figure 1: Modeling. First stage. In this figure we can see the contribution of the model terms of every assumption to the model building.

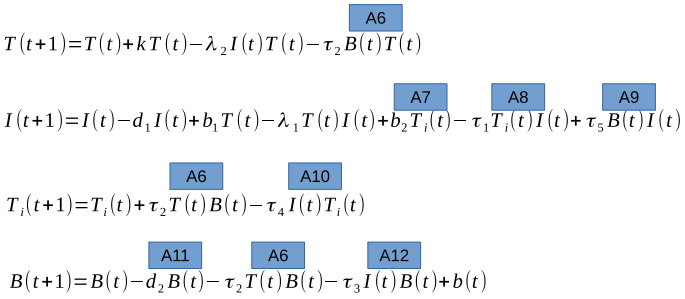

Figure 2: Modeling. Second stage. In this figure we can see the contribution of the model terms of every assumption to the model building.

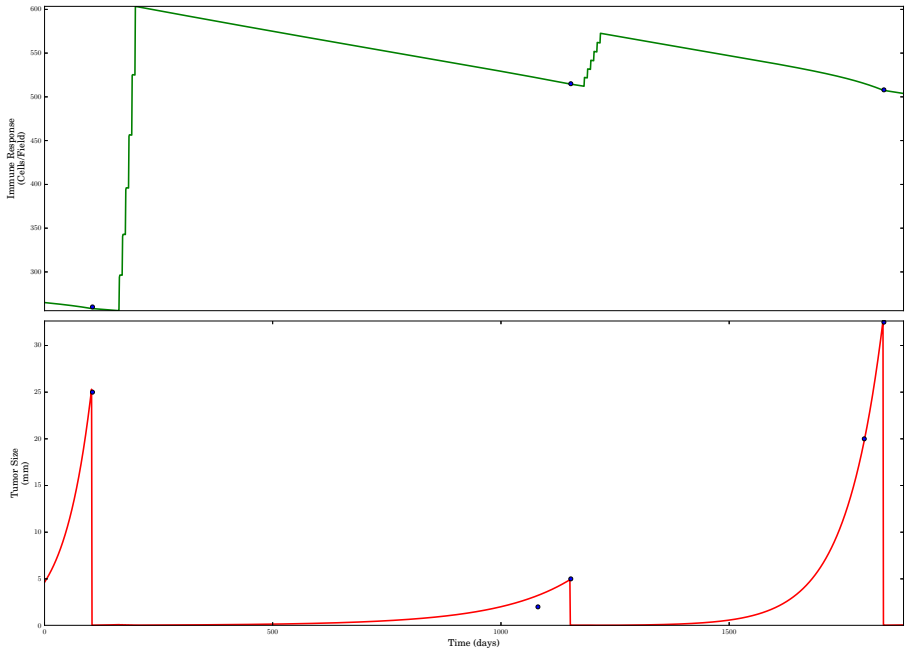

Figure 3: Here we show the graphs with the evolution of the immune response (upper) and the tumor size (lower) with the parameters obtained in the model calibration. The points represent the available data in Table 1. The sudden drops in the lower graph correspond to the TURs, when tumors are removed. The sudden increasings in the upper graph correspond to the administration of the BCG. Time $t = 0$ corresponds to 01/Mar/2012 and time step is a day.

