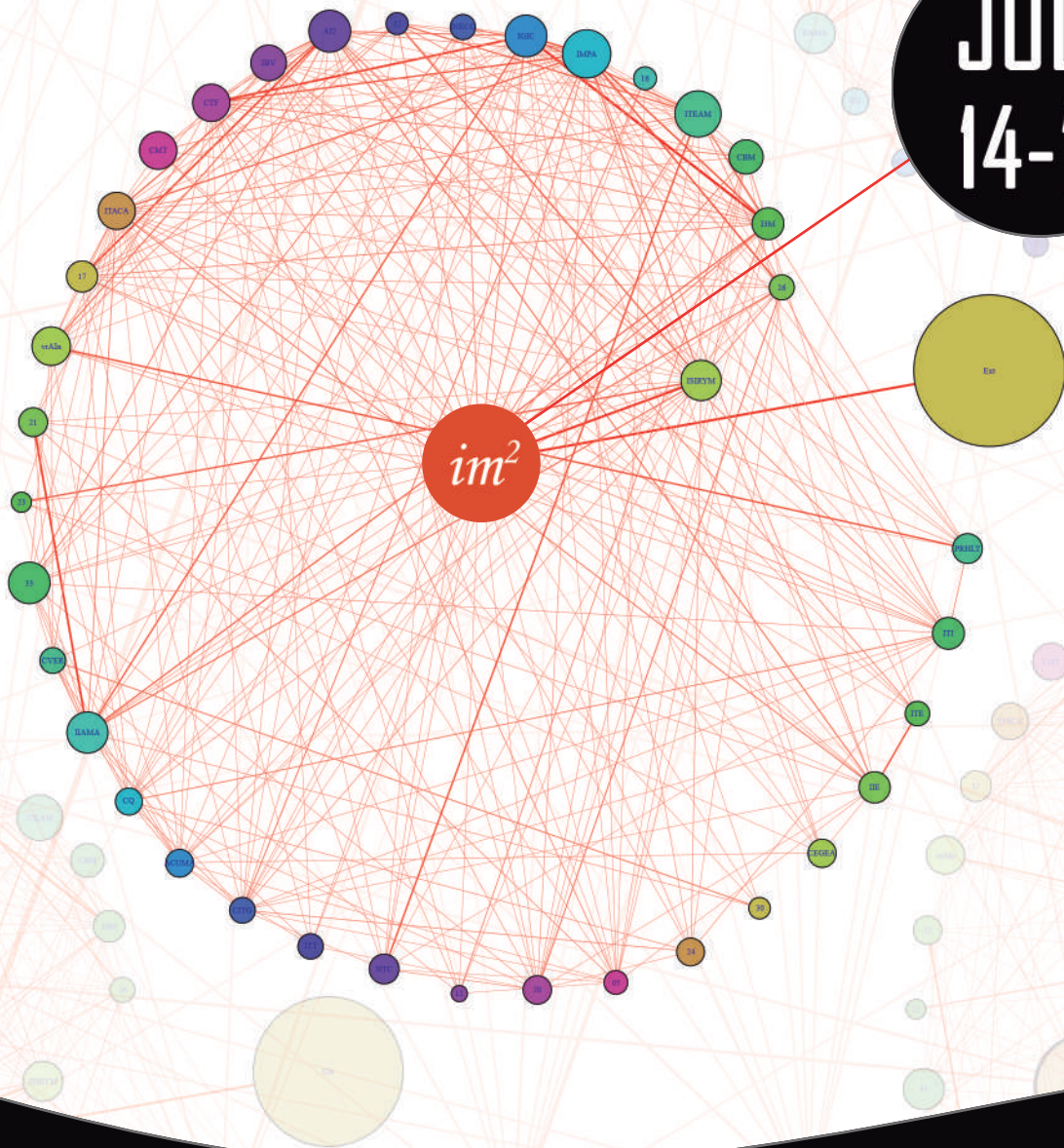


# MODELLING FOR ENGINEERING & HUMAN BEHAVIOUR

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Edited by

Juan Ramón Torregrosa

Juan Carlos Cortés

Antonio Hervás

Antoni Vidal

Elena López-Navarro



UNIVERSITAT  
POLITÈCNICA  
DE VALÈNCIA

*im*<sup>2</sup>

Instituto Universitario  
de Matemática Multidisciplinar



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**Edited by:** I.U. de Matemàtica Multidisciplinar, Universitat Politècnica de València.  
J.R. Torregrosa, J-C. Cortés, J. A. Hervás, A. Vidal-Ferràndiz and E. López-Navarro