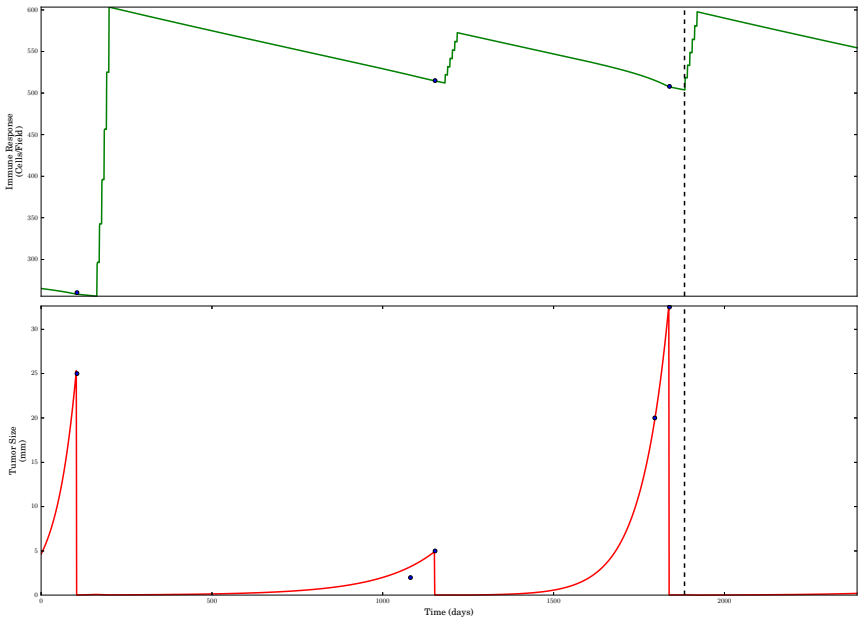

Figure 4: Favorable scenario. The prediction appears on the right of the dashed vertical black line. It can be seen that the tumor does not seem to grow in the prediction time interval, that is, it seems that the BCG treatment will be able to kill the remainder tumor cells. However, after two years, we must say that the model predicts the apparition of new tumors.

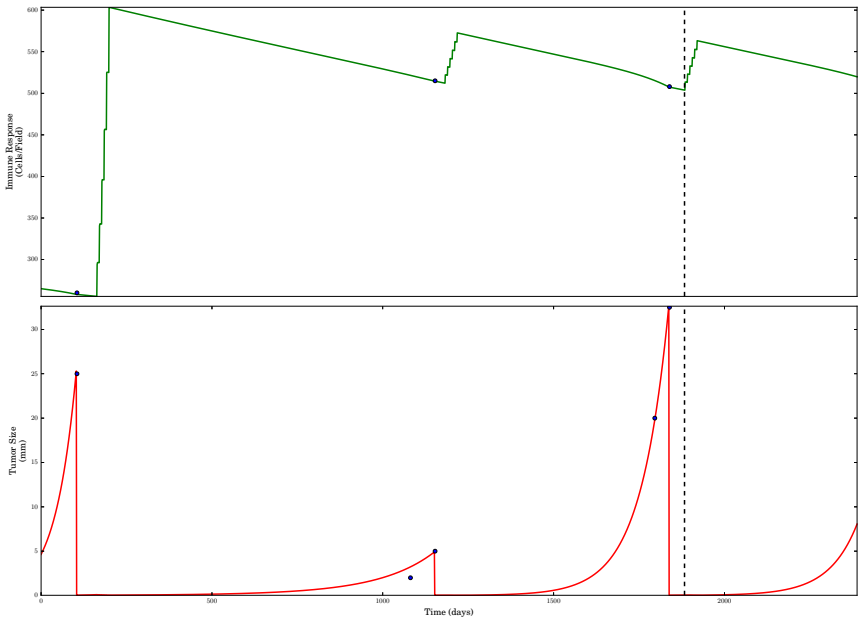

Figure 5: Neutral scenario. The prediction appears on the right of the dashed vertical black line. After a while, the tumor grows again and a recurrence is expected, reaching the size of 7-8 mm in the middle of September 2018 (16 months after the last BCG treatment).

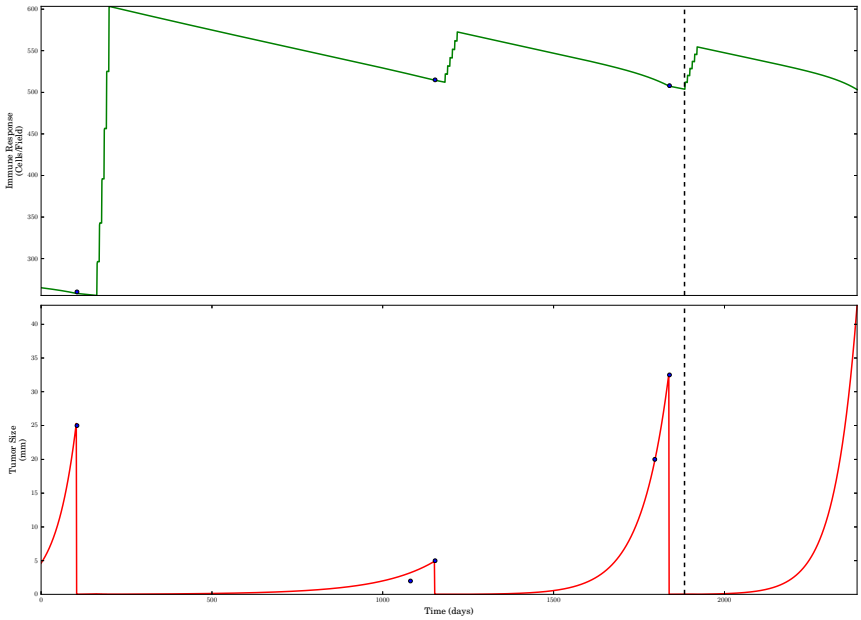

Figure 6: Unfavourable scenario. The prediction appears on the right of the dashed vertical black line. Here, the effect of BCG is almost inexistent and the tumor grows quickly reaching the size of 40-42 mm in the middle of September 2018 (16 months after the last BCG treatment). Time $t = 0$ corresponds to 01/Mar/2012.

Tables

Date	Medical procedure	Diameter of the tumor	Avg inflammatory cells per 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 was diagnosed in the first of 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. The last column shows the average number of inflammatory cells per microscopy field counted by the pathologist after every TUR.

Parameter	Units	Description	Term
k	unitless	Tumor size growing rate.	$kT(t)$
λ_1	mm^{-1}	Inflammatory cells death rate because of uninfected tumor cells.	$-\lambda_1 I(t)T(t)$
λ_2	cells^{-1}	Tumor cell death rate because of inflammatory cells (effectiveness).	$-\lambda_2 I(t)T(t)$
d_1	unitless	Inflammatory cells natural death rate.	$-d_1 I(t)$
b_1	cells $\times$ mm^{-1}	Production rate of inflammatory cells because of the presence of the tumor cells.	$b_1 T(t)$
d_2	unitless	BCG natural disappearance rate by urination.	$-d_2 B(t)$
b_2	cells $\times$ mm^{-1}	Production rate of inflammatory cells because of the presence of the infected tumor cells.	$b_2 T_i(t)$
τ_1	mm^{-1}	Death rate of inflammatory cells because the infected tumor cells.	$-\tau_1 T_i(t)I(t)$
τ_2	ml^{-1}	Infection rate of tumor cells and its effect on the reduction of the BCG.	$\tau_2 T(t)B(t)$
τ_3	cells^{-1}	BCG death rate because of inflammatory cells.	$-\tau_3 I(t)T_i(t)$
τ_4	cells^{-1}	Infected tumor cells death rate because of inflammatory cells (effectiveness of BCG).	$-\tau_4 B(t)I(t)$
τ_5	ml^{-1}	Inflammatory cells growth rate because of BCG.	$\tau_5 B(t)IE(t)$

Table 2: Model parameters, units, description and modeling term. Positive terms mean growth of cells and negative terms mean death or removal of cells. Above the horizontal line, the parameters involved in the first stage. Below the horizontal line, the parameters related to the BCG administration.

Parameters	Value
k	0.0184
λ_1	8.1186×10^{-6}
λ_2	6.8426×10^{-6}
d_1	1.6×10^{-4}
b_1	9.08×10^{-5}

Table 3: Model parameter values calibrated for Patient X in the first stage, until the first TUR. The time step is daily.

Parameters	Value
λ_2	2.393×10^{-5}
d_2	0.8864
b_2	5.89×10^{-3}
τ_1	2.8689×10^{-5}
τ_2	2.1×10^{-3}
τ_3	2.207×10^{-4}
τ_4	8.59×10^{-3}
τ_5	1.85×10^{-3}

Table 4: Model parameter values calibrated for Patient X in the second stage, after the first TUR until the second TUR. The time step is daily.

Parameters	Value
λ_2	1.205×10^{-5}
τ_4	3.9132×10^{-4}
τ_5	2.43878×10^{-4}

Table 5: Model parameter values calibrated for Patient X in the third stage, after the second TUR. The time step is daily.

Parameters	Favourable scenario	Neutral scenario	Unfavourable scenario
λ_2	2.393×10^{-5}	1.205×10^{-5}	5.9822×10^{-6}
τ_5	8.59×10^{-3}	3.9132×10^{-4}	3.7349×10^{-4}
τ_6	3.692×10^{-4}	2.4387×10^{-4}	2.1166×10^{-4}
Tumor size 15/Sep/2018	Non detectable	7-8 mm	40-42 mm

Table 6: Model parameter values in the three different scenarios: favorable, neutral and unfavorable. Expected tumor size the September 15th, 2018 (16 months after the last administration of BCG) in the three scenarios. The time step is daily.