*im<sup>2</sup>*

Instituto Universitario  
de Matemática Multidisciplinar

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# Probabilistic evolution of the bladder cancer growth considering transurethral resection

C. Burgos<sup>b</sup>, J.C. Cortés<sup>b</sup>, E. López-Navarro<sup>b1</sup> and R.J. Villanueva<sup>b</sup>

(b) Instituto Universitario de Matemática Multidisciplinar,  
Universitat Politècnica de València,  
Camino de Vera, s/n, 46022, València.

## 1 Introduction

Cancer is one of the most important public health problems worldwide. In Spain, it is one of the leading cause of death. It represents a total of 240,000 new cases and 100,000 deaths per year. The most frequently diagnosed tumors are colorectal, breast, prostate, lung and bladder cancer, [1]. In this contribution we focus on the latter. Bladder cancer is one of the most common malignant diseases in the urinary system and a highly aggressive neoplasm. The prognosis and the evolution for particular patients is uncertain. About 80% of patients diagnosed with bladder cancer have a non-invasive carcinoma that can be treated by transurethral resection (TUR). The TUR is a surgical procedure that involves inserting a resectoscope through the urethra into the bladder to remove the tumor. After the TUR, the typical treatment consists of instillations of Bacillus Calmette-Guérin (BCG) into the bladder. The BCG stimulates the patient's immune response against the cancer and then, the cancer cells may be eliminated. After treatment for this cancer it is important to have regular medical revisions, because it is characterized by recursiveness for more than 50% of the patients, and several TUR's may be applied to each patient.

Mathematically, this can be modeled by an exponential model where the growth of the tumor is stopped by the TUR and the tumor size is reduced almost to zero. We use data from a real patient to determine the model parameters that describe the known evolution, taking into account data uncertainty (size of the tumor), obtained from visual assessment. After that, we use these calibrated model parameters to predict the evolution of bladder cancer in future relapses. In the particular case of this patient, she has had two relapses. Then, we can provide when the patient should have her next medical revisions. To obtain a prediction, we calculate the probability density function (p.d.f.) of the time until a given tumor size is reached, using Random Variable Transformation method (RVT).

## 2 Data

To carry out our study, we have considered a patient from the database of the Urology Department of the Hospital Universitari i Politècnic La Fe of València. The available data for this patient

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<sup>1</sup>ellona1@upv.es

are collected and summarised in Table 1 at different time instants. As mentioned above, the measurement of tumor diameter is usually visual. For this reason, we will assume the following:

- If the size is given by an interval, we will take the mean as the visually estimated size of the tumour.
- A measurement error of 25% of the observed value,  $\sigma^2 = 0.25\mu$ , where  $\mu$  is the estimated measured value of the tumor diameter.

To quantify the uncertainty of the data, we will consider the data as a normal random variable with mean the data value, and variance the 25% error.

Day t	Date	Medical procedure	Diameter of the tumor	Measure distribution
0	01 Mar 2012	Ultrasound	3-5mm	$N(\mu = 4, \sigma^2 = 1)$
105	14 Jun 2012	TUR	25mm	$N(\mu = 25, \sigma^2 = 6.25)$
1081	15 Feb 2015	Cytoscopy	1-2mm	$N(\mu = 1.5, \sigma^2 = 0.375)$
1153	28 Apr 2015	TUR	5mm	$N(\mu = 5, \sigma^2 = 1.25)$
1796	30 Jan 2017	Cytoscopy	20mm	$N(\mu = 20, \sigma^2 = 5)$
1839	14 Mar 2017	TUR	30-35mm	$N(\mu = 32.5, \sigma^2 = 8.125)$

Table 1: Data of the real patient and chosen measure distribution.

### 3 Model

To describe tumor growth, we have considered a first-order linear growth model. As we have seen, the growth of the tumor is interrupted every time there is a TUR, at which point it starts to grow again from a new initial situation. Therefore, although the growth model may be the same, after each TUR the initial condition changes, which forces us to define the model in three parts. We will take a time step  $t$  of one day, and let  $X(t)$  be the diameter of the tumor on day  $t$ . The first part corresponds to time  $t \in [0, 105]$ , second part to  $t \in [105, 1153]$  and third part to  $t \in [1153, 1839]$ . We have to take into account that the initial conditions of the second and third parts are unknown but some data are known in the middle. Therefore, tumour growth will follow the equations

$$\left\{ \begin{array}{l} X'(t) = K_1 X(t) \\ X(0) = X_{0,1} \end{array} \right. , \quad \left\{ \begin{array}{l} X'(t) = K_2 X(t) \\ X(1081) = X_{0,2} \end{array} \right. , \quad \left\{ \begin{array}{l} X'(t) = K_3 X(t) \\ X(1796) = X_{0,3} \end{array} \right. ,$$

(1)
(2)
(3)

where  $K_1, K_2$  and  $K_3$  are the growth rates and  $X_{0,1}, X_{0,2}$  and  $X_{0,3}$  are the initial conditions. We consider  $K_i, i \in \{1, 2, 3\}$ , unknown random variables and  $X_{0,1}, X_{0,2}$  and  $X_{0,3}$  random variables that follows a normal distribution, as we have seen in Table 1,  $N(4, 1)$ ,  $N(1.5, 0.375)$  and  $N(20, 5)$ , respectively.

The model (1)-(3) has a known stochastic process solution, given by

$$X(t) = X_{0,i} e^{K_i(t-t_{0,i})}, \quad i \in \{1, 2, 3\}, \quad (4)$$

where  $t_{0,1} = 0$ ,  $t_{0,2} = 1081$  and  $t_{0,3} = 1796$ . Our main goal is to find the statistical distribution of the unknown random variables  $K_i, i \in \{1, 2, 3\}$ . We will use the Principle of Maximum Entropy. This method allows us to obtain a closed form expression of the p.d.f. taking into account the



known information of the random variable and maximizing its lack of knowledge [3]. Using Laplace transform we obtain that the p.d.f. of  $K_i$  is given by

$$f_K(k) = e^{-1-\lambda_{0,i}-\lambda_{1,i}k-\lambda_{2,i}k^2}, \quad k \in [k_{1,i}, k_{2,i}] \quad (5)$$

where  $k_{1,i} = 0$  and  $\lambda_{0,i}$ ,  $\lambda_{1,i}$ ,  $\lambda_{2,i}$  and  $k_{2,i}$ ,  $i \in \{1, 2, 3\}$  are values to be determined. It is important to remark that as  $f_K(k)$  has to be a p.d.f., its integral over its domain has to be one. So, we can isolate  $\lambda_{0,i}$  value in terms of the other variables. Consequently, we have to determine  $\lambda_{1,i}$ ,  $\lambda_{2,i}$  and  $k_{2,i}$ ,  $i \in \{1, 2, 3\}$ . To estimate this parameters, we use Particle Swarm Optimization algorithm. In order to do this, we need a fitness function. This function has been obtained minimizing the functional error between the p.d.f. of the stochastic solution 2, given by

$$f_{X(t)}(x) = \mathbb{E}_K \left[ f_{X_{0,i}} \left( x e^{K_i(t_0,i-t)} \right) e^{K_i(t_0,i-t)} \right], \quad i \in \{1, 2, 3\}, \quad (6)$$

obtained via RVT method [2] and the p.d.f. of the data, that follow a normal distribution. In Fig. 1 we can observe graphically the fitting obtained for  $t = 105$ ,  $t = 1153$  and  $t = 1839$ , that correspond to the TURs.

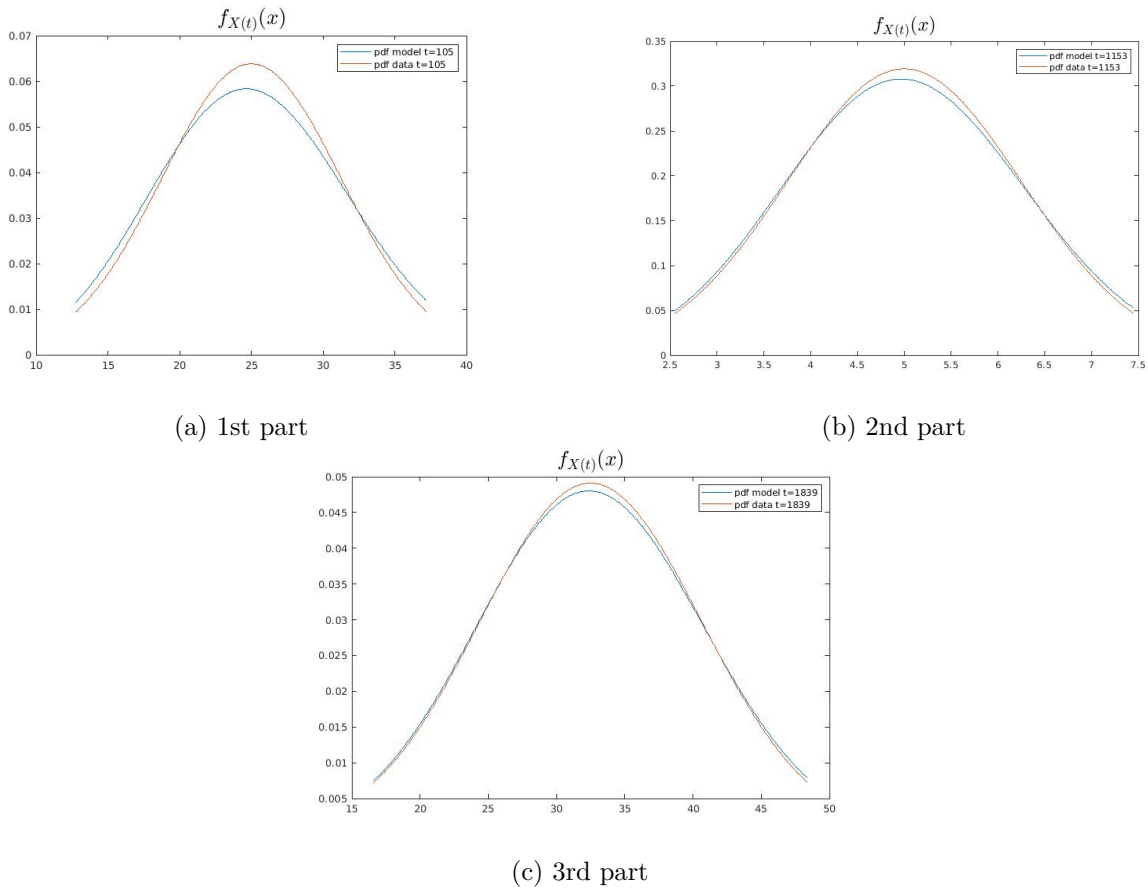


Figure 1: Fitting of the p.d.f. of the model (blue line) and the p.d.f. of the data (red line) for  $t = 105, 1153, 1839$ .

Once we have computed the p.d.f. of  $K_i$ ,  $i \in \{1, 2, 3\}$ , we can obtain the mean and the variance of the growth rate in each part. In Table 2 we can observe the decreasing tendency of the mean of  $K$ .

In Figure 2 we have plot the mean and the confidence interval for the three different stages considering the growth rates obtained in the optimization procedure. The orange dots are the

	Part 1	Part 2	Part 3
Mean	0.01740707	0.0167186	0.01130548
Variance	0.000001109	0.000000831	0.00000137

 Table 2: Mean and variance of  $K_i$ ,  $i \in \{1, 2, 3\}$ .

real patient data. We have to take into account that the initial conditions of the second and third parts are unknown. But, with the p.d.f. we can go backwards to estimate these initial conditions, which will tell us how good the resection has been. We have obtained that at  $t = 105$ , the mean of the initial condition in the second part is  $\mu = 1.25043110e - 07$  and at  $t = 1153$ ,  $\mu = 0.0127380$ . As we can observe, the surgery done in the second part has cleared most of the tumor. But, it does not seem the same happened in the surgery done in the third part.

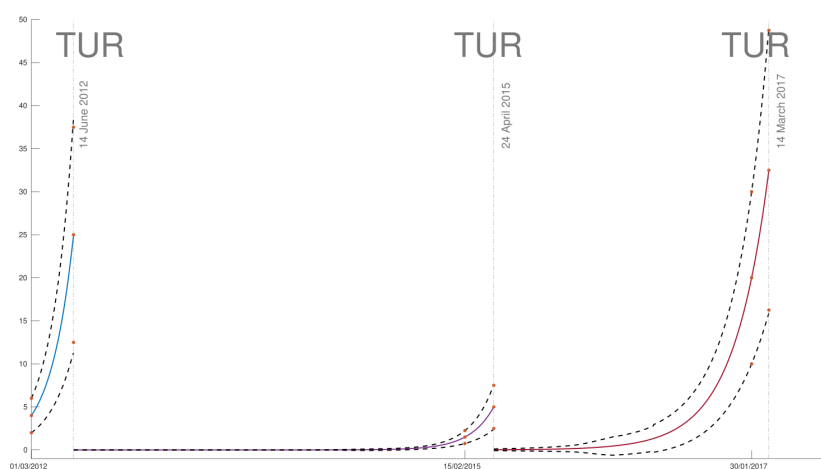


Figure 2: Mean and confidence interval for the three different stages.

## 4 Prediction

This section is devoted to study how to predict the evolution of bladder cancer in future relapses. Also, we can predict when the patient should have her next medical revisions. We deal with the following model

$$\begin{cases} X'(t) &= KX(t) \\ X(1839) &= X_0, \end{cases} \quad (7)$$

with known stochastic solution

$$X(t) = X_0 e^{K(t-1839)}, \quad (8)$$

where  $X_0$  is the initial condition and  $K$  the growth rate. Both are random variables.  $X_0$  follows a normal distribution, but in two different scenarios. This two scenarios correspond to the clean capacity of the TURs. Scenario 1 corresponds to a better cancer cleaning ( $\mu = 1.25043110e - 07, \sigma = 0.25\mu$ ) and scenario 2 to a worse cleaning ( $\mu = 0.0127380, \sigma = 0.25\mu$ ). To obtain the statistical distribution of  $K$  will be use the Principle of Maximum Entropy. To use this, we need the mean and second order moment of  $K$ . We use the information we have obtained in the previous three parts. We use linear regression for the mean and for the variance the mean of the variances.

To obtain a prediction, we calculate the p.d.f. of the time until a given tumor size is reached, using RVT method. It is given by

$$f_{T(x)}(t) = \mathbb{E}_{X_0} \left[ f_K \left( \frac{\log \left( \frac{x}{x_0} \right)}{t - 1839} \right) \left| -\frac{\log \left( \frac{x}{x_0} \right)}{(t - 1839)^2} \right| \right]. \quad (9)$$

From expression (9) we can obtain the mean and the standard deviation of the time for a specific tumor size. In Table 3 we can observe that the results obtained are very different in the two scenarios. There is more than a thousand days of difference between scenario 1 and 2. To our knowledge, the patient has had 3 revisions and none of them have shown any trace of cancer. It seems that we are in a favorable scenario. That is, we are in scenario 1, where there has been a better cleaning of the tumor.

Diameter of the tumor (mm)	Scenario 1 (Mean Days, standard deviation)	Scenario 2 (Mean Days and standard deviation)
0.5	$\mu = 3405.8, \sigma = 516.5$	$\mu = 2225.7, \sigma = 139.9$
1	$\mu = 3473.2, \sigma = 539.4$	$\mu = 2297.7, \sigma = 163.1$
5	$\mu = 3657.5, \sigma = 593.6$	$\mu = 2464.1, \sigma = 216.7$
20	$\mu = 3806.4, \sigma = 646.2$	$\mu = 2606.1, \sigma = 262.8$
25	$\mu = 3829.2, \sigma = 652.9$	$\mu = 2628.8, \sigma = 270.3$

Table 3: Prediction of the time until a given tumor size is reached in two different scenarios.

## 5 Conclusions

In this contribution, we propose a mathematical model of bladder cancer growth, taking into account the reduction of the tumor by the surgical intervention known as transurethral resection (TUR). TURs generate jumps in the continuity of cancer growth, for this reason we consider the model divided into 3 parts, corresponding to the periods between TURs. We use real data from a patient to determine the model parameter values that describe the known evolution, taking into account data uncertainty. After that, we use these calibrated model parameters to predict the evolution of bladder cancer in future relapses.

## Acknowledgements

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